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Vertebral Fracture Prediction From MRI-based Vertebral Bone Quality Scores in Postmenopausal Women

A Longitudinal Cohort Study

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Study Design. A longitudinal cohort study.

Objective. The study aims to assess the lumbar MRI-based vertebral bone quality (VBQ) score and dual energy x-ray absorptiometry (DXA) T score in a longitudinal cohort of postmenopausal women and to evaluate the performance of these scores in predicting VF over 5 years of follow-up.

Summary of Background Data. VBQ scores can be used for osteoporosis screening and identification of vertebral fractures (VFs). However, due to limitations in prior cross-sectional studies, definitive conclusions about the causal associations between the VBQ score and incident VF have not been drawn.

Methods. Postmenopausal women with baseline DXA and lumbar MRI data were enrolled. Follow-up assessments were conducted over 5 years after the baseline examination; both anteroposterior- and lateral-view thoracolumbar spine radiographs were captured to evaluate incident VF. At baseline, correlation analyses between the VBQ score and osteoporosis or preexisting VF were performed. A Cox regression model for multivariate logistic regression was used to analyze the risk factors for incident VF. The hazard ratio (HR) was calculated.

Results. One hundred thirty-seven postmenopausal women were included. The VBQ score was moderately correlated with lumbar bone mineral density at baseline ($r = 0.4$, $P < 0.001$). Patients with incident VF had significantly lower T scores (−3.4 *vs.* −1.87, $P < 0.001$) and higher VBQ scores (4.62 *vs.* 4.03, $P < 0.001$) at baseline than those without incident VF. After adjusting for age, weight, creatinine clearance, and alkaline phosphatase levels, the HRs for the VBQ score and T score were 1.93 and 0.71, respectively. After adjusting for the T score, an increased VBQ score was independently associated with an increased risk of incident VF, with an HR of 1.87.

Conclusions. The VBQ score was moderately correlated with the DXA T score and was a predictor of incident VF risk independent of bone mineral density in postmenopausal women.

Key words: magnetic resonance imaging, vertebral bone quality, bone mineral density, risk factor, vertebral fracture, longitudinal study

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval statement: This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. This study was carried out in accordance with relevant regulations of the US Health Insurance Portability and Accountability Act (HIPAA). Details that might disclose the identity of the subjects under study have been omitted. Ethical approval was obtained from the Institutional Review Board of Shunde Hospital of Southern Medical University (LWLS202207003).

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Osteoporotic vertebral fractures (VFs) commonly occur in postmenopausal women with reduced bone strength and can occur after minor trauma or in women with no definite trauma history.[1] VFs constitute a major health care problem because of their direct and indirect effects on health-related quality of life and health care expenditures.[2,3] Approximately 21% of women older than 50 years are reported to have VFs.[4]

Risk factors associated with VFs include advanced

age, prior fragility fracture, and osteoporosis.[5,6] Bone mineral density (BMD), a surrogate measure of bone health, is a commonly used index for evaluating the risk of fracture from osteoporosis. Patients with osteoporosis have a 50% greater risk of VF within 1 year than those without osteoporosis.[7] Due to its convenience, accessibility, and comparability, dual-energy x-ray absorptiometry (DXA) is a widely used method for measuring BMD and is accepted as the gold standard for diagnosing osteoporosis.[8,9]

Considering the availability of lumbar magnetic resonance imaging (MRI), an MRI-based vertebral bone quality (VBQ) score was recently developed for the opportunistic screening of osteoporosis and for evaluating complications in patients who underwent spinal surgery.[10–12] This so-called VBQ score, based on the demonstrably excellent soft tissue contrast provided by MRI, is regarded as an indicator of the degree of detrimental fat infiltration within the vertebral body. A higher VBQ score indicates more fat content, which may indicate a relatively reduced trabecular BMD in the vertebral body.[13] Previous studies have demonstrated that the VBQ scores of patients with osteoporosis are significantly higher than those of patients without osteoporosis and that up to 89% of patients with osteoporosis can be identified according to their VBQ score.[14] However, the VBQ score is less accurate in discriminating the presence of VFs,[15] which could limit its clinical application in predicting the risk of fracture. Compared with screening undiagnosed preexisting fractures, the ability to predict the future occurrence of VF in individuals may be more helpful for designing preventive strategies and improving clinical decision-making.[16,17] Nevertheless, due to the cross-sectional design of previous studies, no definitive conclusions regarding the causal associations between the VBQ score and subsequent VF events have been drawn, which limit the application of this imaging score for further clinical studies.

Therefore, this study assessed the lumbar VBQ score and DXA T score in a longitudinal cohort of postmenopausal women and evaluated the performance of these scores in predicting VF over 5 years of follow-up. Considering the mutual independence between fat infiltration and bone mineral intake, we hypothesized that VBQ score is a risk factor for new VFs in postmenopausal women, independent of BMD.

MATERIALS AND METHODS

Study Design and Population Cohort

This study was approved by the local institutional review board (LWLS202207003) and conducted in accordance with the Declaration of Helsinki guidelines. An informed consent was obtained and witnessed. We retrospectively analyzed the medical records of postmenopausal women who visited the spine service of a single academic institution between January 2012 and December 2015. All postmenopausal women with available DXA and lumbar MRI data at baseline were included in the study. Clinical information, including sex, age, weight, primary diagnosis and comorbidities, and serological and imaging data, were collected from inpatient medical records at baseline. The exclusion criteria were as follows: patients with (1) a history of metabolic bone disease or bone cancer; (2) a history of spinal instrumentation surgery; (3) spinal infection; (4) severe spinal deformity; (5) high-energy trauma, defined as either a motor vehicle accident, a fall from a height or polytrauma; and (6) MR images of unsatisfactory quality. Follow-up assessments took place over 5 years after the baseline examination, and thoracolumbar spine radiographs (lateral and antero-posterior views) were captured. Only patients for whom data were available both at baseline and at the final follow-up examination were included in the analysis. The flowcharts of the study are shown in Figure 1.

BMD Evaluation and Fracture Identification

DXA scans were performed using GE Lunar DXA (GE Luar Prodigy and DPX Brovo DXA scanners, GE Healthcare, WI, USA) according to the manufacturer's standard protocol. Areal BMD was assessed at L1 to L4 by a well-trained radiologist to ensure the scan quality and was subsequently presented as a T score, where the T score = (measure value – peak BMD)/standard deviation of BMD in normal adults. The diagnostic criteria for osteoporosis recommended by the World Health Organization (WHO) in 1994 were used to establish the diagnosis of osteoporosis based on the DXA T score (normal, −1.0 or above; osteopenia, between −1.0 and −2.5; osteoporosis, −2.5 or below and those with osteopenia in the presence of a fragility fracture).

Morphometrical VFs were assessed from the lateral

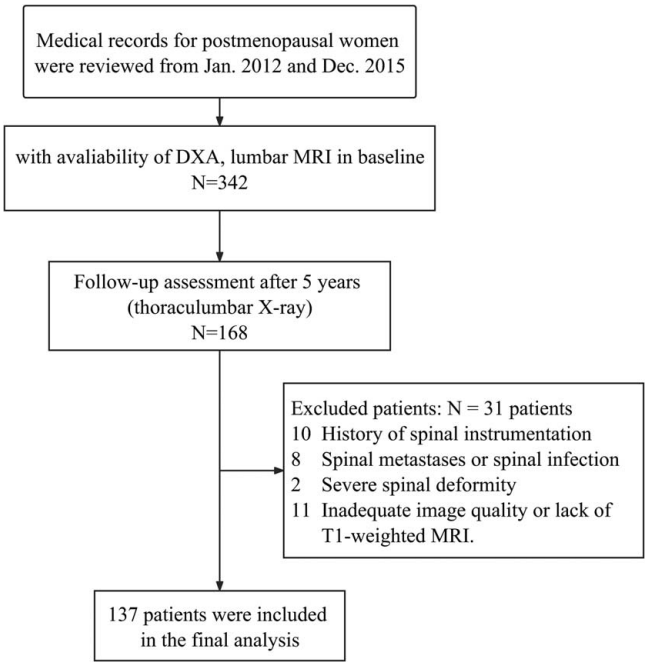

Figure 1. The flow chart of patient enrollment.

projection from T1 to S1 scans using Genant's semiquantitative (SQ) grading system. VFs were classified as follows: grade 1, reduction of 20%–25%; grade 2, reduction of 25%–40%; and grade 3, reduction of >40%.[18] The primary outcome was the incidence of radiographically determined morphometrical new or worsening VFs. The former was defined as a decrease of ≥20% in height at the anterior, posterior, or central vertebra from the normal baseline, while the latter was defined as an increase of at least 1 SQ grading scale in a vertebral body with a preexisting fracture. Radiographs were evaluated by an experienced radiologist and verified by the investigators. VFs that were associated with severe trauma, defined as a fall from a height higher than a stool, chair, or first rung of a ladder, or severe trauma other than a fall were excluded. Patients were stratified into 2 groups based on whether new or worsening VFs were identified: incident VF group and without incident VF group.

MRI-based VBQ Score

All patients underwent lumbar MRI on the same machine (Philips Achieva 1.5 Tesla, Philips Medical Systems, Best, the Netherlands) at baseline. The VBQ scores were determined by two experienced spinal surgeons using a picture archiving and communication system (PACS). According to previous methods,[10] regions of interest (ROIs) were drawn on mid-sagittal MR images using the oval selection tool and labeled within the ROI manager to measure the average vertebral signal intensity (SI) at the medulla portion of the L1-L4 vertebral body as well as the average cerebral spinal fluid (CSF) SI posterior to the L1-L3 vertebral body. If the ROI within the vertebral body was not visible due to abnormalities such as a Modic change, Schmorl's nodes, vertebral hemangiomas, or a compression fracture, the adjacent vertebral body was used to calculate the VBQ score. All analyses were performed on contrast-free T1-weighted MR images acquired in the sagittal plane. The VBQ score was calculated according to the following equation:

$$\text{VBQ score} = \text{mean vertebral SI (L1} - \text{L4)} / \text{mean CSF SI(L1} - \text{L3)}.$$

Statistical Analysis

Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as frequencies and percentages, respectively. Differences in the baseline characteristics between the incident VF group and the without incident VF group were evaluated using one-way ANOVA or the χ^2 test. The distribution of the levels of VFs was described using histograms. The VBQ score was plotted against the DXA T score, after which the line of best fit was calculated based on linear regression. To assess the independent risk factors for VFs, factors with statistical significance in the univariate analysis were included in the Cox regression model for multivariate logistic regression. The hazard ratios (HRs) and 95% CIs for the VBQ score and osteoporosis status were calculated to distinguish between risk factors (HR >1) and protective factors (HR <1). Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of the VBQ score for osteoporosis and preexisting VFs, from which the corresponding area under the curve (AUC) was calculated. Statistical analyses were carried out using the SPSS statistics software package (version 25.0; SPSS, Inc., Chicago, IL). $P < 0.05$ indicated statistical significance.

RESULTS

Table 1 describes the clinical characteristics of the study population. A total of 137 postmenopausal women were included, with a mean age of 71.3 ± 7.2 years and an average follow-up time of 6.4 ± 1.5 years. In accordance with the osteoporosis diagnosis criteria recommended by

TABLE 1. Baseline Characteristics of Study Participants

Variables	Total (N = 137)	Incident VF (N = 54)	Without incident VF (N = 83)	*P*
Age, yr	67 ± 9.3	73.7 ± 7.8	62.7 ± 7.6	**<0.001**
Weight, kg	57 ± 10.3	51.9 ± 10	57.1 ± 8.8	**0.002**
Serum ionized calcium, mmol/L	2.35 ± 0.28	2.32 ± 0.26	2.38 ± 0.29	0.225
Serum phosphorus, mmol/L	1.15 ± 0.19	1.13 ± 0.17	1.17 ± 0.2	0.144
Serum uric acid, μmol/L	325.4 ± 112.5	313.1 ± 104.5	333.4 ± 117.4	0.304
Creatinine clearance, mL/min	71.9 ± 27.8	63.6 ± 30.8	77.4 ± 24.3	**0.004**
Alkaline phosphatase, pg/mL	85.8 ± 30.5	94.8 ± 36.7	80 ± 24.2	**0.005**
Blood glucose, mmol/L	5.8 ± 1.7	5.64 ± 1.15	5.96 ± 1.96	0.275
VBQ score	4.26 ± 0.73	4.62 ± 0.67	4.03 ± 0.68	**<0.001**
BMD, T score	−2.48 ± 1.6	−3.4 ± 1.41	−1.87 ± 1.41	**<0.001**
DXA category				
Normal, n (%)	23 (16.8)	3 (5.6)	20 (24.1)	—
Osteopenia, n (%)	41 (29.9)	9 (16.7)	32 (38.6)	—
Osteoporosis, n (%)	73 (53.3)	42 (77.8)	31 (37.3)	**<0.001**
Follow-up time, yr	6.4 ± 1.5	6.4 ± 1.4	6.4 ± 1.6	0.968
History of VF, n (%)	50 (36.5)	42 (77.8)	8 (9.6)	**<0.001**

Bold values denote statistical significance. $P < 0.05$.
*Continuous variables were expressed as means and standard deviation; categorical variables represent counts and frequencies.
BMD indicates bone mineral density; DXA, dual x-ray absorptiometry; VBQ, vertebral bone quality; VF, vertebral fracture.

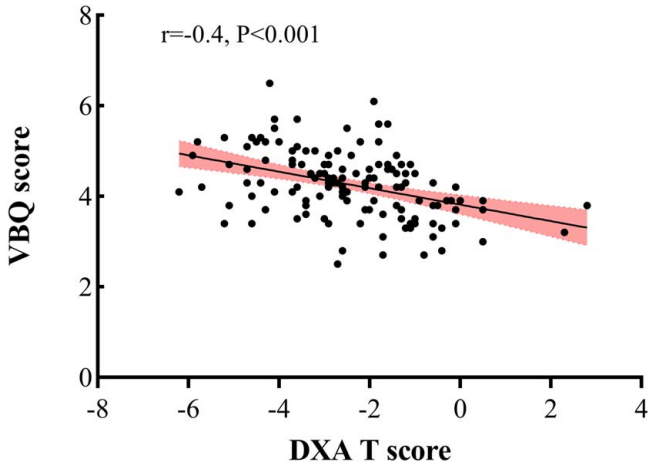

Figure 2. Scatter plot was drawn to demonstrate the relationship between the VBQ score (*y*-axis) and DXA T score (*x*-axis).

the WHO, 53.3% of the 137 patients were diagnosed with osteoporosis, 29.9% had osteopenia, and 16.8% had a normal BMD. Scatter plots (Figure 2) were drawn to analyze the correlations between the VBQ score and lumbar BMD, and the results revealed a significant correlation ($r = 0.4$, $P < 0.001$). According to the ROC curve analysis (Figure 3), the VBQ score was a significant predictor of osteoporosis (AUC = 0.67, 95% CI = 0.57–0.76). At the maximum Youden's index, the cutoff value of the VBQ score was 3.95, with a sensitivity of 0.52 and a specificity of 0.79. In discriminating patients with or without preexisting VFs, the T score (AUC = 0.78, 95% CI = 0.7–0.86; sensitivity, 76%; specificity, 70%) demonstrated better diagnostic performance than the VBQ score (AUC = 0.72, 95% CI = 0.64–0.81; sensitivity, 41%; specificity, 91%; cutoff value = 3.85).

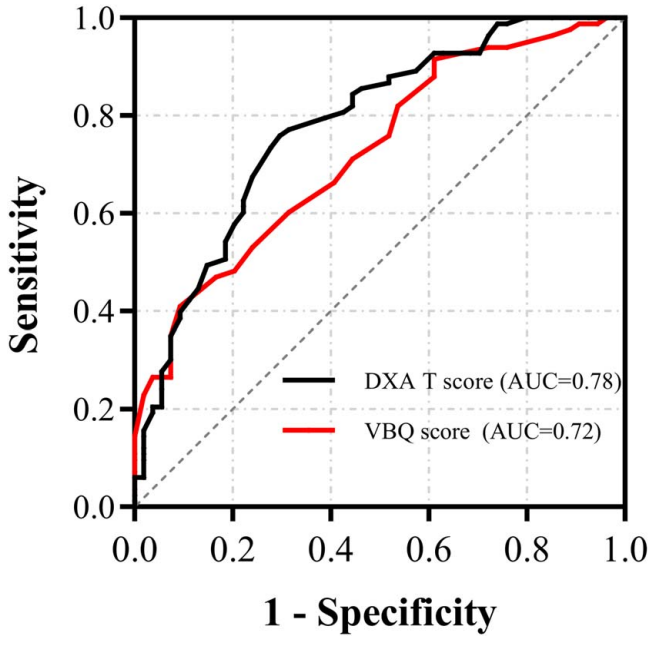

Figure 3. ROC plots for the VBQ score and DXA T score used for the identification of patients with preexisting VF in the baseline.

Occurrence of VFs

After a final follow-up, 54 patients were subsequently found to have an incident VF of at least one anatomic level. Thirty-six of these patients had a new-onset VF, 5 had a worsened preexisting VF, and 13 had both a new-onset and a worsened preexisting VF at different vertebral levels. Moreover, 42 (77.8%) patients with subsequent VFs had a history of previous fragility fractures. Details regarding the VF status are shown in Figure 4. The largest distribution of VFs involved the thoracolumbar junction, with 17 involving the L1 level, followed by 12 involving the T12 or L3 level. A comparison of baseline characteristics between patients with incident VF and those without incident VF is shown in Table 1. Overall, the incident VF patients tended to have lower weight and older age. Patients with VF had significantly lower T scores (–3.4 *vs.* –1.87, $P < 0.001$) and higher VBQ scores (4.62 vs. 4.03, $P < 0.001$) at baseline than those without VF. There are 11 patients without osteoporosis at baseline who suffered a subsequent VF at the final follow-up, with a relatively high mean VBQ score of 4.7 (Supplementary Table, Supplemental Digital Content 1, http://links.lww.com/BRS/C563).

Risk Factor Analysis

On the basis of univariate analysis, those factors that were significantly correlated with subsequent VF were further included in the multivariate Cox proportional hazard regression. An unadjusted model (Model 1) (Table 2) revealed that both a high VBQ score and a low T score significantly increased the risk of subsequent VF, with HRs of 2.29 (95% CI = 1.59–2.38) and 0.7

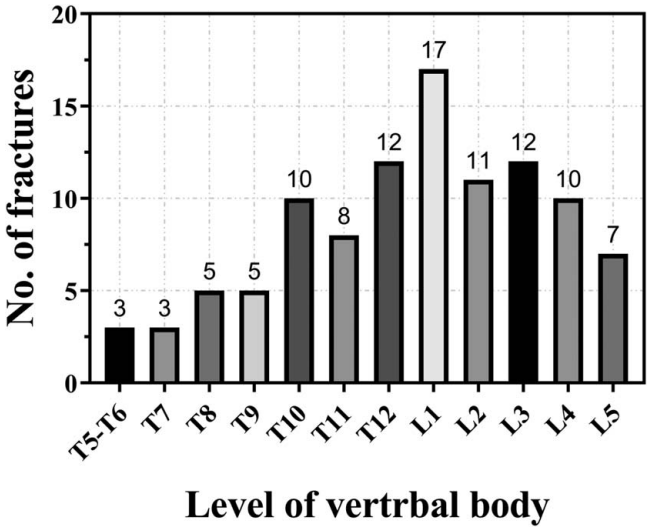

Figure 4. The distribution of incident VF at different vertebral levels.

TABLE 2. Cox Regression Analysis of Risk Factors Associated With VF

	Incident VF	
Models and variables	**HR (95% CI)**	***P***
Unadjusted model		
VBQ score	2.29 (1.59–3.28)	**< 0.001**
DXA T score	0.7 (0.59–0.83)	**< 0.001**
History of VF	6.6 (3.4–12.8)	**< 0.001**
Model 1*		
VBQ score	1.93 (1.3–2.87)	**< 0.001**
DXA T score	0.71 (0.57–0.88)	**0.002**
Model 2†		
VBQ score	1.87 (1.26–2.78)	**0.002**
DXA T score	0.76 (0.63–0.92)	**0.006**

Bold values denote statistical significance. $P < 0.05$.

*Model 1 adjusted for age, weight, creatinine clearance, and alkaline phosphatase.

†Model 2 adjusted for VBQ score or T score.

DXA indicates dual x-ray absorptiometry; HR, hazard ratio; VBQ, vertebral body quality; VF, vertebral fracture.

(95% CI = 0.59–0.83), respectively. After adjusting for age, weight, creatinine clearance, and alkaline phosphatase level (Model 2), the HR for the VBQ score was reduced to 1.93 (95% CI = 1.3–2.87), while the HR for the T score did not change appreciably (0.71, 95% CI = 0.57–0.88). In Model 3, an increased VBQ score was independently associated with an increased risk of subsequent VF after adjusting for the T score (adjusted HR 1.87, 95% CI = 1.26–2.78).

DISCUSSION

Osteoporotic VFs occur frequently in postmenopausal women with decreased BMD, resulting in a series of organic, psychological, social, and economic problems.[18,19] This study provides the first evidence to demonstrate the value of the VBQ score in predicting VF events over a long period of follow-up. High VBQ is a risk factor for new VFs in postmenopausal women, independent of BMD.

In this study, 137 postmenopausal women were followed up for more than 5 years to monitor the occurrence of new or worsening VFs. During follow-up, subsequent VFs were observed in 54 patients. A lower BMD was shown to be associated with a greater risk of VF, and each standard deviation decrease in the lumbar BMD increased the risk of VF by 30%. This finding was consistent with the 27% increased risk reported in a previous investigation.[20] Despite the pivotal role of BMD in predicting the occurrence and development of VFs, nearly a quarter of patients without osteoporosis at baseline suffered a subsequent VF at the final follow-up. It is interestingly these patients exhibited relatively higher VBQ scores. The reason why VF happens in such patients may be attributed to a more severe fatty infiltration within the vertebral body and instead of a lower BMD.[21] Moreover, 42/50 patients with a history of VF suffered a subsequent VF, and a prior history of VF appears to be the strongest risk factor for subsequent fracture, suggesting that rather than low BMD alone, a history of VF often indicates worse bone quality. Thus, it may be more important to evaluate bone status rather than BMD.[22]

One indirect marker of bone status is MRI-derived VBQ score,[23] which has been proposed as a novel parameter mainly for evaluating detrimental fat infiltration within the vertebral body and confirmed to be significantly associated with areal BMD and volumetric BMD of the lumbar spine.[13,24] In addition, multiple cross-sectional and retrospective studies have also demonstrated that the VBQ score could be helpful in identifying occult VFs, with accuracies in identifying the presence of VFs ranging from 59% to 80%, an overall sensitivity ranging from 56% to 75%, and a specificity ranging from 55% to 86%.[14,15] Like in previous cross-sectional analyses, a VBQ score of 3.85 was found to indicate occult VF in the baseline, with an AUC of 0.72, a sensitivity of 76%, and a specificity of 70%. However, the occurrence of a new VF, from the perspective of VF prevention, may have a greater impact on health and socioeconomics than occult fractures.[25,26] Most spine surgeons focus on the occurrence of VF rather than preexisting VF, as the former implies that patients suffer from both physical and mental burdens and may require surgical intervention. Ehresman *et al*[14] first reported that the VBQ score significantly predicted the occurrence of new VFs in patients with spinal metastases. However, sites of metastasis are also hypointense on T1-weighted MRI, which can confound signal intensity measurements of VBQ to some extent.[27] It is also unreasonable to generalize the research results to the entire population due to the heterogeneity of patients with malignancies. A later retrospective study with a 2-year follow-up in older adults showed that the occurrence of incident fracture was independently associated with a higher VBQ score (odds ratio 2.4 per point) but was not significantly associated with age, female sex, or BMD.[28] The result underpinning this study appears somewhat implausible and should be interpreted with caution, as the above-mentioned risk factors for VF (*e.g.*, BMD) have long been confirmed by high-quality clinical evidence.[29,30] The small sample sizes, heterogeneity of populations, inadequate follow-up periods, and lack of subgroup analyses may be the causes of this deviation.

The lack of evidence-based evidence data regarding the association between the VBQ score and the risk of VF prompted us to conduct this longitudinal study in postmenopausal women, which focused on evaluating the potential role of VBQ in the occurrence of VF events during long-term follow-up. In our study, patients with new or worsening VFs had significantly higher VBQ scores than those without new or worsening VFs. We also found that every 1 unit increase in the VBQ score in baseline was associated with a 129% increase in the risk of VF during a follow-up of more than 5 years, which is to be expected given the considerable concordance between VBQ and osteoporosis.[13,15] Notable, after adjusting for the T score, the VBQ score continued to be a significant independent predictor of the risk of incident VF at follow-up, which indicates that lumbar BMD cannot fully explain this correlation. This finding is consistent with our

hypothesis. Abnormal bone metabolism and fatty infiltration in vertebrae, two pathophysiological processes, are more tightly correlated and relatively independent. The former is reflective of the pathophysiology of bone loss observed in vivo. During the loss of bone minerals, the bone microstructure is also destroyed, causing an increased risk of bone fragility and fracture.[31] Meanwhile, local adipocytes invade evertebral body, indicated by abnormal accumulation of adipocytes in the bone marrow cavity, replacing trabecular bone and accelerating disruption of the bone microarchitecture.[32] Owing to a common embryonic origin between bone marrow adipocytes and osteoblasts, adipogenesis is also considered a competitive process that interferes with bone formation.[33] To the best of our knowledge, we provide the first evidence that an MRI-based assessment of bone quality is independently associated with the risk of incident VF in postmenopausal women with a high incidence of osteoporosis. The VBQ score could be used in combination with BMD assessment to reflect different physiological and metabolic effects during degeneration.[34] Hence, a comprehensive evaluation approach may be more useful for evaluating bone health and predicting fracture risk than a single assessment tool.

Nevertheless, this study has several limitations. First, the study population was highly homogeneous, which might limit the generalizability of the findings to healthy individuals and other patient groups. Second, we performed an analysis using only the baseline data of the VBQ score and T score, and no data were available for analysis at the final follow-up, so we were unable to assess the effect of changes in bone quality on incident VFs. Osteoporosis treatment and changes could have a significant impact on the predictability of fractures; however, this information was unknown. Third, newly developed VFs were diagnosed by a variety of different methods. x-rays tend to miss nonapparent fractures and those with bone marrow edema only.[35]

In conclusion, the VBQ score was moderately correlated with BMD and may be a potential predictor of incident VF risk independent of BMD in postmenopausal women. In addition, we recommend the use of the MRI-based VBQ score as a complementary method for assessing bone quality to optimize VF risk management strategies.

➢ Key Points

- ❑ In discriminating patients with or without preexisting vertebral fractures (VFs), the T score demonstrated better diagnostic performance than the vertebral bone quality (VBQ) score.
- ❑ After adjusting for age, weight, creatinine clearance, and alkaline phosphatase level, a high VBQ score and a low T score significantly increased the risk of subsequent VF.
- ❑ An increased VBQ score was independently associated with an increased risk of subsequent VF after adjusting for the T score.

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