Retrospective Study

Risk Factors for Refracture following Primary Osteoporotic Vertebral Compression Fractures

Chengyue Ji, MD[1], Yuluo Rong, MD[1], Jiaxing Wang, MD[1], Shunzhi Yu, MD[2], Guoyong Yin, MD[1], Jin Fan, MD[1], Pengyu Tang, MD[1], Dongdong Jiang, MD[1], Wei Liu, MD[1], Fangyi Gong, MD[1], Xuhui Ge, MD[1], and Weihua Cai, MD[1]

From: [1]Department of Orthopedics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China; [2]Department of Orthopedics, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

Address Correspondence: Weihua Cai, MD, PhD Department of Orthopedics The First Affiliated Hospital of Nanjing Medical University 300 Guangzhou Road Nanjing , Jiangsu Province, China E-mail: caiweihuazhuren@163.com

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Background: In the aging population, osteoporosis and related complications have become a global public health problem. Osteoporotic vertebral compression fractures are among the most common type of osteoporotic fractures and patients are at risk of secondary vertebral compression fracture.

Objectives: To identify risk factors for secondary vertebral compression fracture following primary osteoporotic vertebral compression fractures.

Study Design: Retrospective study.

Setting: Department of Orthopedic, an affiliated hospital of a medical university.

Methods: This retrospective cohort study evaluated the risk factors for secondary vertebral compression fracture in 317 consecutive patients with systematic osteoporotic vertebral compression fractures who received percutaneous vertebroplasty and kyphoplasty or conservative treatment. Patients were divided into secondary vertebral compression fracture (n = 43) and non- secondary vertebral compression fracture (n = 274) groups. We retrospectively analyzed clinical characteristics and radiographic parameters, including gender, age, body mass index, number of primary fractures, primary treatment (percutaneous vertebroplasty and kyphoplasty or conservative treatment), nonspinal fracture history before primary fracture, primary fracture at the thoracolumbar junction, steroid use, bisphosphonate therapy, and Hounsfield units value of L1.

Results: Comparison between the groups showed significant differences in age ($P = 0.001$), nonspinal fracture history ($P < 0.001$), and Hounsfield units value of L1 ($P < 0.001$). The receiver operating characteristic curves demonstrated that the optimal thresholds for age and Hounsfield units value of L1 were 75 (sensitivity: 55.8%; specificity: 67.5%) and 50 (sensitivity: 88.3%; specificity: 67.4%), respectively. In multivariate logistic regression analysis, nonspinal fracture history (OR = 6.639, 95% CI = 1.809 – 24.371, $P = 0.004$) and Hounsfield units value of L1 < 50 (OR = 15.260, 95% CI = 6.957 – 33.473, $P < 0.001$) were independent risk factors for secondary vertebral compression fracture.

Limitations: The main limitation is the retrospective nature of this study.

Conclusion: Patients with low Hounsfield units value of L1 or non-spinal fracture history are an important population to target for secondary fracture prevention.

Key words: Risk factor, vertebral, secondary fracture, osteoporosis

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With the aging population, osteoporosis and related complications have become a global public health problem. Approximately 40% of women over the age of 50 years will experience major osteoporotic fractures in their lifetime (1). Vertebral fractures are generally considered among the most common type of osteoporotic fractures, affecting 1.4 million patients annually worldwide (2). Osteoporotic vertebral compression fractures (OVCFs) cause chronic back pain, spinal kyphosis, and lead to decreased quality of life and survival (3,4). The majority of patients can achieve adequate pain relief following conservative treatments, consisting of bed rest, immobilization, analgesics, and use of bracing (5). Minimally invasive spinal surgery, such as percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) can also be used when pain persists after conservative treatment (6,7). However, regardless of the treatment, patients are at risk of secondary vertebral compression fracture (SVCF). The increased socioeconomic burden makes SVCF a major issue that needs to be resolved. Therefore, this study evaluated the risk factors for SVCF.

Methods

Study Population

This retrospective study was approved by Ethics Committee of The First Affiliated Hospital of Nanjing Medical University. We included 317 patients with systematic OVCF who received PVP/PKP or conservative treatment between February 2015 and December 2017. All patients had follow-up for at least 2 years. SVCF was discovered by recurrence of back pain and acute vertebral marrow edema with high signal intensity on T2-weighted fat suppression magnetic resonance imaging (MRI). According to this definition, patients were divided into 2 groups: those with SVCF (n = 43) and those without SVCF (n = 274). Exclusion criteria included (1) acute vertebral compression fracture caused by severe trauma such as car accidents and falling injury; (2) primary or metastatic tumors; (3) multiple myeloma or other systemic diseases; (4) infection; and (5) previous spinal surgery.

Surgical Procedure

The procedure was performed with the patient in the prone position. Every treated patient received a low level of sedation and local anesthesia. Vital signs including blood pressure, pulse, and respiration were closely monitored during the operation. Under C-arm x-ray machine (Siemens Medical Systems), an 11- or 13-gauge bone mineral biopsy needle (Kyphon, Sunnyvale, CA, USA) was introduced into the collapsed vertebral body via a unipedicular or bipedicular approach until the needle tip advanced to the anterior third of the vertebral body. For PKP, expanded balloons were placed into the vertebra to restore the height of the collapsed vertebral body. The bone cement consisted of polymethylmethacrylate (PMMA, Kyphon) and barium sulfate was injected through the needle until it reached the posterior third of the vertebral body to reduce bone cement leakage. Symptoms were relieved almost immediately after the procedure and x-ray films were obtained on the next day after the operation. Patients were usually discharged within 24 hours. No major complications were observed during the procedure.

Data Collection

To clarify the risk factors for SVCF, we retrospectively analyzed clinical characteristics and radiographic parameters including: gender, age, body mass index (BMI), number of primary fractures, primary treatment (PVP/PKP or conservative treatment), nonspinal fracture history before primary fracture, primary fracture at the thoracolumbar (TL) junction, steroid use, bisphosphonate therapy, and Hounsfield units (Hu) value of L1. BMI was calculated by dividing patients' weight (kg) by height squared (m^2). T11 to L1 was defined as TL junction. Via standard picture archiving and communication system (PACS), the Hu value of L1 was measured using a technique first described by Schreiber et al (Fig. 1) (8). The largest elliptical region of interest (ROI) encapsulating only trabecular bone was drawn on 3 images of L1: inferior to the upper end plate, mid-body, and superior to the lower endplate. The software automatically calculated the mean Hu value of the ROI and the average from the 3 axial slices was defined as the mean Hu value of L1. If compression fracture was located in the L1 vertebra, the Hu value for T12 and L2 was measured using the same technique and the average of the 2 was considered as the mean Hu value of L1.

Statistical Analysis

Data analysis was performed using SPSS version 23.0. Continuous variables were summarized as mean ± SD values. Differences between the patients with and without SVCFs were assessed by using Student's t-test, Mann Whitney U test, and chi-square test. Receiver-

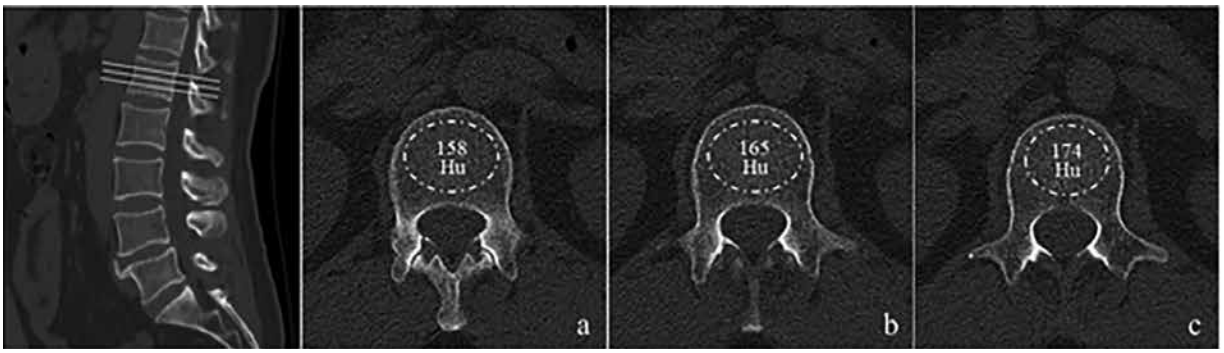

Fig. 1. *Using standard picture archiving and communication system (PACS), the largest elliptical region of interest (ROI) encapsulating only trabecular bone was drawn on 3 images of L1: inferior to the upper end plate (a), mid-body (b), and superior to the lower endplate (c). The software automatically calculated the mean Hu value of the ROI and the average from the 3 axial slices was defined as the mean Hu value of L1.*

operating characteristic (ROC) curve analysis was used to obtain the optimal predictive value of the parameters. Logistic regression analysis was conducted to analyze the risk factors for SVCFs. A *P* value of < 0.05 was deemed statistically significant.

Results

Patient Demographics and Clinical Characteristics

A total of 317 patients (384 fractured vertebrae) were included in our study. There were 82 (25.9%) men and 235 (74.1%) women. The mean age was 70.26 years (from 56 to 97). Figure 2A shows the distribution of the primary compression fractures. During mean follow-up of 32.46 ± 3.86 months, 43 (13.6%) patients returned with secondary new compression fractures. Among the 43 patients (64 fractured vertebrae), nine were men and 34 were women, with a median age of 75.58 years (from 63 to 90). Fourteen patients initially received PVP/PKP and 29 underwent conservative treatment. Thirty-two patients were successfully managed by surgery while another 11 received conservative treatment. Figure 2B shows the distribution of secondary fractures. TL junction was the most frequent site for primary and subsequent fractures.

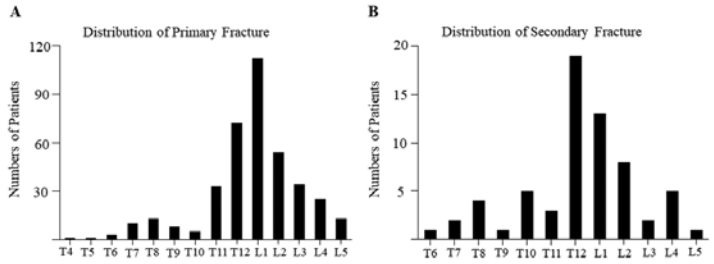

Fig. 2. *Distribution of the primary vertebral fracture (A) and secondary new compression fracture (B).*

Risk Factors for SVCF

Comparisons between the SVCF and non-SVCF group showed that age (*P* = 0.001), nonspinal fracture history (*P* < 0.001), and Hu value of L1 (*P* < 0.001) were significantly correlated with SVCF (Table 1). The ROC curves further demonstrated that the optimal thresholds for age and Hu value of L1 were 75 (sensitivity: 55.8%; specificity: 67.5%) and 50 (sensitivity: 88.3%; specificity: 67.4%) (Fig. 3). Multivariate logistic regression analysis showed that non-spinal fracture history (OR = 6.639, 95% CI = 1.809 – 24.371, *P* = 0.004) and Hu value of L1 < 50 (OR = 15.260, 95% CI = 6.957 – 33.473, *P* < 0.001) were independent risk factors for SVCF (Table 2).

Discussion

With the growing aging population, osteoporosis has become a major health issue worldwide (9,10). OVCF is one of the most common manifestations of osteoporosis that usually occurs in post-menopausal women, causing chronic pain, long-term disability, and progressive kyphosis (11). Acute pain can be relieved following conservative management or minimally inva-

Table 1. *Comparison of the SVCF and Non-SVCF groups.*

Factor	SVCF Group (n = 43)	Non-SVCF Group (n = 274)	*P* value
Age*(years)	75.58 ± 8.11	69.42 ± 11.02	0.001
Gender (Men:Women)	9:34	73:201	0.426
BMI	21.45 ± 2.34	22.94 ± 3.89	0.131
Number of primary fractures	1.37 ± 0.92	1.19 ± 0.54	0.064
Treatment of primary fracture			
PVP/PKP	14	127	
Conservative	29	147	0.091
Thoracolumbar junction			
yes	29	176	0.682
no	14	98	
Nonspinal fracture*			
yes	7	9	< 0.001
no	36	265	
History of steroid use			
yes	1	3	0.501
no	42	271	
Bisphosphonate use			
yes	26	178	0.567
no	17	96	
Hu value of L1	56.56 ± 34.43	98.34 ± 44.23	< 0.001

*Statistically significant difference
SVCF, secondary vertebral compression fracture; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; BMI, body mass index; Hu, hounsfield unit

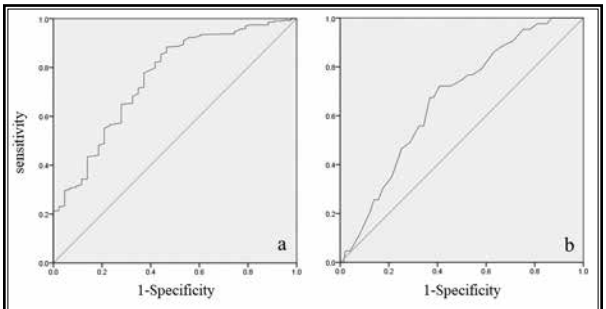

Fig. 3. *Area under the receiver operating curve was 0.757 (P < 0.001), 0.666 (P < 0.001) for (a) Hounsfield Units (HU) value of L1 and (b) age.*

Table 2. *Multivariate logistic regression analysis.*

Factor	Odds Ratio (95 % CI)	*P* value
Age > 75	1.390 (0.643 – 3.005)	0.402
Nonspinal fracture	6.639 (1.809 – 24.371)	0.004
Hu value of L1 < 50	15.260 (6.957 –33.473)	< 0.001

CI indicates confidence interval
Hu Hounsfield unit

sive spinal surgery (4,12,13). However, for people with a history of OVCF, the risk of refracture associated with osteoporosis cannot be ignored. Unfortunately, much of the existing literature focuses on risk of refracture only in surgical patients, and there has been limited clinical research concerning recompression following OVCFs regardless of treatment modality.

In the current study, 13.6% of the patients experienced vertebral refracture following primary OVCF. TL junction was the most frequent site for primary and subsequent fractures. To clarify the risk factors for SVCF, we analyzed clinical and radiographical parameters including gender, age, BMI, number of primary fractures, primary treatment (PVP/PKP or conservative treatment), non-spinal fracture history, primary fracture at the TL junction, steroid use, bisphosphonate therapy, and HU value of L1. Elderly postmenopausal women are considered at increased risk of refracture, and previous studies showed that old age was independently associated with incidence of refracture, while our study reported that there was no significant difference in terms of age and gender (14). It is commonly thought that obesity leads to higher lumbar spine load, however, BMI did not reach significance in our study. Due to the immediate pain relief and spinal stability, PVP and PKP have been considered the gold standards for treatment of OVCFs since they were first introduced in 1987 (15). Despite great success of these techniques, many authors have indicated that, compared with patients receiving conservative treatment, PVP/PKP increases the risk of vertebral refracture, especially at the adjacent level (16,17). However, there were no significant differences between the conservative treatment and PVP/PKP groups in our study. TL junction is the most frequent site for vertebral fracture owing to the maximal spinal flexion and extension (18). Previous studies reported that treatment at the TL junction affects subsequent fractures after vertebroplasty, while primary fracture at the TL junction did not increase the risk of refracture (19). Moreover, history of steroid and bisphosphonate therapy did not influence the risk of secondary compression fracture in our study, which is consistent with other studies (19,20).

Low bone mineral density (BMD) is significantly associated with risk of OVCF, and deterioration of bone quality increases the incidence of compression fracture

(21,22). To evaluate bone quality preoperatively, dual-energy x-ray absorptiometry (DXA) is considered to be the gold standard for diagnosis of osteoporosis. However, the disadvantages of DXA have been gradually recognized in recent years. Many investigators have reported that degenerative disorders, including osteophytes, bone sclerosis, and severe disc herniation can significantly affect the accuracy of results (23,24). This limitation has stimulated the search for the alternative approach for evaluating bone quality (25). Quantitative computerize tomography (QCT) has attracted significant attention over the last few years. Despite the assessment of cancellous bone, the high cost of QCT makes it difficult to apply this technology extensively (26). Hendrickson et al (27) have revealed that CT Hu value can achieve high sensitivity and specificity when examining bone mineral density. Zou et al (28) demonstrated that T-score obtained from DXA overestimated the BMD due to degenerative changes and thresholds methods based on CT Hu values can be employed as a supplement to DXA for identifying undiagnosed spinal osteoporosis. Due to the high cost and inaccuracy of DXA, the measurement of CT Hu value is recommended as an alternative method to represent BMD, and as part of routine preoperative examination, the measurement of Hu value from CT scans can offer more valuable diagnostic information without extra cost or radiation exposure (26,29,30). Moreover, nonspinal fracture history, which is an indirect reflection of bone quality, was significantly associated with increased risk of refracture. Careful elicitation of history and anti-osteoporosis treatments may exert beneficial effects on patients with osteoporotic vertebral fractures to prevent the appearance of new fragility fractures. Figure 4 shows a typical case of an 89-year-old man who experienced T12 compression fracture. He had a history of femoral neck fracture 8 years ago and Hu value obtained from CT scans was low. He was successfully treated with PKP, however, he returned with a new osteoporotic compression fracture 10 months later.

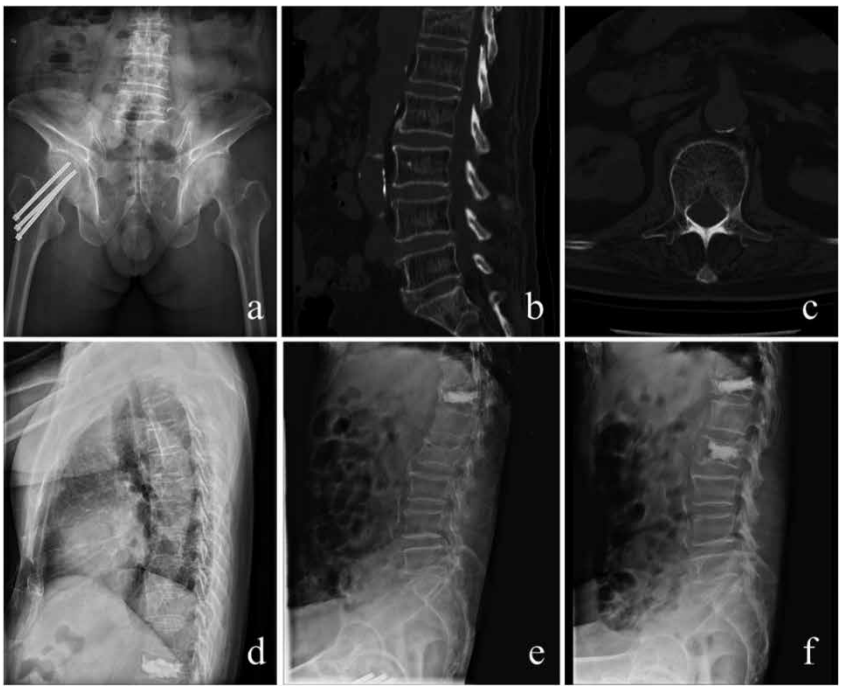

Fig. 4. *An 89-year-old man who had a history of femoral neck fracture 8 years ago (a) experienced T12 compression fracture (b). The Hu value of L1 obtained from CT scans was low (c). He was successfully treated with percutaneous kyphoplasty (PKP) (d). However, he returned with a new osteoporotic compression fracture L2 10 months later (e). To relieve chronic pain, he received PKP treatment again (f).*

The present research has some limitations. First, the retrospective nature of the study. Second, although we analyzed several factors, other potential parameters need to be compared between the 2 groups. Third, this was a single center study with limited follow-up time. Therefore, prospective studies with larger sample sizes are needed to confirm the findings of our study.

Conclusion

In our study, 43 (13.6%) patients returned with secondary new compression fractures. Our findings suggested that we can make full use of CT scans, and Hu value of L1 < 50 was independently associated with increased risk of SVCF. Moreover, patients with non-spinal fracture history represent an important population to target for secondary fracture prevention.

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