



# The temporal and spatial relationship between percutaneous vertebral augmentation and new symptomatic fractures

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## PURPOSE

This study aimed to explore the relationship between the time from percutaneous vertebral augmentation (PVA) until subsequent fracture and the risk of new symptomatic fractures (NSFs) in untreated vertebrae at different distances from "augmented vertebrae".

## METHODS

Patients who underwent PVA for the treatment of osteoporotic vertebral compression fractures at the West China Hospital of Sichuan University from May 2014 to April 2019 were retrospectively recruited. Vertebrae not treated during PVA were stratified based on their distance from the nearest augmented vertebra and the time elapsed since PVA. Survival curves were plotted to compare the risk of NSFs in untreated vertebrae at different distances from augmented vertebrae. The Cox proportional hazards model was used to identify risk factors of NSFs in untreated vertebrae.

## RESULTS

In total, 162 patients with 228 NSFs (2.760 vertebrae) were analyzed. More than half of the NSFs (56.6%) occurred within the first year after PVA. Rates and hazard ratios (HRs) of NSFs were higher in vertebrae located one segment away from the augmented vertebrae (21.0%, HR: 3.99,  $P < 0.001$ ), two segments away (10.6%, HR: 1.97,  $P = 0.003$ ), or three segments away (10.5%, HR: 2.26,  $P < 0.001$ ) than in vertebrae located five or more segments away (3.81%, HR: 1.00). Similar results were observed regardless of whether the untreated vertebrae were located in the thoracolumbar junction. In addition to distance, other risk factors of NSFs were the thoracolumbar location of untreated vertebrae, the number of augmented vertebrae, and percutaneous vertebroplasty.

## CONCLUSION

The risk of NSFs is greater for untreated vertebrae located closer to augmented vertebrae than for untreated vertebrae further away. This distance dependence occurs mainly within the three segments closest to the augmented vertebra. The risk of NSFs decreases with time after augmentation, and it is also related to the number of augmented vertebrae, the type of augmentation, and whether the untreated vertebrae are thoracolumbar or not.

## KEYWORDS

Vertebral augmentation, new symptomatic fracture, osteoporotic vertebral compression fracture, percutaneous kyphoplasty, percutaneous vertebroplasty

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Since the first use of bone cement for the treatment of invasive cervical hemangioma in 1987,<sup>1</sup> percutaneous vertebral augmentation (PVA) has been considered an effective treatment for osteoporotic vertebral compression fractures (OVCFs). This technique, which can involve percutaneous kyphoplasty (PKP) or percutaneous vertebroplasty (PVP), can provide immediate, effective analgesia, as well as quick recovery of daily activities.<sup>2-9</sup> The use of PVA can also reduce mortality associated with OVCFs.<sup>10</sup> Despite these benefits, new symptomatic fractures (NSFs) after augmentation remain a vexing problem.

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The American Society for Bone and Mineral Research has developed guidelines on how to prevent secondary fractures for patients with osteoporotic fractures.<sup>11</sup> However, these guidelines should be adapted for patients undergoing PVA, given the potential effects of bone cement on the biomechanics of the spine and subsequent NSF after PVA.<sup>12-14</sup> Therefore, it is necessary to study the occurrence and risk of NSFs after PVA. At the patient level, several studies have shown that the occurrence of NSFs after augmentation depends on bone mineral density (BMD), age, and several other factors.<sup>15-21</sup> Vertebra-level studies of patients with OVCF who underwent PVA have suggested that adjacent vertebrae, especially the sandwich vertebrae, are more prone to NSFs.<sup>17,18</sup> However, the risk of NSFs in different untreated vertebrae within the same patient, and the factors that affect that risk, are still unknown.

An analysis of the time course and location of NSFs after PVA can provide further information about this risk. Therefore, the present study compared the risk of post-PVA fracture in untreated vertebrae at different distances from augmented vertebrae using vertebra-level survival analysis. It also analyzed different potential risk factors using the Cox proportional hazards model.

## Methods

### Eligibility criteria

This retrospective study was approved by the Ethics Committee of West China Hospital of Sichuan University (approval number: 2019-992). The requirement for informed consent was waived because, at the time of surgery, patients gave written consent for their anonymized medical data to be analyzed and published for research purposes.

#### Main points

- The risk of new fractures is greater for untreated vertebrae nearest to the augmented vertebra.
- This distance dependence occurs mainly within the three segments closest to the treated vertebra, and the risk of new fractures decreases with time since augmentation.
- Distance from the treated vertebrae, thoracolumbar location, percutaneous vertebroplasty, and higher number of treated vertebrae were identified as risk factors for new symptomatic fractures after percutaneous vertebral augmentation.

This study retrospectively examined clinical and imaging data from patients with OVCFs who underwent PVA at our institution between May 2014 and April 2019. The OVCFs were defined as vertebral compression fractures without obvious cause or those caused by low-energy injury. Patients with OVCFs were included if they were (a)  $\geq 70$  years old or had a dual-energy X-ray absorptiometry (DXA) BMD T-score  $\leq -2.5$  (when BMD was measured) and (b) complained of recurrent pain associated with NSFs. These NSFs were confirmed using magnetic resonance imaging (MRI). Patients were followed up for at least 12 months after PVA.

Patients who (a) received PVA because of pathological fractures caused by spinal neoplasms, (b) had a history of PVA at other hospitals for whom relevant data was inaccessible, (c) experienced new fractures caused by high-energy trauma during follow-up, or (d) had a history of thoracic or lumbar internal fixation were excluded.

### Surgical procedures

All PVA procedures were performed after MRI had confirmed acute OVCF. The purpose of the PVA and the surgical procedures involved were explained to the patients in detail. All PKP and PVP procedures were performed based on standard guidelines.<sup>18,21</sup> The same bone cement (Osteopal V, Germany) was used in all procedures.

### Postoperative treatment and follow-up care

After surgery, patients rested in the supine position for three hours and gradually resumed activities out of bed. Routine anteroposterior and lateral X-ray examinations were performed to assess the distribution and leakage of bone cement after procedures. After surgery, all patients were routinely given calcium (800 mg daily) and active vitamin D (0.5  $\mu\text{g}$  daily), which they were told to continue indefinitely. A total of 28 patients also opted for zoledronic acid therapy at the time of the initial fracture.

After discharge, patients were followed up with via telephone every three months to enquire about pain levels and daily activities. Patients complaining of back or lower back pain that lasted longer than three days or those who did not experience significant relief after taking non-steroidal anti-inflammatory drugs were requested to come to the hospital for an X-ray examination. In the case of a suspected NSF, MRI was performed.

### Assessment indices

Baseline data on sex, age, BMD, body mass index (BMI), augmentation method (PKP or PVP), puncture method (unilateral or bilateral), and cause of fractures, were collected, as well as imaging data from X-ray and MRI examinations. All radiographic results were independently evaluated by a spine surgeon with 11 years of experience and a radiologist with seven years of experience in musculoskeletal system imaging. If there was a dispute, a radiology professor with more than 30 years of experience in musculoskeletal system imaging was consulted for the final evaluation. The inter-observer correlation coefficient (ICC) was excellent (ICC: 0.84,  $P < 0.001$ ).

Fracture data were also collected, including the number of fractures; location of fractures [thoracolumbar (T11–L2) or non-thoracolumbar], which was defined as the region with the higher number of OVCFs in patients with multiple OVCFs; degree of compression of fractures, which was defined as the worst degree in patients with multiple OVCFs; kyphosis angle between the upper and lower endplates of the fractured vertebra, which was defined as the greatest angle in patients with multiple OVCFs; cleft signs in OVCF vertebrae; distribution of bone cement; intradiscal cement leakage; and number of vertebrae treated.

The distribution of bone cement was evaluated using the 12-score method (Figure 1).<sup>21</sup> The distance between untreated vertebrae in the T4–L5 segment and the nearest treated vertebra was measured. The date of surgery at the nearest treated vertebra served as a start time for each untreated vertebra. When the distances between the untreated vertebrae and two separate treated vertebrae were equal, the date of the most recent surgery was considered as the start time. The time of diagnosis served as the end point for calculating survival time of newly fractured vertebrae, while the end of follow-up was the end point for calculating survival time of unfractured vertebrae.

Based on the interval between the occurrence of NSF and the last augmentation procedure, patients were stratified into those who suffered early (within 3 months), mid-term (3–12 months), or late NSFs (>12 months). The interval between the occurrence of NSF and the final augmentation procedure was defined as the time from the most recent PVA until the definitive diagnosis of NSF.

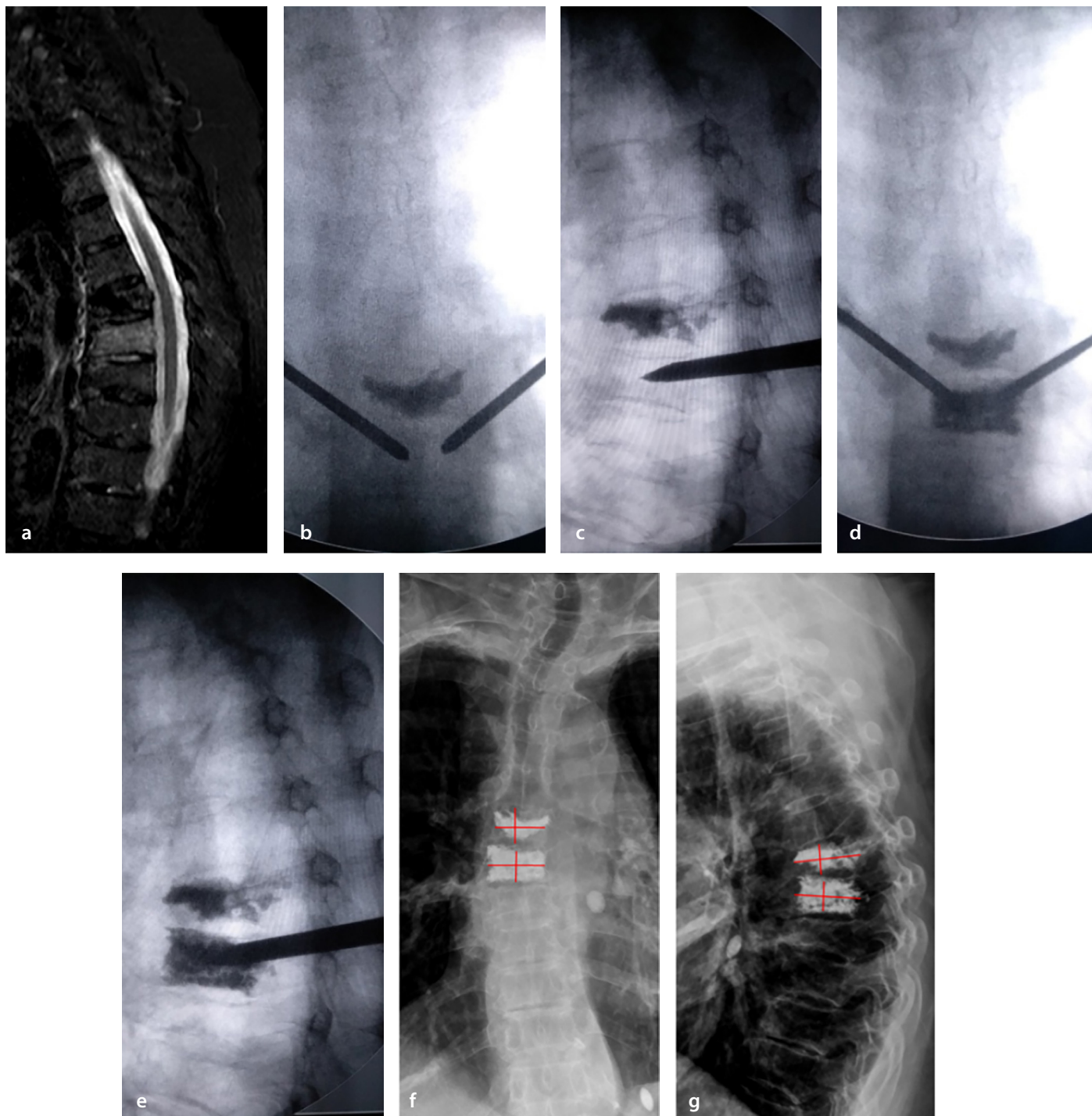
## Statistical analysis

Statistical analyses were conducted using SPSS version 23.0 (IBM, Armonk, New York, USA). Normally distributed continuous data were presented as mean  $\pm$  standard deviation. Enumeration data were reported as median (minimum–maximum). Categorical data were expressed as frequencies with

percentages. Where appropriate, results were reported as hazard ratio (HR), along with 95% confidence intervals.

Differences in normally distributed continuous data were assessed for significance using One-Way analysis of variance and pairwise comparisons using the least significant difference (LSD) test. Skewed data

were assessed using the Kruskal–Wallis test for significance assessment, while the Wilcoxon rank–sum test was used for pairwise comparisons. Differences in categorical data were assessed using chi-squared tests, and pairwise comparisons were conducted using chi-squared tests with Bonferroni correction.<sup>22</sup> The Bonferroni correction compensated by raising the test standard



**Figure 1.** An 81-year-old female was treated with percutaneous vertebroplasty (PVP) at T6 in our hospital. She was admitted to the hospital because of back pain for the preceding 24 hours. Magnetic resonance imaging showed fresh compression fracture of T7, which was treated by repeat PVP. (a) New compression fracture at vertebra T7. (b, c) Intraoperative fluoroscopic X-ray images of puncture. (d, e) Intraoperative fluoroscopic X-ray images of bone cement injection. (f, g) Anteroposterior and lateral X-ray images after repeat PVP. The red line shows quadrants for evaluating cement distribution. Cement was distributed across nine quadrants at vertebra T6 and across 12 quadrants at vertebra T7.



for each individual hypothesis at the level of significance. Survival curves were drawn using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazards model was used to identify risk factors of NSF. Level of significance was taken as  $\alpha$ : 0.050.

## Results

### Study population

Among the 1,280 patients with OVCFs who were treated with PVA in our hospital, 190 (14.8%) suffered NSFs. In the end, 228 NSFs in 162 patients met the eligibility criteria; in these patients, 432 vertebrae had been augmented. A total of 2,760 non-treated T4–L5 vertebrae before NSFs were analyzed, of which 273 were affected by the 228 NSFs. The median number of NSFs was similar between patients who took bisphosphate at the time of initial fracture [1.19 (1–3)] and those who did not [1.35 (1–4);  $P = 0.131$ ].

### Characteristics of new symptomatic fractures after percutaneous vertebral augmentation

The median follow-up time for all patients enrolled in the study was 39.8 (12.7–71.6) months, and the median time until occurrence of NSFs was 11.4 (0.2–66.0) months. Most new fractures (56.6%, 129/228) occurred within the first year after PVA, while 21.0% (48/228) occurred in the second year, 13.2% (30/228) in the third year, 5.26% (12/228) in the fourth year, and 3.95% (9/228) after the fourth year.

The NSFs were also stratified into those occurring early (<3 months after PVA;  $n = 79$ ), in the mid-term (3–12 months after PVA;  $n = 50$ ), or late (>12 months after PVA;  $n = 99$ ) (Table 1). In the patients who underwent DXA testing, there was no overall significant difference between the three groups ( $P = 0.823$ ). No significant differences were found in the average BMD T-score between the three groups ( $P = 0.099$ ), but the pairwise comparison found that BMD was lower for

patients who suffered early NSFs than for those who suffered late ones ( $P = 0.033$ ). No significant differences were found between the patients who suffered mid-term NSFs and those who suffered early or late ones ( $P = 0.280$ ,  $P = 0.475$ ).

The average age of the three groups was different ( $P = 0.044$ ). Pairwise comparisons using the LSD method revealed no significant difference in age between the early and mid-term groups ( $P = 0.725$ ), but there was a significantly younger age in the late group than in the early group ( $P = 0.042$ ) and mid-term group ( $P = 0.033$ ; Appendix Table 1). Significant differences were also observed between the three groups in kyphosis angle, thoracolumbar location, number of treated vertebrae, and augmentation method (PKP

or PVP) ( $P \leq 0.037$ ) (Table 1). However, there were no significant differences between the three groups in BMI, sex, cause of fractures, cleft sign, puncture method (unilateral or bilateral), bone cement distribution, intradiscal cement leakage, and degree of compression ( $P > 0.05$ ).

### New symptomatic fractures at different distances from the nearest treated vertebra

Significant differences in cumulative NSF rates among vertebrae that were one, two, three, four, or five or more segments away from the nearest treated vertebra were observed ( $P < 0.001$ ; Table 2). Similar results were observed regardless of whether the untreated vertebrae were located in the thoracolumbar junction ( $P < 0.001$ ; Table 2) or not ( $P < 0.001$ ; Table 2). Pairwise comparisons

**Table 1.** Baseline demographic and clinical characteristics of patients with new symptomatic fractures, stratified based on time since the last percutaneous vertebral augmentation

| Characteristic                                   | Timing of fracture since last surgical procedure |              |              |                  |
|--|--|--------------|--------------|------------------|
|  | Early  | Mid-term     | Late         | <i>P</i>         |
| New symptomatic fractures                        | 79   | 50           | 99           | -                |
| Age (years)                                      | 76.64 ± 8.33                                     | 77.10 ± 7.38 | 74.22 ± 7.44 | <b>0.044</b>     |
| Female   | 67 (84.8)  | 40 (80.0)    | 82 (82.8)    | 0.779            |
| Body mass index (kg/m <sup>2</sup> )             | 21.98 ± 3.39                                     | 21.89 ± 3.53 | 22.02 ± 3.14 | 0.977            |
| Distribution of bone cement (no of quadrants)    | 10.69 ± 1.33                                     | 10.46 ± 1.53 | 10.27 ± 1.57 | 0.176            |
| T-score of bone mineral density*                 | -3.47 ± 0.46                                     | -3.39 ± 0.59 | -3.26 ± 0.42 | 0.099            |
| No of treated vertebrae                          | 2 (1-6)  | 2 (1-6)      | 1 (1-5)      | <b>&lt;0.001</b> |
| DXA results available                            | 42 (53.2)  | 24 (48.0)    | 49 (49.5)    | 0.823            |
| Presence of clefts                               | 17 (21.5)  | 5 (10.0)     | 13 (13.1)    | 0.150            |
| Cause of injury known                            | 18 (22.8)  | 15 (30.0)    | 39 (39.4)    | 0.058            |
| Degree of compression of previous fractures ≥50% | 21 (26.6)  | 9 (18.0)     | 17 (17.2)    | 0.266            |
| Kyphosis angle of previous fractures ≥10°        | 49 (62.0)  | 20 (40.0)    | 58 (58.6)    | <b>0.037</b>     |
| Thoracolumbar                                    | 43 (54.4)  | 23 (46.0)    | 69 (69.7)    | <b>0.012</b>     |
| PKP  | 14 (17.7)  | 16 (32.0)    | 53 (53.5)    | <b>&lt;0.001</b> |
| Unilateral puncture                              | 20 (25.3)  | 10 (20.0)    | 20 (20.2)    | 0.667            |
| Intervertebral leakage                           | 11 (13.9)  | 6 (12.0)     | 10 (10.1)    | 0.735            |

\*For patients with new symptomatic fractures for whom data on bone mineral density were available. Values indicated as n, n (%), median (minimum–maximum) or mean ± standard deviation, unless otherwise noted. DXA, dual-energy X-ray absorptiometry; PKP, percutaneous kyphoplasty.

**Table 2.** Incidence of new symptomatic fractures inside or outside the thoracolumbar region, stratified by distance from the nearest treated vertebra

| Location of fracture#            | No of segments away from treated vertebra* |                 |                 |                 |                  | <i>P</i>         |
|----------------------------------|--|-----------------|-----------------|-----------------|------------------|------------------|
|                                  | One  | Two             | Three           | Four            | Five or more     |                  |
| Within the thoracolumbar region  | 87 (211)                                   | 23 (151)        | 15 (85)         | 11 (47)         | 7 (53)           | <b>&lt;0.001</b> |
| Outside the thoracolumbar region | 38 (232)                                   | 23 (236)        | 25 (254)        | 11 (260)        | 33 (958)         | <b>&lt;0.001</b> |
| Total                            | <b>125 (443)</b>                           | <b>46 (387)</b> | <b>40 (339)</b> | <b>22 (307)</b> | <b>40 (1011)</b> | <b>&lt;0.001</b> |

\*The data in the table represent the number of vertebrae, including the number of fractured vertebrae outside the brackets and the number of unfractured vertebrae inside the brackets, sample size (n) = fractured + unfractured vertebrae. #All the vertebrae located in T4–L5 that were studied were divided into two types: those located in the thoracolumbar (T11–L2) region and those not located in the thoracolumbar region (T4–T10, L3–L5).

showed that rates of NSF's affecting vertebrae that were one (21.0%), two (10.6%), or three (10.5%) segments away were significantly higher than rates of NSF's affecting vertebrae that were five or more segments away (3.81%;  $P < 0.001$ ; Table 3). There was no difference in rates of NSF's affecting vertebrae that were four or five or more segments away ( $P = 0.028$ , Bonferroni correction method).

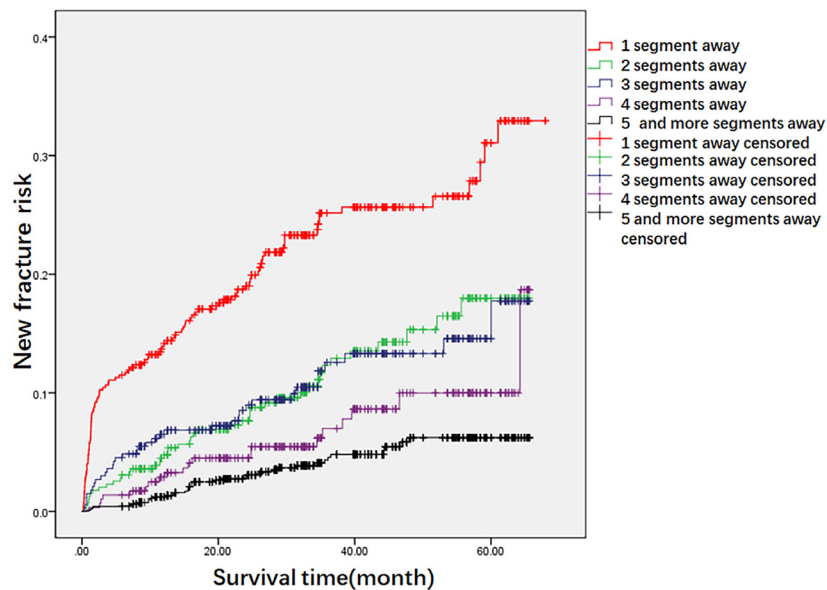
Risk curves of NSF's were plotted for varying distances from the nearest treated vertebrae using the Kaplan–Meier method (Figure 2), and a log-rank test confirmed significant differences between them ( $P < 0.001$ ). The Cox proportional hazards model and forward stepwise method based on the conditional likelihood ratio and several categorical variables (Appendix Table 2) were used to investigate risk factors associated with

NSF's occurring in 2,760 untreated vertebrae in segments T4–L5. An omnibus test of the Cox model coefficient was statistically significant ( $P < 0.001$ ). The following variables were identified as significantly related to the occurrence of NSF's: distance from the nearest treated vertebrae  $\leq 3$ , thoracolumbar junction of untreated vertebrae, higher number of treated vertebrae, and method of vertebral augmentation (PVP) ( $P < 0.001$ ).

**Table 3.** Pairwise comparison of rates of new symptomatic fractures in segments at different distances from the treated vertebra

|                            | One segment away | Two segments away | Three segments away | Four segments away | Five or more segments away |
|----------------------------|------------------|-------------------|---------------------|--------------------|----------------------------|
| One segment away           | -                | -                 | -                   | -                  | -                          |
| Two segments away          | <0.001           | -                 | -                   | -                  | -                          |
| Three segments away        | <0.001           | 0.974             | -                   | -                  | -                          |
| Four segments away         | <0.001           | 0.059             | 0.069               | -                  | -                          |
| Five or more segments away | <0.001           | <0.001            | <0.001              | 0.028              | -                          |

The adjusted  $P$  value according to Bonferroni correction:  $\alpha: 0.05/10 = 0.005$ .



**Figure 2.** Curves showing the risk of new symptomatic fractures (NSFs) at one, two, three, four or five or more segments away from the nearest treated vertebra. Data were obtained from 228 NSF's affecting 2,760 untreated vertebrae located in segments T4–L5.

**Table 4.** Cox proportional hazards modeling to identify risk factors for the occurrence of new symptomatic fractures

| Factor*                                       | B (regression coefficient) | SE    | $P$ value | HR    | 95% CI |       |
|---|----------------------------|-------|-----------|-------|--------|-------|
|   |                            |       |           |       | Lower  | Upper |
| <b>Distance from nearest treated vertebra</b> | -                          | -     | <0.001    | -     | -      | -     |
| One segment away                              | 1.384                      | 0.201 | <0.001    | 3.989 | 2.689  | 5.916 |
| Two segments away                             | 0.676                      | 0.227 | 0.003     | 1.967 | 1.260  | 3.071 |
| Three segments away                           | 0.814                      | 0.228 | <0.001    | 2.258 | 1.444  | 3.532 |
| Four segments away                            | 0.438                      | 0.267 | 0.100     | 1.550 | 0.919  | 2.614 |
| <b>Whether thoracolumbar or not</b>           | 0.842                      | 0.136 | <0.001    | 2.322 | 1.780  | 3.028 |
| <b>No of augmented vertebrae</b>              | 0.109                      | 0.054 | 0.043     | 1.115 | 1.004  | 1.239 |
| <b>Augmentation method (PVP vs PKP)</b>       | 0.405                      | 0.129 | 0.002     | 1.499 | 1.164  | 1.930 |

\*Definitions of categorical variables: distance from the nearest augmented vertebra, 1: one segment away, 2: two segments away, 3: three segments away, 4: four segments away; location of the untreated vertebra, 0: thoracolumbar segment, 1: non-thoracolumbar segment; augmentation method, 1: PVP, 2: PKP. CI, confidence interval; HR, hazard ratio; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; SE, standard error.

The HR of NSF was higher at one (HR: 3.99,  $P < 0.001$ ), two (HR: 1.97,  $P = 0.003$ ), and three (HR: 2.26,  $P < 0.001$ ) segments away from the nearest treated vertebrae than at five or more segments away (Table 4). The HRs were similar for NSFs four or five or more segments away ( $P = 0.100$ ). The HR for NSFs was 1.499 times higher among patients who underwent PVP than among those who underwent PKP ( $P = 0.002$ ). The HR of NSFs in the untreated vertebrae of the thoracolumbar junction was 2.322 times higher than in those of the non-thoracolumbar junction ( $P < 0.001$ ), and it was 1.115 times higher for each increase in the number of treated vertebrae ( $P = 0.043$ ).

## Discussion

A PVA is a minimally invasive procedure that has been shown to significantly benefit patients with acute pain caused by OVCF,<sup>2-9</sup> so it has become the main surgical method for treating OVCF. However, new fractures after augmentation remain a substantial concern. In this study, 228 NSFs at the vertebra level in 162 patients were retrospectively analyzed, and the risks of fractures in untreated vertebrae at different distances from augmented vertebrae were compared. The results of the study suggest that the risk of NSFs is greater for untreated vertebrae located closer to augmented vertebrae. This distance dependence occurred mainly within the three segments adjacent to the treated vertebra, while the risk of NSFs decreased with time since augmentation. Closer proximity to the treated vertebrae, thoracolumbar location, PVP as the method of vertebral augmentation, and a higher number of treated vertebrae were identified as risk factors for NSFs after PVA.

Several studies have identified risk factors for new vertebral fractures,<sup>18,23-30</sup> but most of them assessed risk at the level of the patient, not individual vertebrae. This approach can help identify patients at high risk of new fractures, but only comparisons of fracture risk at different untreated vertebrae in the same patient can help predict which vertebrae are at increased risk. The patterns identified in the present study may provide clues to clinicians and radiologists about which vertebrae require greater attention after augmentation. Comparisons within the same patient should also be free of confusion caused by factors other than the distance between untreated and treated vertebrae and their location. The present study suggests that the rate of NSFs decreases with increasing distance from the nearest treated vertebra. This result confirms and extends previous vertebra-level analy-

ses.<sup>17,18,24</sup> Adjacent vertebrae are more prone to NSFs, while the “sandwich” vertebrae, defined as the untreated vertebrae either side of the augmented vertebrae, are understandably at highest risk of NSF. While the thoracolumbar junction may be inherently prone to fractures,<sup>18,24,26</sup> the present study found that the distance dependence of the risk of NSFs applies inside and outside this region. In fact, the Cox proportional hazards analysis suggested that proximity to augmented vertebrae may influence risk of NSFs in untreated vertebrae to a greater extent than thoracolumbar location.

The present study also found that augmentation method (PKP or PVP) influenced the risk of NSFs.<sup>9</sup> Although similar numbers of patients underwent each procedure, PVP was associated with a larger proportion of early (82.3%) and mid-term NSFs (68.0%) and a smaller proportion of late NSFs (46.5%). These results are consistent with the idea that PKP is superior to PVP for improving local kyphosis of the fracture: PKP can restore vertebral height, reduce the negative effects of load transfer, and decrease the risk of NSFs;<sup>29,30</sup> PVP, in contrast, may be less effective at counteracting biomechanical changes at the fracture site,<sup>13,14</sup> increasing the risk of NSFs.

Augmentation exerts biomechanical effects on the spine, although it is unclear whether these effects increase the risk of NSFs.<sup>12-14</sup> The risk of NSFs has been previously shown to increase with the number of cement-filled vertebrae,<sup>18</sup> and the present study found similar results, reflecting greater deleterious biomechanical effects with a higher number of augmented vertebrae. A higher number of augmented vertebrae inevitably expands the reach of their influence on untreated vertebrae, and more fractures may also mean lower BMD.

Low BMD is another important risk factor for NSFs,<sup>23-27</sup> and the present study found that patients with lower BMD experienced NSFs earlier than those with higher BMD. At the vertebra level, it was also found that the closer an untreated vertebra was to an augmented vertebra, the more likely it was to suffer an NSF. This difference in the risk of NSFs in the same patient's untreated vertebrae likely reflects the effect of augmentation on NSFs.<sup>22-24</sup> Differences in the risk of NSF when patients, rather than individual vertebrae, are the unit of analysis may be more closely related to BMD.<sup>23</sup>

Previous studies have suggested that the risk of new fractures can depend on puncture

method (unilateral or bilateral puncture),<sup>18,31</sup> excess bone cement distribution,<sup>21,26</sup> and intradiscal cement leakage.<sup>24,26</sup> The puncture method can affect the distribution of bone cement, and one study<sup>21</sup> concluded that cement distribution slightly alters the risk of NSFs. This conclusion may not be generalizable, however, given that the average distribution of bone cement in the study was 10.5 points on a 12-point scale, which was already close to the optimal distribution.<sup>21</sup> Just under 12% of patients in the present study showed leakage into the intervertebral space, but this may not be unusually high given that all patients in the study had already suffered NSFs.

The present study had several limitations. Its retrospective nature increased the risk of various types of bias. In addition, BMD data was unavailable for some patients, so it was not possible to include BMD in the Cox proportional hazards analysis. Prospective studies are therefore needed to examine the occurrence of NSFs in different vertebrae.

In conclusion, although a causal relationship between augmentation and subsequent vertebral fractures cannot be conclusively demonstrated, the data in the present study add valuable information to the continuing question of how PVA affects risk of NSFs in vertebrae at different distances from the augmented site. The results of the present study suggest that fracture risk depends on proximity to treated vertebrae and on time since augmentation. This distance dependence appears to hold mainly within the three segments closest to the treated vertebra. The risk of NSFs is also related to the location of the untreated vertebrae, the number of augmented vertebrae, and the type of augmentation.

## Conflict of interest disclosure

The authors declared no conflicts of interest.

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**Appendix Table 1.** Pairwise comparison of demographic and clinical characteristics of patients with early, middle, and late new symptomatic fractures\*

| Characteristic                                   | Early vs. mid-term | Early vs. late | Mid-term vs. late |
|--|--------------------|----------------|-------------------|
| Age (years)                                      | 0.725              | 0.042          | 0.033             |
| Female   | 0.479              | 0.722          | 0.672             |
| Body mass index (kg/m <sup>2</sup> )             | 0.884              | 0.942          | 0.830             |
| Distribution of bone cement                      | 0.393              | 0.062          | 0.462             |
| T-score of bone mineral density                  | 0.280              | 0.033          | 0.475             |
| No of treated vertebrae                          | <0.001             | <0.001         | 0.952             |
| DXA results available                            | 0.568              | 0.627          | 0.863             |
| Presence of clefts                               | 0.090              | 0.137          | 0.580             |
| Cause of injury known                            | 0.360              | 0.018          | 0.260             |
| Degree of compression of previous fractures ≥50% | 0.261              | 0.128          | 0.900             |
| Kyphosis angle of previous fractures ≥10°        | 0.015              | 0.642          | 0.032             |
| Thoracolumbar                                    | 0.351              | 0.036          | 0.005             |
| PKP  | 0.061              | <0.001         | 0.013             |
| Unilateral puncture                              | 0.486              | 0.417          | 0.977             |
| Intervertebral leakage                           | 0.753              | 0.432          | 0.724             |

\*The adjusted *P* value according to Bonferroni correction:  $\alpha: 0.05/3 = 0.017$ . Numbers are *P* values. The intervals for defining “early,” “mid-term,” and “late” are explained in the methods section of the manuscript.

Differences in normally distributed continuous data were assessed for significance using One-Way analysis of variance and pairwise comparisons using the least significant difference test, including data of age, body mass index, distribution of bone cement, and T-score of bone mineral density. Skewed data were assessed using the Kruskal-Wallis test for significance assessment or Wilcoxon tests for pairwise comparisons, including data of number of treated vertebrae. Differences in categorical data were assessed using chi-squared tests, including data of sex, presence of clefts, cause of injury known, degree of compression of previous fractures ≥50%, kyphosis angle of previous fractures ≥10°, thoracolumbar location, PKP or PVP, unipedicular puncture, intervertebral leakage, and DXA results available. DXA, dual energy X-ray absorptiometry; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty.

**Appendix Table 2.** Definitions of categorical variables used to identify potential risk factors for new symptomatic fractures

| Variable                                     | Categories                    | No of vertebrae with/without NSF |
|--|-------------------------------|----------------------------------|
| Sex  | 0: female                     | 222/2.069                        |
|  | 1: male                       | 51/418                           |
| Distance from the nearest augmented vertebra | 1: one segment away           | 125/443                          |
|  | 2: two segments away          | 46/387                           |
|  | 3: three segments away        | 40/339                           |
|  | 4: four segments away         | 22/307                           |
|  | 5: five or more segments away | 40/1.011                         |
| Location of the untreated vertebra           | 0: thoracolumbar segment      | 130/1.940                        |
|  | 1: non-thoracolumbar segment  | 143/547                          |
| Location of the nearest augmented vertebra   | 0: thoracolumbar segment      | 162/1.498                        |
|  | 1: non-thoracolumbar segment  | 111/989                          |
| Intradiscal cement leakage                   | 0: no                         | 266/2.459                        |
|  | 1: yes                        | 7/28                             |
| Degree of compression ≥50%                   | 0: no                         | 220/2.033                        |
|  | 1: yes                        | 53/454                           |
| Cleft sign                                   | 0: no                         | 240/2.124                        |
|  | 1: yes                        | 33/363                           |
| Augmentation method                          | 1: PVP                        | 160/1.467                        |
|  | 2: PKP                        | 113/1.020                        |
| Puncture method                              | 0: bilateral                  | 57/536                           |
|  | 1: unilateral                 | 216/1.951                        |
| Cause of injury                              | 0: no                         | 182/1.689                        |
|  | 1: yes                        | 91/798                           |

NSF, new symptomatic fracture; PKP, percutaneous kyphoplasty; PVP, percutaneous vertebroplasty.