Prediction model of adjacent vertebral compression fractures after percutaneous kyphoplasty: a retrospective study

Yi Mao, Wangsheng Wu, Junchao Zhang, Zhou Ye

ABSTRACT

Objectives The purpose of this study was to develop a prediction model to assess the risk of adjacent vertebral compression fractures (AVCFs) after percutaneous kyphoplasty (PKP) surgery.

Design A retrospective chart review.

Setting and participants Patients were collected from the Quzhou People’s Hospital, from March 2017 to May 2019. Patients were included if they suffered from osteoporotic vertebral compression fractures (OVCFs), underwent PKP surgery and were followed up for 2 years.

Interventions None.

Methods This was a retrospective cohort study of all PKP surgery procedures of the thoracic, lumbar and thoracolumbar (TL) spine that have been performed for OVCF from 1 March 2017 up to 1 May 2019. The least absolute shrinkage and selection operator (LASSO) regression model was used to optimise feature selection for the AVCF risk model. Multivariable logistic regression analysis was applied to build a predicting model incorporating the feature selected in the LASSO regression model. The C-index, calibration plot and decision curve analysis were applied to assess this model.

Results Gender, age, the number of surgical vertebrae, cement volume, bone mineral density, diabetes, hypertension, bone cement leakage, duration of anti-osteoporosis treatment after surgery and TL junction were identified as predictors. The model displayed good discrimination with a C-index of 0.886 (95% CI 0.828–0.944) and good calibration. High C-index value of 0.833 could still be reached in the interval validation. Decision curve analysis showed that the AVCF nomogram was clinically useful when intervention was decided at the AVCF possibility threshold of 1%.

Conclusions This study developed a clinical prediction model to identify the risk factors for AVCF after PKP surgery, and this tool is of great value in sharing surgical decision-making among patients consulted before surgery. The AVCF nomogram was clinically useful when intervention was decided at the AVCF possibility threshold of 1%.

INTRODUCTION

Vertebral compression fractures account for approximately one quarter of osteoporotic fractures and constitute a major source of morbidity and increased mortality.1 2 The Canadian Multicentre Osteoporosis study reported that the 21.5% of men and 23.5% of women over 50 years of age have at least one vertebral compression deformity.2 In the USA, annual direct management costs for vertebral fractures are over 1 billion dollars.3 Symptomatic osteoporotic vertebral compression fractures (OVCFs) can cause significant pain and decrease a patient’s mobility with substantial impact on a patient’s quality of life.4

The conservative treatment protocol for OVCFs has many disadvantages, including slow pain relief, long treatment time and the long-term bed rest easily causes complications such as bedsores, respiratory and urinary tract infections, and constipation.5 6 Therefore, percutaneous kyphoplasty (PKP), which can achieve low injury, rapid symptom relief and restore vertebral height, has become an accepted treatment for osteoporotic compression fractures.7 However, the results of recently published trials have called this belief into question. Not only does the incidence of cement leakage appear considerable with clear sequelae, but also the loss

STRENGTHS AND LIMITATIONS OF THIS STUDY

Previous studies have identified several factors associated with an increased risk of adjacent vertebral compression fracture (AVCF), these risk factors are usually reported as relative risk (RR) or OR. However, these RRs and ORs are correlated measures and are not sufficient to estimate personal risk for individual AVCF. In this study, risk factors were incorporated into a predictive model to assess individual risk for AVCF.

According to the prediction model, clinicians can screen people at high risk for early intervention to reduce the incidence of adjacent vertebral fractures.

Since this is a historical retrospective study, the included observations rely on the medical records of the original data.

External validation has not been performed.
of vertebral height, aggravation of kyphosis and fracture in adjacent vertebral segments often occur after PKP which might cause pulmonary embolism and neurological complications.8–10 Some studies have reported an increased risk of new compression fractures in adjacent vertebrae after vertebroplasty, with reported rates ranging from 6.2% to 51.9%.7 11–13 Previous studies have identified several factors associated with an increased risk of adjacent vertebral compression fractures (AVCFs) after PKP, such as bone mineral density (BMD), age, gender and bone cement leakage (BCL).14–16 These risk factors are usually reported as relative risk (RR) or OR. However, the RRs and ORs in the literature are unadjusted and not based on models with multiple predictors and are not sufficient to estimate personal risk for individual AVCF.

Incorporating risk factors into a predictive model is an appropriate preoperative patient counselling tool when assessing individual risk of postoperative AVCF. Assessing individual risk of AVCF may help identify high-risk patients, thereby optimising patient selection and early intervention to reduce the incidence of adjacent vertebral fractures. The purpose of this study was to develop a prediction model to assess the risk of AVCF after PKP surgery.

**Patients and methods**

**Patients**

This was a retrospective cohort study of all PKP surgery procedures of the thoracic, lumbar and thoracolumbar (TL) spine that have been performed in the Quzhou People’s Hospital for OVCFs from 1 March 2017 up to 1 May 2019. Exclusion criteria included TL fractures caused by violence, pathological fractures due to bone tumours or infection, and those with bone metabolic disease (including Cushing’s, disease, hyperthyroidism and hyperparathyroidism). Patients for whom the medical files for at least up to 2 years after surgery were not available were also excluded. All included patients provided written informed consent. This study was reported in line with the STROCSS criteria17 and was approved by the local medical ethics committee prior to patient enrolment.

**Patient and public involvement**

None.

**Kyphoplasty technique**

The patients were in the prone position, with two transverse bolsters under the chest and pelvis to maintain the spine in a position of extension. The surface position of the target vertebral body was marked under fluoroscopy. As a pain reducing measure, all newly fractured vertebrae underwent vertebral augmentation with the use of bone cement. All the PKP surgical procedures were performed under local anaesthesia combined with sedation and used a bilateral or unilaterally approach. Heraeus OSTEOPAL V spinal cement with precision cement delivery was used (Heraeus, Hanau, Germany). Anteroposterior and lateral images were performed using a mobile C-arm fluoroscopic X-ray system during surgery. Other procedures were standard surgical procedures. All the procedures
were completed successfully by three experienced orthopaedic surgeons.

Data collection
Clinical data included patients’ demographic characteristics (age, gender, height and weight), BMD, number and level of fractured vertebrae, duration of anti-osteoporosis treatment after surgery, educational background, history (smoking, hypertension and/or diabetes) and BCL. BCL was evaluated by X-ray on the first postoperative day and blind diagnosis was performed by three experienced orthopaedic surgeons. All included patients underwent conventional X-ray investigations with the central beam centred on the level of the vertebra that underwent PKP at final follow-up. Images were read by two surgeons independently to determine whether there was a fracture of the adjacent vertebra. For symptomatic patients, MRI was performed to identify the fracture.

Data were collected through medical records and telephone follow-up was further supplemented. Cases with missing data were excluded.

Feature selection
Regarding demographic, disease and treatment features, considering China’s national conditions, the elderly population with a high education level is small and almost none elderly female smokes, education background and smoking history were excluded.

Remaining features included gender, age, the number of surgical vertebrae, cement volume, BMD, diabetes, hypertension, BCL, duration of anti-osteoporosis treatment after surgery, TL junction and body mass index (BMI).

Statistical analysis
The least absolute shrinkage and selection operator (LASSO) method was used to select the optimal predictive features of risk factors for AVCFs after PKP. Features with non-zero coefficients in the LASSO regression model were selected. Multivariable logistic regression analysis was used to establish a prediction model by incorporating the features selected from the LASSO regression model. The effects of the features are presented as ORs with 95% CIs and p values. The statistical significance levels were all two sided. All potential predictors were applied to develop a predicting model for AVCF risk by using the cohort.

Calibration curves were plotted to assess the calibration of the predicted probability of the AVCF nomogram. Significant test statistics mean that the model is not perfectly calibrated. Harrell’s C-index and corrected C-index were calculated to quantify the recognition performance of the nomogram. The AVCF nomogram was subjected to bootstrapping validation (1000 bootstrap resamples) to calculate a relatively corrected C-index. Decision curve analysis was conducted to determine the clinical usefulness of the AVCF nomogram by quantifying the net benefits at different threshold probabilities in the cohort. The net benefit was calculated by subtracting the proportion of all patients who are false positive from the proportion of the patients who are true positive and by weighing the relative harm of forgoing interventions compared with the negative consequences of an unnecessary intervention.

R software (V.4.0.5; https://www.R-project.org) was used to develop and assess the nomogram. The ‘glmnet’ package was used for LASSO regression. The ‘glm’ function was used for the logistic regression analysis. The

<table>
<thead>
<tr>
<th>Factors</th>
<th>Prediction model</th>
<th>Regression coefficient</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td>−6.559</td>
<td>0.001 (&lt;0.001 to 0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>1.179</td>
<td>3.253 (1.031 to 12.113)</td>
<td>0.050</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.004</td>
<td>2.730 (1.017 to 7.945)</td>
<td>0.050</td>
</tr>
<tr>
<td>The number of surgical vertebrae</td>
<td></td>
<td>1.340</td>
<td>3.158 (1.122 to 9.163)</td>
<td>0.012</td>
</tr>
<tr>
<td>Cement volume</td>
<td></td>
<td>1.273</td>
<td>3.573 (1.365 to 9.893)</td>
<td>0.011</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td>1.504</td>
<td>1.504 (1.690 to 13.167)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>1.239</td>
<td>3.452 (1.140 to 10.625)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0.361</td>
<td>1.435 (0.496 to 4.085)</td>
<td>0.497</td>
</tr>
<tr>
<td>BCL</td>
<td></td>
<td>2.169</td>
<td>8.748 (2.970 to 27.845)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of anti-osteoporosis treatment</td>
<td></td>
<td>−0.881</td>
<td>0.465 (0.119 to 2.626)</td>
<td>0.256</td>
</tr>
<tr>
<td>TL junction</td>
<td></td>
<td>1.044</td>
<td>2.840 (0.964 to 9.092)</td>
<td>0.065</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>0.458</td>
<td>1.580 (0.600 to 4.158)</td>
<td>0.350</td>
</tr>
</tbody>
</table>

AVCFs, adjacent vertebral compression fractures; BCL, bone cement leakage; BMD, bone mineral density; BMI, body mass index; PKP, percutaneous kyphoplasty; TL, thoracolumbar.
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Figure 2  The risk of the AVCF nomogram. AO, duration of anti-osteoporosis treatment; AVCF, adjacent vertebral compression fracture; BCL, bone cement leakage; BMD, bone mineral density; BMI, body mass index; CV, cement volume; HLJ, thoracolumbar junction; NOTV, the number of the surgical vertebrae.

‘rms’ package was used to generate nomogram and calibration curves. The net benefits of our model were evaluated by a decision curve, which was plotted using the ‘rmda’ package.

RESULTS

Patient characteristics
In total of 436 patients (582 fractured vertebrae) were initially included in the study. Of these 436 cases, there were 118 males (27.1%) and 318 females (72.9%). The average age was 76 years (range: 52–91 years). At the last follow-up, 78 patients had suffered from at least 1 adjacent vertebral fracture. Of these, 56 were treated again with PKP and the remaining 22 experienced symptomatic relief with conservative treatment. All the characteristics of the AVCF and non-AVCF groups are shown in online supplemental table 1.

Development of an individualised prediction model
All included 11 features were enrolled as potential predictors on the basis of 436 patients in the cohort and were with non-zero coefficients in the LASSO regression model (figure 1).

The logistic regression analysis results of the included factors are shown in table 1. A model containing the above independent predictors was established and presented in the form of a nomogram (figure 2).

Apparent performance of the AVCF risk nomogram in the cohort
There was a relatively close agreement between the observed and predicted risk of AVCF after PKP in this cohort (figure 3). The C-index for the prediction nomogram was 0.886 (95% CI 0.828 to 0.944) for the cohort and was confirmed to be 0.833 through bootstrapping, which suggested the model’s good discrimination and good prediction capability.

Clinical use
The decision curve analysis for the AVCF nomogram is presented in figure 4. The decision curve showed that if the threshold probability was between 1% and 99%, respectively, applying this nomogram to predict AVCF risk adds more benefit than the schemes. For example, if the personal threshold probability of a patient is 60% (ie, the patient would opt for treatment if his probability of AVCF was >60%), then the net benefit is 0.279 when using the nomogram to make the decision of whether to undergo treatment, with added benefit than the intervention-all-patients scheme or the intervention-none scheme.

DISCUSSION

In the literature, risk factors are usually reported as RRs or ORs.14 15 Although these measures of association are important for understanding what causes a person to develop AVCF, they are difficult to translate into a decision-making tool and cannot be used to calculate a person’s probability of developing AVCF. It is the first time to assess the risk of adjacent vertebrae fractures by establishing a prediction model in this manuscript, which could be used to predict the individual risk of AVF after PKP.

This model may help to identify patients at high risk for AVCF in the clinical setting, optimise patient selection
and potentially prevent adverse outcomes of AVCF after surgery through additional preventive measures such as adherence to anti-osteoporosis therapy, appropriate intraoperative reduction of bone cement injection, avoidance of BCL and weight control.

PKP has been a safe and effective method for the treatment of OVCFs, with minimal trauma, rapid recovery and reconstruction of vertebral height. Therefore, some scholars advocated early surgical intervention. However, several complications such as neuraxial anaesthesia, severe cement embolism and new vertebral fractures have been observed. And the incidence of adjacent vertebral fracture associated with PKP has been widely reported. However, the conservative treatment protocol for OVCF also has many disadvantages, including slow pain relief, long treatment time and the long-term bed rest easily causes complications such as bedsores, respiratory and urinary tract infections, and constipation. So how to choose between conservative treatment and surgical treatment is very important for patients and surgeons. This tool is of great value in sharing surgical decision-making among patients consulted before surgery. Identifying patients at risk for postoperative adjacent vertebral fractures allows for individualised patient risk assessment, better patient-specific counselling and more appropriate choice between conservative and surgical treatment. For patients at high risk of adjacent vertebral fracture after PKP surgery, conservative treatment or appropriate extension of conservative treatment may be more appropriate.

At present, the mechanism of adjacent vertebral fractures after the PKP procedure is considered to be multifactorial. On the one hand, after PKP surgery, the stiffness, strength and structure of the injured vertebra changed, resulting in a load gradient in the adjacent vertebra. The bone cement leaked into the intervertebral space leads to loss of buffering function, stress concentration destruction of adjacent vertebral bodies and a high risk of AVCF. On the other hand, the progression of osteoporosis may also lead to new fractures. In this research, BCL was considered as the most important risk factor for AVCF. During PKP surgery, the incidence of BCL ranges from 9% to 79.9%. As the diagnostic value of plain radiographs is far less than that of CT, the statistical incidence fluctuates greatly. Yeom et al classified cement leakage into three types based on how it leaked, and Chang Gao et al drew the conclusion that leakage through a cortical defect (type C) was an important predictor of new OVCFs. Komemushi et al found that the risk of a new vertebral fracture was nearly 4.6 times higher than that in an operation without leakage into the intervertebral disc. Ren et al found that factors affecting cement leakage included cortical defects, cement viscosity and volume and history of pulmonary disease. Controlling the cement volume below 4.17 mL could ensure efficacy and reduce the occurrence of BCL. With continued research, bone-filling containers have been applied to OVCFs. Several studies have proved that the incidence of cement leakage in bone-filling containers is lower than that in PKP surgery.

In this study, patients with a BMD below −3.5 had a higher risk of AVCF. Many studies have shown that low BMD is a strong predictor of AVCF. Lindsay et al noted that patients with osteoporotic compression fractures were five times more likely to develop a new vertebral fracture in the natural history of osteoporosis. Siris et al analysed the follow-up information of nearly 165,000 participants and found that the association between osteoporosis and fracture rates was approximately four times that of normal BMD. Cummings et al reported that every 1% increase in spine BMD reduced the risk of fracture by 0.03%. However, Zhang et al compared the incidence of AVCF after conservative treatment with that after PKP, and demonstrated that PKP made no contribution to AVCF, which was due to the natural progression of osteoporosis.

Gender and age are risk factors associated with osteoporosis, and several prediction models based on sex, age and body weight have been developed to assess the risk of osteoporosis. The incidence of OVCFs in women aged...
between 85 years and 89 years was shown to be almost 8 times higher than that in women aged between 60 years and 64 years.41–43 The incidence of OVCFs in women was reported to be between 2 times and 3.5 times more than that in men.41–43 Among the patients enrolled in this study, 72.9% were female and 56.4% were older than 75 years. These data also reached 82.1% and 69.2%, respectively, in the patients with AVCFs after PKP surgery.

Since the flexion and extension of the spine are maximised at the TL junction, most of TL fractures occur at the TL junction.44 The risk of new AVCFs at the TL junction was 2.7 times higher than that at the non-TL junction.45 Sun et al.46 followed 175 patients for 1 year and demonstrated that the location of the TL junction after percutaneous vertebroplasty (PVP) was significantly associated with subsequent fracture. However, Wang et al.47 noted that there was no relationship between the risk of AVCF and the surgical vertebral level. The influence of diabetes on AVCF is also controversial. Several studies have shown that diabetes is a risk factor contributing to AVCF48 49; however, Wang et al.50 proposed that diabetes is not a significant risk factor.

LIMITATIONS
Several limitations existed in this study. First, since this was a historical retrospective study, the included observations relied on the medical records of the original data. Second, the number of cases used to establish the model was small and the cohort did not represent all Chinese patients undergoing PKP surgery, resulting in limited reliability of the prediction model. Third, the risk factor analysis did not include all potential factors affecting AVCF. In addition, although the robustness of the nomogram was extensively verified internally using the bootstrap test, external validation has not been performed and generalisation to the populations in other regions and countries with PKP surgery is uncertain. It would be most valuable if it could be generalised to future patients and patients from different hospital. Therefore, it should be externally validated to evaluate how the prediction model performs in patients sampled independently from the derivation cohort.

CONCLUSION
This study developed a clinical prediction model to identify the risk factors for AVCF after PKP surgery, and this tool is of great value in sharing surgical decision-making among patients consulted before surgery. This nomogram requires external validation, and further research is needed to determine whether individual interventions based on this nomogram reduce the risk of AVCF.

Contributors YM, WW and ZY were responsible for the conception and design, data synthesis and analysis, interpretation of data and drafting the manuscript. JZ contributed to validate the data, reviewed and edited the manuscript. All authors read and approved the final manuscript. ZY accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Approval was obtained from the Medical Ethics Committee of Quzhou People's Hospital. The relevant judgement’s reference number: 2021-186. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data from this study are available upon reasonable request to the corresponding author.

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