

# Development and validation of a prognostic model of vertebral refracture after percutaneous kyphoplasty

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## Research article

**Keywords:** Percutaneous kyphoplasty, Prognostic model, Vertebral refracture, Last absolute shrinkage and selection operator regression

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# Abstract

**Purpose:** To investigate the factors influencing refracture after percutaneous kyphoplasty and to develop and validate a prognostic model.

**Method:** We retrospectively collected clinical data in 392 patients with osteoporotic vertebral compression fractures who underwent percutaneous kyphoplasty at the Affiliated Hospital of Xuzhou Medical University from 1 January 2018 to 1 January 2020. Predictors significantly associated with refracture after PKP were selected based on least absolute shrinkage and selection operator regression. Then a prognostic model was developed and internally validated using enhanced Bootstrap validation.

**Results:** Among the 392 patients who included in this study, there were 19 refracture after percutaneous kyphoplasty (4.8%). Four factors were selected by least absolute shrinkage and selection operator regression for significant association with refracture after percutaneous kyphoplasty, including body mass index, bone mineral density, unilateral puncture, and bone cement leakage. After enhanced Bootstrap validation, the bias-corrected curve of the model fitted well with the apparent curve, with the area under ROC curve of 0.931 and 95% CI of (0.789, 0.936).

**Conclusion:** The prognostic model developed based on four clinical profiles: body mass index, bone mineral density, unilateral puncture, and bone cement leakage can be used to identify those at most risk of refracture after percutaneous kyphoplasty.

## Introduction

Percutaneous kyphoplasty (PKP) is a minimally invasive procedure for the treatment of osteoporotic vertebral compression fractures (OVCFs) [1, 2]. It is performed primarily by injecting bone cement into vertebrae. Reinforcing the fractured vertebrae by injecting bone cement provides rapid pain relief and improves kyphosis. However, statistics show that the rate of new vertebral compression fractures in patients after PKP was approximately 8.7%-18.4% [3–6], which makes postoperative refracture an important issue for clinicians. Previous retrospective studies have reported several possible risk factors for refracture, including associations between age, body mass index (BMI), clinical complication rate, bone mineral density (BMD), number of initial surgical segments, and surgical puncture method [3, 6–13]. Despite years of research, there is no relevant literature that provides a valid prognostic model to predict the risk of refracture after PKP. Therefore, a prognostic model to predict the risk of refracture in patients after PKP would be of clinical value. This retrospective study analyzed the clinical data of refracture after PKP, and used the least absolute shrinkage and selection operator (LASSO) regression to select predictors of refracture after PKP. A prognosis model was then developed and validated to provide a reliable incidence of postoperative refracture. In order to identify people at high risk of refracture at an early stage and provide a scientific basis for subsequent clinical treatment.

This report follows the TRIPOD (Transparent Reporting of a Multivariate Prediction Rule for Individual Prognosis or Diagnosis) guidelines. Additional details are presented in the Supplementary Material.

## Material And Methods

Retrospective analysis of inpatient records from the Department of Spine Surgery, Xuzhou Medical University Hospital. We collected clinical data from 553 patients who were diagnosed with OVCFs and treated with percutaneous kyphoplasty between 1 January 2018 and 1 January 2020. All surgeries were performed by the same group of experienced and highly qualified chief surgeons. All patients were informed about the contents of the procedure and signed the Informed Consent Form for Surgery.

Inclusion criteria: ☐ patients with thoracolumbar compression fractures caused by osteoporosis and fresh fractures within 2 weeks; ☐ complete imaging data, no obvious intravertebral vacuum cleft and osteonecrosis manifestations on CT, and obvious bone marrow edema signals visible on MRI; ☐ patients without contraindications to surgery and with obvious indications for surgery; ☐ postoperative follow-up time greater than 1 years and regular use of anti-osteoporosis drugs during the follow-up.

Exclusion criteria: ☐ pathological fractures due to tumor, infection or long-term use of hormonal drugs; ☐ those with severe liver and kidney dysfunction, coagulation dysfunction or psychiatric disorders; ☐ burst fractures due to a clear history of trauma to the first fracture and refracture. ☐ without undergone standard and scientific anti-osteoporosis treatment after surgery. Standard and scientific antio-osteoporosis treatment was defined as regular oral calcium, vitamin D or use of zoledronic acid medication at least 1 time.

This study was approved by the Institutional Ethics Committee of the Affiliated Hospital of Xuzhou Medical University.

The basic information, surgical records, and follow-up of patients were retrospectively collected, including age, gender, general condition, history of cardiovascular disease, surgical segment, BMI, bone cement leakage, and surgical puncture method. BMI was measured by dual energy X-ray absorptiometry (Hologic Inc., Waltham, MA, USA) with preoperative lumbar spine (L1-L4) T values. Postoperative refractures were diagnosed mainly by clinical presentation and imaging data. Two prognostic outcomes were defined by imaging data and grouped according to the prognostic outcome. Patients who showed fresh bone edema on magnetic resonance imaging (MRI) were categorized as the "Refracture". Those who did not show clinical symptoms related to OVCFs and obvious signs of fracture on imaging were categorized as the "Non-refracture". If MRI was contraindicated or could not be performed, a bone scan was required to determine the presence of increased uptake compatible with recent fracture. The imaging data were evaluated separately by two orthopedic surgeons on the Picture Archiving and Communication Systems (PACS), and any differences in measurements were re-evaluated by the two surgeons to achieve agreement.

## Statistical analysis

Analyses were performed using R ® (version 4.0.3). Descriptive and inferential statistics were calculated to describe the sample. Continuous variables were expressed as means ± standard deviation (SD)

according to the distribution. The Kruskal-Wallis rank sum test was used for comparison between groups for continuous variable. Categorical variables were shown as frequencies (percentages), and compared by  $\chi^2$  test.  $P < 0.05$  was considered as significant.

LASSO regression is used to select variables by narrowing the regression coefficients. By making the sum of the mean (or likelihood function) of the squared residuals adding  $\lambda$  times the absolute value of the regression coefficients minimal. LASSO regression can be used to filter variables by adjusting the penalty coefficient  $\lambda$ . The larger  $\lambda$  is, the stronger the penalty of the model. Since it can avoid the problem of overfitting, it is often used to deal with data with multiple cointegration.

Among the many influential factors associated with refracture, we considered those that could be routinely and accurately assessed: age, sex, BMI, BMD, number of initial surgical segments, history of cardiovascular disease, and surgical puncture method. We selected the predictors to be included in the final model based on the LASSO regression analysis to build the column line graph model. After 1000 enhanced Bootstrap validations, the receiver operating characteristic curve (ROC) and 95% CI were calculated. Area under the receiver operating characteristic curve (AUC) and calibration plots (comparing the mean predicted risks with the observed risk) were used to calculate model performance.

## Results

### Patient characteristics

A total of 392 patients who underwent PKP surgery for OVCFs at our institution were included in this study. The mean age was 73.1 years. All patients were followed for 20 months on average (range, 14 months to 26 months). A total of 19 patients had refracture after PKP with an incidence of 4.8%. A comparison of the clinical data and associated risk factors between two groups is shown in Table 1.

Table 1  
 Compared of the clinical data and associated risk factors between two groups

Variable	Refracture (19 /392)	Non- refracture (373/392)	Odds Ratio	95%Confidence Interval	$\chi^2$	<i>P</i> - value
Gender					0.06	0.494
Female,n(%)	14(74)	284(76)	-			
Male,n(%)	5(26)	89(24)	1.05	0.25, 3.90		
Age(years)	74.84 ± 5.85	73.09 ± 8.73	0.98	0.92, 1.05	1.24	0.229
≥ 65	19	308				
<65	0	65				
BMI(kg/m <sup>2</sup> )	19.55 ± 1.56	22.8 ± 3.38	0.58	0.43, 0.73	19.771	0.000
≥ 18.5	15	330				
< 18.5	4	43				
BMD	-4.29 ± 0.53	-3.42 ± 0.76	0.11	0.04, 0.26	22.206	0.000
Number of initial surgical segments			0.95	0.42, 1.89	0.352	0.553
1,n(%)	12 (63)	258 (69)				
2,n(%)	4(21)	77 (21)				
≥ 3,n(%)	3(16)	38 (10)				
Leakage						
No,n(%)	3 (16)	183 (49)	-	-		
Yes,n(%)	16 (84)	190 (51)	8.48	2.21, 46.3		
Cardiovascular disease					0.049	0.503
No,n(%)	9 (47)	167 (45)	-	-		
Yes,n(%)	10 (53)	206 (55)	1.06	0.34, 3.32		
Puncture method					2.065	0.115
Bilateral,n(%)	16 (84)	256 (69)	-	-		
Unilateral,n(%)	3 (16)	117 (31)	0.27	0.04, 1.08		

## Development of the prognostic model

Logistic models were used to estimate the coefficients for each risk factor in refracture. Refracture after PKP outcome was used as the dependent variable. Eight predictor variables, including age, gender, BMD, BMI, number of initial surgical segments, history of cardiovascular disease, surgical puncture method and the occurrence of bone cement leakage, were included in the LASSO regression model to select variables associated with refracture after PKP. When  $\log(\lambda)$  was 0.0045, it showed that the model obtained excellent performance with the least number of independent variables(Fig. 1). BMD, BMI, number of initial surgical segments, surgical puncture method were included in the prognostic model. The final model:  $\text{Logit}(P)=0.5387+(2.1041\times\text{Leakage})+(-0.5345\times\text{BMI})+(-2.2157\times\text{BMD})+(-1.3430\times\text{Unilateral})$ . Based on the LASSO results, a nomogram model was developed using R software to predict refracture after percutaneous kyphoplasty(Fig. 2).

## Evaluation and internal validation of the prognostic model

Internal validation was performed using the enhanced Bootstrap validation. After 1000 Bootstrap validations, the prognostic model calibration curves were plotted. The curves show that the apparent curve of the model fits well with the bias-corrected curve, indicating that the prognostic model is in good agreement (Fig. 3). After 1000 Bootstrap resamplings, the prognostic model had an AUC of 0.931 and 95% CI of (0.789,0.936) proving that the model discriminates well. (Fig. 3)

## Discussion

PKP has become increasingly popular in the treatment of OVCFs since the first case of PKP was successfully treated. PKP not only quickly eliminates the severe pain that is difficult to relieve with bed rest, but also effectively reduces cement leakage due to the presence of the expandable balloon [1, 14]. After surgery, patients can recover vertebral height, improve the kyphosis and maintain the normal sequence of the spine in a short time. As an enhanced recovery after surgery (ERAS) technique, PKP allows patients to get out of bed early for functional exercises after surgery, reducing multiple complications caused by long-term bed rest and improving patients' quality of life. However, any new clinical technique is often accompanied by a series of complications. Common complications after PKP surgery include bone cement leakage, pulmonary embolism, refracture and increased postoperative back pain. Refracture have received a significant amount of attention in previous studies due to the increased pain of reoperation as well as the financial cost to the patient. Lee [1] found that PKP did not increase the risk of refracture in patients with OVCFs compared to conventional conservative treatment. PKP is not a major risk factor for vertebral fracture, but only a progressive process of osteoporosis. A total of 392 patients were included in our study, 19 of whom developed refracture after PKP, with an incidence of approximately 4.8%. There are no uniform criteria for the factors affecting refracture after PKP. Therefore,

adequate assessment to predict the risk of refracture after PKP. Early identification of high-risk patients and intervention can reduce the incidence of refracture and improve patient prognosis.

PKP can be injected into vertebrae by unilateral or bilateral injection. A cement-free section exists between the bone cement and the upper and lower endplate. The cancellous bone in this area is susceptible to collapse under prolonged stress. Therefore, the strength of the vertebrae is positively correlated with the rate of contact between the bone cement and the upper and lower endplate[11]. When the bone cement was injected into the vertebrae with adequate dispersion, the risk of postoperative refracture would be reduced. The ideal distribution is when the postoperative bone cement is uniformly diffused over the anterior two-thirds of the vertebrae [15]. Previous meta-analyses have shown no difference in clinical efficacy between unilateral and bilateral injection. By creating a vertebral compression fracture model, Chen [16] concluded that both unilateral and bilateral punctures can significantly increase vertebral stiffness. Unilateral puncture creates a biomechanical imbalance secondary to the uneven diffusion of the bone cement within the vertebrae [17, 18]. The imbalance of spinal biomechanics is an essential influence on vertebral fractures. When vertebrae were under prolonged high load, the side with poorer biomechanics is more at risk for refracture. He [19] evaluated the effect of different bone cement distribution on the clinical efficacy by a retrospective analysis. After more than 1 year of follow-up, patients with bilateral punctures are mostly “H” distributed on both sides of vertebrae, and they can achieve better outcomes in the short term. Currently, many surgeons commonly treat patients using unilateral puncture in their clinical practice [9, 20–22]. They concluded that unilateral puncture could achieve acceptable biomechanical stability with cement filling beyond the midline of vertebrae [16]. However, the unilateral puncture approach inevitably fails to effectively diffuse the bone cement into vertebrae due to its limited puncture angle [23]. Therefore, we recommend that bilateral puncture remains the preferred approach when bone cement filling is less effective or when the patient suffers from severe osteoporosis.

Lower BMD reflects the severity of osteoporosis. With decreasing T-values, the incidence of refracture increases [6, 8–10, 12]. Meanwhile lower BMD means that bone cement is more likely to leak from cancellous bone. The value of BMD was closely related to the course of OVDFs. Qi [24] concluded from examining bone biopsy specimens and blood samples from 206 patients with OVCFs that low BMD is often associated with reduced bone formation capacity, severe loss of vertebral height and large amounts of necrotic bone. Lower BMI often means that patients have a lower long-term protein intake. Protein and amino acids are the raw materials for bone production. When protein is chronically deficient, bone production is reduced, further aggravating the process of osteoporosis.

The more vertebrae fractured in the initial surgery, the greater disruption of the normal spinal biologic force line [25]. Bone cement infusion in multiple segments has a significant impact on the biomechanics and load transfer of the entire spine. Among the bone cement leaks that lead to refractures, intervertebral disc leakage is the most common [6, 13]. Sun [26] showed that if there is no leakage, the refracture is 7%. However, when disc leakage occurs, this rate increases to 14%. Leakage of bone cement in the

intervertebral disc accelerates the degeneration of the disc and other structures. The bone cement weakens the mechanical cushioning effect of the disc, resulting in uneven mechanical conduction. In addition, the bone cement can produce mechanical damage to the endplate. Leakage of the bone cement triggers multiple destructive mechanisms that combine to cause refracture.

However, this study has several limitations. First, refracture occurred mostly within 6 months after surgery. However, the long-term follow-up results show that vertebral fractures were inevitable with the progressive course of osteoporosis. In contrast, the mean follow-up time of the study was 12 months, which limits our investigation of the change in the probability of postoperative vertebral refracture over time. Second, our study is a single-center retrospective study. Although internal validation using enhanced Bootstrap can be effective in evaluating model performance, additional large-scale clinical cohorts are still needed for external validation.

## Conclusion

In summary, this study selected four predictors associated with refracture after PKP by LASSO regression. A prognostic model was developed based on these four predictors. The results of internal validation show that this model has good comprehensive performance. The model can well predict the probability of refracture after PKP, which provides a basis for prognosis prediction and personalized treatment plan development for patients with OVCFs.

## Declarations

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**Data availability** The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

**Ethics approval** This study was approved by the Institutional Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Consent to participate** Not applicable.

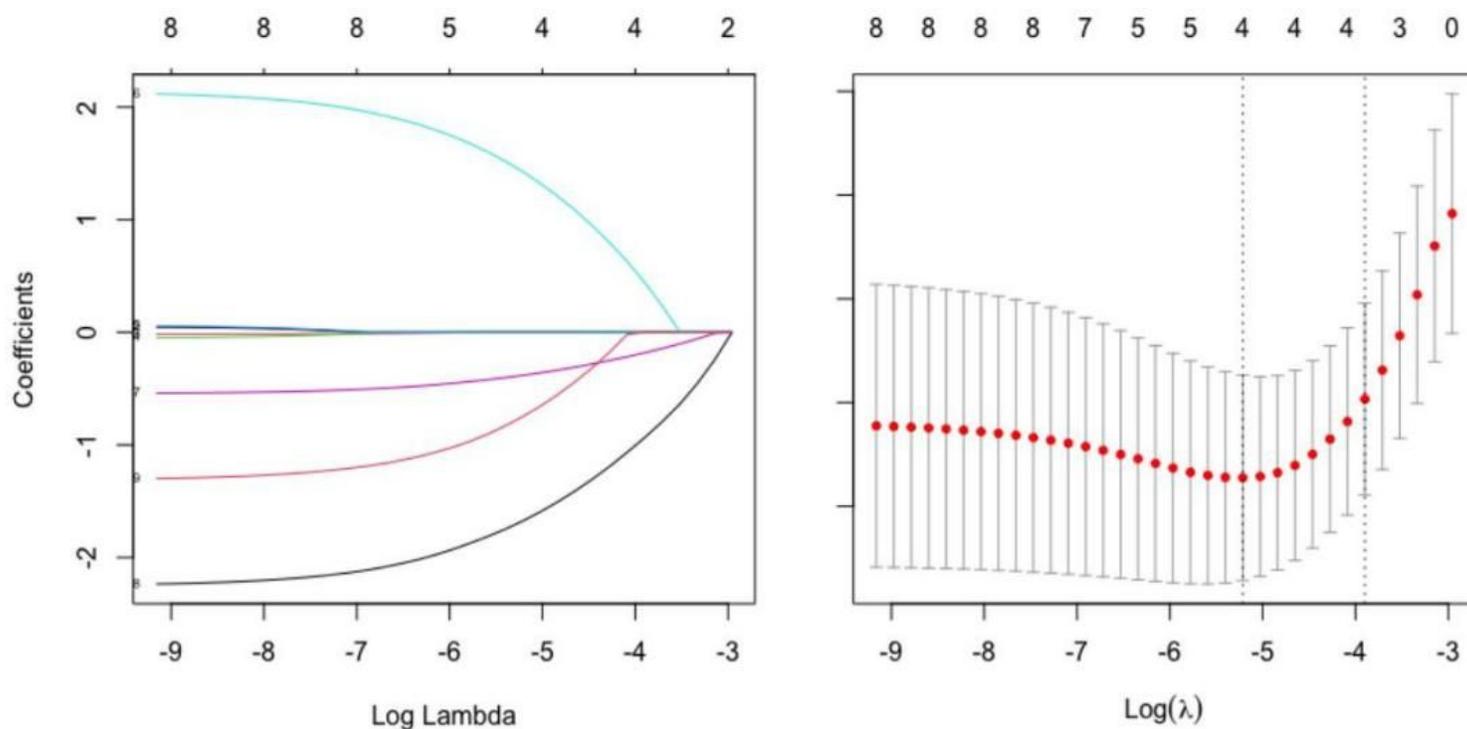
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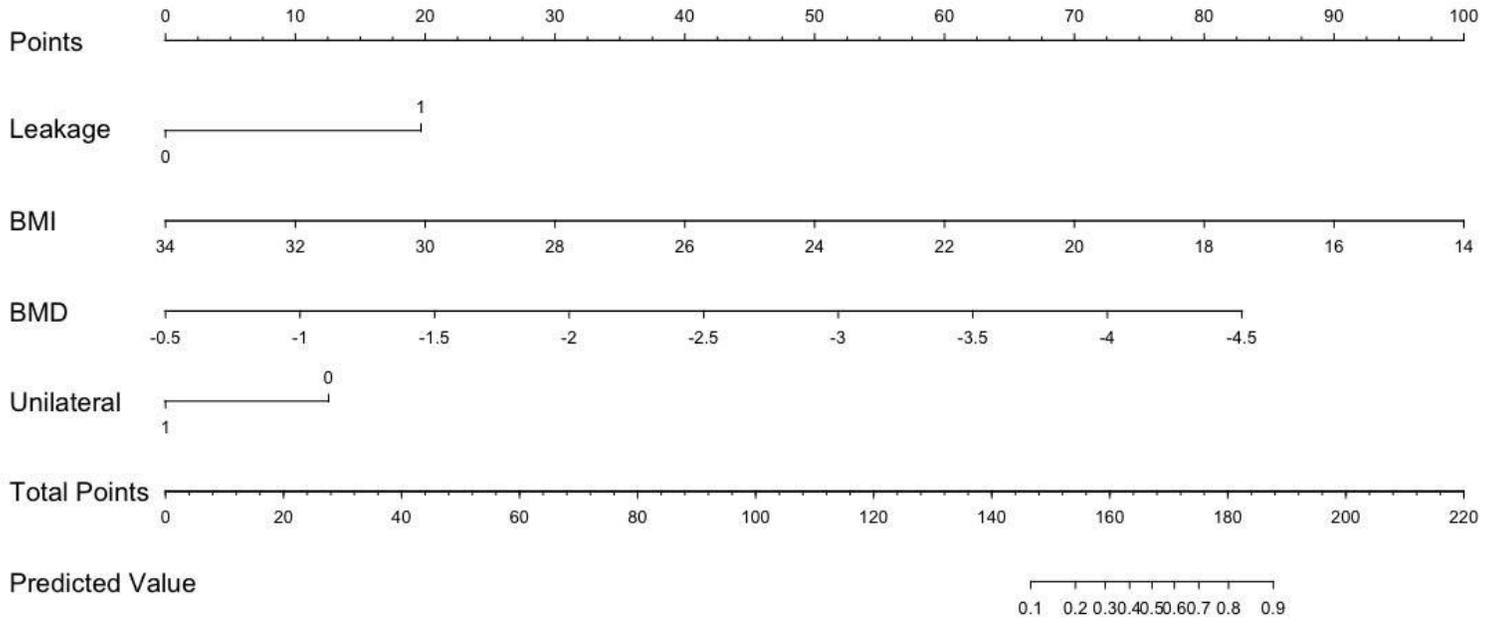
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## Figures



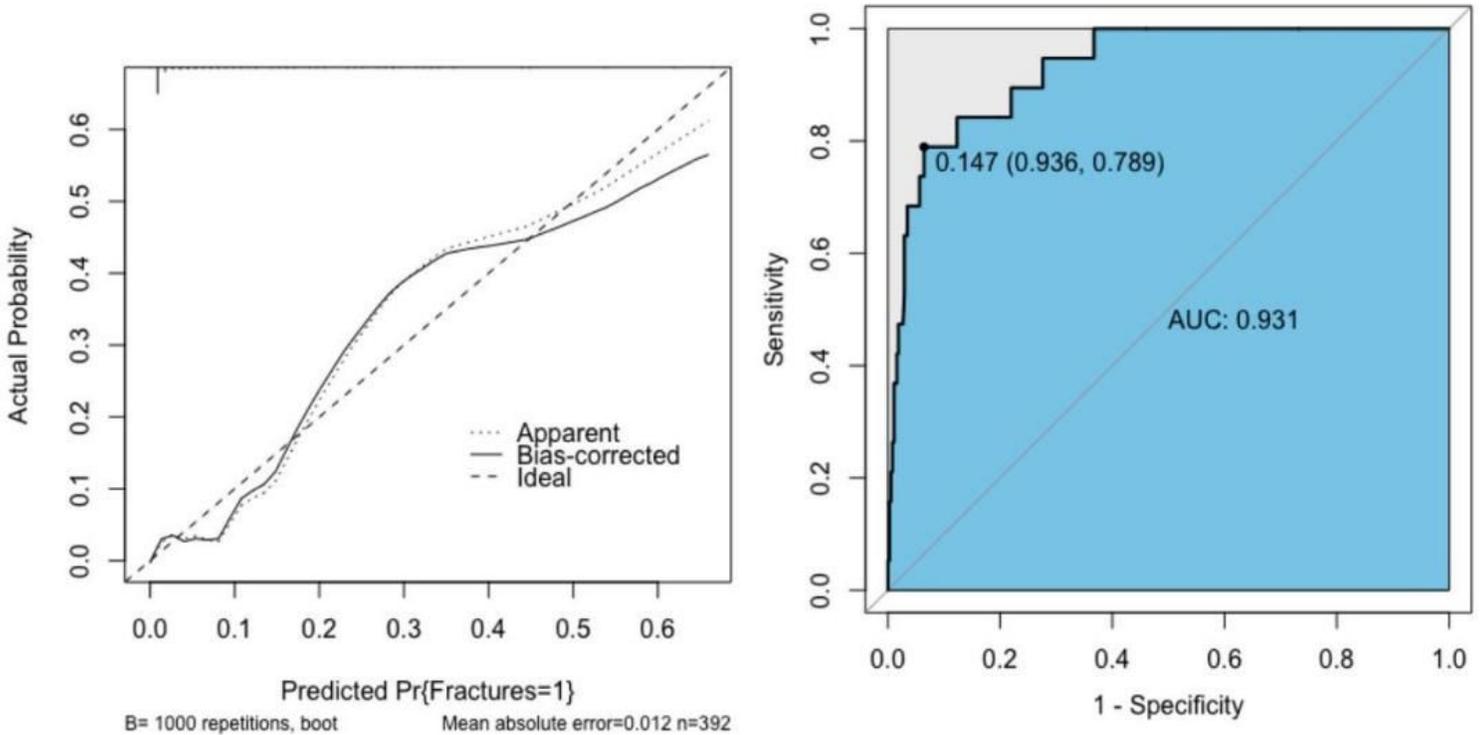
**Figure 1**

Refracture variable selection by using LASSO regression



**Figure 2**

Nomogram predicting refracture after percutaneous kyphoplasty



**Figure 3**

Calibration plot and ROC curve of the prognostic model

## Supplementary Files

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