

Retrospective Study

Predictive Factors for Adjacent Vertebral Fractures After Percutaneous Kyphoplasty in Patients With Osteoporotic Vertebral Compression Fracture

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Background: Adjacent vertebral fracture (AVF) seemed to be a frequent and severe complication in osteoporotic vertebral compression fracture (OVCF) patients receiving percutaneous vertebroplasty or percutaneous kyphoplasty (PKP), resulting in poor long-term outcome and recurrence of pain-related symptoms. Nonetheless, its mechanism remains unclear.

Objectives: To investigate the potential predictor of AVF after PKP and figure out whether the intervertebral disc plays a role during the process of AVF.

Study Design: Retrospective study.

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

Methods: Clinical data of OVCF patients receiving PKP were reviewed in our hospital from January 2016 to December 2020. Four hundred and forty-five patients were recruited who met the abovementioned criteria in this study. The clinical data, including age, gender, bone mineral density (BMD), vertebral height, vertebral kyphosis angle, cement volume, cement distribution, as well as adjacent disc degeneration extent, were recorded for each patient. Independent-sample t tests and chi-squared tests were performed to compare these indexes. Bivariate correlation tests and multiple linear regression analyses were performed among potential predictors. Receiver operator characteristic (ROC) analysis and Kaplan-Meier plotter were applied to evaluate the diagnostic efficiency of parameters for predicting the occurrence of AVF.

Results: Patients in both groups gained obvious improvements in symptomatic and radiographic indexes after first PKP. Statistically significant difference ($P < 0.05$) was only found between 2 groups with respect to BMD, kyphosis angle at last follow-up before second PKP, cement distribution, and disc degeneration grade. The ROC analysis showed that $BMD \leq -3.45$ was weakly associated with AVF after PKP (sensitivity, 33.3%; specificity, 40.4%; area under curve, 0.324, $P = 0.000$). In addition, kyphosis angle at last follow-up before second surgery $\geq 15.5^\circ$ was highly predictive of AVF after PKP (sensitivity, 92.2%; specificity, 24.6%; area under curve, 0.569, $P = 0.109$). Statistically significant difference of AVF incidence amongst patients with different cement distribution ($P = 0.018$) and similar trend was also found amongst patients with different disc degeneration ($P = 0.000$). Statistically significant difference was noted in terms of disc degeneration grade between 2 adjacent discs in AVF group.

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

Conclusions: The risk of AVF should be focused, especially when OVCF patients with the following predictors: (1) $BMD < -3.45$; (2) kyphosis angle at last follow-up $> 15.5^\circ$; (3) I or II cement distribution; and (4) IV or V disc degeneration. More prophylactic treatment should be prescribed for these patients to avoid the occurrence of AVF.

Key words: Predictive factors, adjacent vertebral fracture, percutaneous kyphoplasty, osteoporotic vertebral compression fracture

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Osteoporotic vertebral compression fracture (OVCF), a common and severe consequence of osteoporosis, is estimated to affect 1.4 million cases each year all over the world (1,2). Debilitating and chronic pain was the most common complaint of OVCF patients, leading to an obvious drop of their self-care ability. Due to the global demographic aging, this disease would constitute a major worldwide health issue (3,4). Although conservative treatment could also alleviate patients' suffering, continuous bed resting for one month or more would result in further aggravation of osteoporosis, deterioration of cardiorespiratory function, deep venous thrombosis, bedsores, as well as a sharp decrease in activities of daily living (5-8). And even though conservative treatment is generally accepted, residual kyphosis might still lead to intractable lumbago and sagittal imbalance. Hence, an ideal treatment was essential for OVCF patients to supply rapid recovery of spinal stability and adequate correction of kyphosis deformity.

Compared with pedicle screw fixation, percutaneous vertebroplasty (PVP) was a minimally invasive and effective surgical approach for OVCF patients, especially for those with poor health conditions (9). It could provide instant pain relief and obvious improvement in quality of life (10). On the basis of PVP, the step of balloon inflation, which further reduced cement leakage incidence and restored vertebral height, was added before cement injection and this new surgery was entitled percutaneous kyphoplasty (PKP) (11,12). Due to the abovementioned advantages, PKP gradually has replaced PVP and been recommended as best treatment for OVCF. Adjacent vertebral fracture (AVF) seemed to be a frequent and severe complication in OVCF patients receiving PVP or PKP, resulting in poor long-term outcomes and recurrence of pain-related symptoms (11). PKP was reported to have a lower AVF incidence than PVP; however, the incidence of AVF after PKP remains unclear, with the values widely varying (3%-29%) (11,13,14). Hence, many researchers focused on its mechanisms and related risk factors. In their studies (11,14-16), low bone mineral density (BMD), regional kyphosis, asymmetrical cement distribution, and excessive cement volume were identified as risk factors of AVF after PKP. Nonetheless, its mechanism remains unclear. It was deduced that loss of mechanical absorption ability and vertebral stiffness might be the main cause of AVF after PKP. Based on this evidence, the opinion was firstly proposed by our team that the change of intervertebral disc might also play an important role in the occurrence of AVF; and

its effect was ignored in most of the abovementioned studies. Therefore, a retrospective study was carried on investigating the potential predictor of AVF after PKP and figure out whether intervertebral discs play a role during the process of AVF.

METHODS

Patients

Under the approval of the ethics committee of our university, clinical data of OVCF patients receiving PKP were reviewed in our hospital from January 2016 to December 2020. The inclusion criteria were shown as follows: (1) age > 60 years; (2) fresh vertebral fracture was identified under T5 level by magnetic resonance imaging (MRI); (3) T score, measured by dual-emission x-ray absorptiometry, was < -2.5 and then diagnosis of osteoporosis was confirmed; (4) symptomatic and radiographic evaluations were performed preoperatively, postoperatively, and at each follow-up. Patients with other pathologic fractures or < 6 months follow-up duration were excluded from this study.

Four hundred and forty-five patients were recruited who met the abovementioned criteria in this study. In follow-up duration, a secondary vertebral fracture took place in 73 patients (16.9%) and was located at an adjacent segment in 51 patients (11.5%). Two patients (0.6%) suffered a third vertebral fracture even though receiving anti-osteoporosis treatment.

Surgical Interventions

PKP surgery was operated by senior spinal surgeons under local anesthesia. Patients were placed in a prone position, and their abdomens were kept suspended. The projection of target pedicle was marked on the skin, and a gentle force was exerted at the marked area to make target vertebrae reduced. Trocar and cannula systems (KMC; Kinetic Medical Co Ltd, Shanghai, China) were adopted in this study. The trocar was punctured at the lateral margin of pedicle and then was stuck through pedicle into the vertebral body. The trocar was replaced by the cannula with the guidance of a pin. The kyphoplasty balloon was inserted into the anterior part of the vertebral body through the cannula. Contrast agent was propelled meticulously into the balloon to restore vertebral height gradually. Finally, polymethyl methacrylate was injected steadily into the vertebral body after balloon withdrawal. The injection would be ended until cement area was not changed anymore or cement leaked from vertebral body.

Radiographic Assessment

Deformity severity of fractured vertebra was evaluated through the whole process of the study. Vertebral kyphosis angle was measured by researchers with Cobb method from the upper endplate of fractured vertebra to its lower endplate on sagittal radiographs. According to the coronal radiographic presentation, cement distribution was divided into 3 grades: grade I, in which cement gathered around injected point and didn't cross midline; grade II, in which cement went through vertebral midline, but did not reach inner margin of contralateral pedicle; and grade III, in which cement went across inner margin of contralateral pedicle and was defined to be distributed bilaterally. On MRI, Pfirrmann grading system was used to evaluate the extent of adjacent disc degeneration.

Data Analysis

The clinical data, including age, gender, BMD, vertebral height, vertebral kyphosis angle, cement volume, cement distribution, as well as adjacent disc degeneration extent, were recorded for each patient. All data were analyzed with special statistical software (SPSS 26.0, IBM Corporation, Armonk, NY). The included patients were divided into 2 groups according to whether AVF was identified or not: AVF group and non-AVF group. Before first PKP surgery, disc degeneration grade between 2 fractured vertebrae was chosen to analyze in AVF group, while the severer 1 of 2 adjacent disc degeneration grades was chosen in non-AVF group. According to whether variance was homogeneous or not, corresponding independent-sample t tests were performed to compare age at operation, BMD, and symptomatic and radiographic parameters between AVF group and non-AVF group. Chi-squared tests were used to compare gender, cement distribution, as well as disc degeneration grade. Bivariate correlation tests were performed among potential predictors. Multiple linear regression analyses were utilized for further investigation of those predictors. Statistically significant difference was set at $P < 0.05$.

Receiver operator characteristic (ROC) analysis was applied to evaluate the diagnostic efficiency of continuous parameters for predicting the occurrence of AVF. Sensitivity and specificity were calculated at each potential cut point. Then ROC curves were then generated by plotting the true-positive fraction against the false-positive one for each cut point. The area under ROC curve either close to 1.0 (high) or 0.0 (low) implies a strong predictive power, while it close to 0.5 indicates

that the parameter can't be used to predict. Then Kaplan-Meier plotter was used to assess the effect of nonparametric factors on AVF prognosis in follow-up duration.

RESULTS

Four hundred forty-five patients who met the criteria were included in our study. According to whether AVF took place or not, 51 patients (age: 77.7 ± 5.6) were divided into AVF groups, and the remaining patients (age: 76.5 ± 7.4) were assigned into non-AVF group. There were 10 men (19.6%) and 105 men (27.9%) in AVF group and non-AVF group, respectively. Six patients (11.8%) received PKP via bilateral approach in AVF group and 85 patients (21.9%) were bilateral approach in non-AVF group. The mean cement volume was 6.0 ± 0.7 mL in AVF group and 5.9 ± 0.7 mL in non-AVF group (Table 1).

It could be noted from Table 1 that patients in both groups gained obvious improvements in symptomatic and radiographic indexes after first PKP. Statistically significant difference ($P < 0.05$) was only found between 2 groups with respect to BMD, kyphosis angle at last follow-up before second PKP, cement distribution, and disc degeneration grade, which suggests that the 4 factors might be positively correlated with the occurrence of AVF after PKP. Bivariate correlation analysis was used to investigate associations of potential predictors. As shown in Table 2, BMD was not associated with kyphosis angle at last follow-up or cement distribution, but was positively associated with cement distribution. Multiple linear regression analysis was carried out on BMD and cement distribution to compare the 2 potential predictors between 2 groups after adjusting for their associated predictors. Table 3 showed that the 2 groups differed significantly in terms of BMD, kyphosis angle at last follow-up, and disc degeneration grade, implying that the BMD and cement distribution were independent predictors of AVF.

The ROC analysis showed that $BMD \leq -3.45$ was weakly associated with AVF after PKP (sensitivity, 33.3%; specificity, 40.4%; area under curve, 0.324, $P = 0.000$) (Fig. 1). In addition, kyphosis angle at last follow-up before second surgery $\geq 15.5^\circ$ was highly predictive of AVF after PKP (sensitivity, 92.2%; specificity, 24.6%; area under curve, 0.569, $P = 0.109$) (Fig. 2). The results of Kaplan-Meier plotter (Figs. 3 and 4) showed that most AVF occurred within one years after first PKP. And results of Log Rank test showed statistically significant difference of AVF incidence amongst patients with dif-

Table 1. The general data of patient in AVT and non-AVT groups.

	AVF Group	Non-AVF Group	P value
Number	51	394	
Age/Year Old	77.7 ± 5.6	76.5 ± 7.4	0.16
Gender			
Men	10	105	0.28
Women	41	289	
BMD	-3.49 ± 0.53	-3.12 ± 0.65	0.000
Surgical Approach	Bilateral 6 Unilateral 45	Bilateral 85 Unilateral 309	0.153
Surgical Time/min	27.1 ± 4.4	27.8 ± 4.4	0.27
Cement Volume/mL	6.0 ± 0.7	5.9 ± 0.7	0.41
VAS (Pre-op)	7.5 ± 0.6	7.4 ± 0.7	0.55
VAS (Post-op)	3.3 ± 0.5	3.3 ± 0.5	0.79
VAS (Last Follow-up Before Second PKP)	2.2 ± 0.5	2.1 ± 0.5	0.21
ODI (Pre-op)	33.1 ± 1.9	33.48 ± 1.9	0.26
ODI (Post-op)	17.8 ± 2.2	18.1 ± 2.1	0.27
ODI (Last Follow-up Before Second PKP)	16.1 ± 1.8	16.5 ± 1.8	0.16
Vertebral height (Pre-op)/mm	18.3 ± 2.7	17.9 ± 2.5	0.29
Vertebral Height (Post-op)/mm	20.5 ± 2.4	20.2 ± 2.3	0.36
Vertebral Height (Last Follow-up Before Second PKP)/mm	18.1 ± 2.7	17.8 ± 2.5	0.37
Kyphosis Angle (Pre-op)/°	18.3 ± 1.7	18.2 ± 1.5	0.49
Kyphosis angle (Post-op)/°	15.2 ± 1.5	15.0 ± 1.7	0.45
Kyphosis Angle (Last Follow-up Before Second PKP)/°	17.1 ± 1.3	16.5 ± 1.8	0.04
Cement Distribution	I 32; II 13; III 6	I 202; II 70; III 122	0.02
Disc Degeneration Grade (First PKP)	I 5 (9.8%); II 11 (21.6%); III 19 (37.2%); IV 10 (19.6%); V 6 (11.8%)	I 74 (18.8%); II 231 (58.6%); III 65 (16.5%); IV 11 (2.8%); V 13 (3.3%)	0.000

Abbreviations: AVF, adjacent vertebral fracture; BMD, bone mineral density; VAS, Visual Analog Scale; PKP, percutaneous kyphoplasty; ODI, Oswestry Disability Index.

ferent cement distribution ($P = 0.018$) and similar trend was also found amongst patients with different disc degeneration ($P = 0.000$).

For further investigation of the influence of disc degeneration on AVF, an extra chi-squared test was

Table 2. Correlation coefficients among the potential predictors of AVF.

	BMD	Kyphosis Angle at Last Follow-up	Cement Distribution
Kyphosis Angle at Last Follow-up	0.01		
Cement Distribution	0.184*	0.067	
Disc Degeneration Grade (First PKP)	-0.09	0.078	0.031

Abbreviations: BMD, bone mineral density; PKP, percutaneous kyphoplasty.

* Significant correlation at the 0.05 level

Table 3. Multivariate regression analysis of the factors influencing the occurrence of AVF.

Factor	Cement Distribution Regression Coefficient (r)	P value
BMD	0.184	0.00*
Kyphosis angle	0.073	0.118
Disc Degeneration Grade (First PKP)	0.057	0.24
Group	0.113	0.022*

Abbreviations: BMD, bone mineral density; PKP, percutaneous kyphoplasty.

* Significant difference

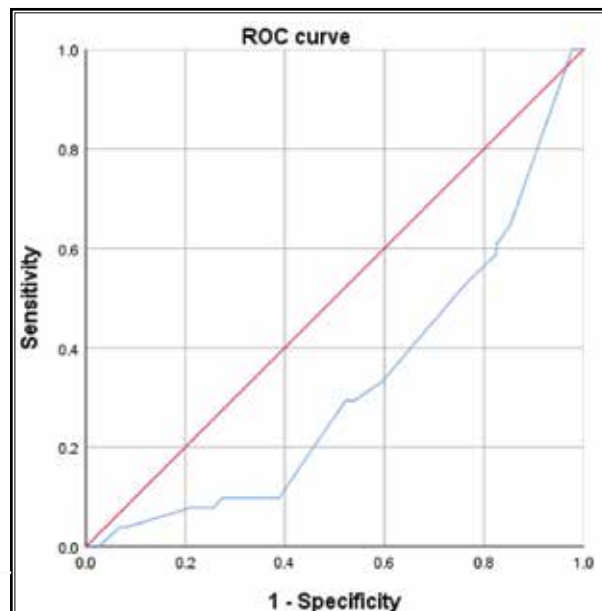


Fig. 1. The ROC curve of BMD for predicting the occurrence of AVF.

BMD, bone mineral density; AVF, adjacent vertebral fracture.

performed to compare disc degeneration grade between adjacent disc at the AVF side and adjacent disc at the other side. Table 4 illustrated that statistically significant difference was noted in terms of disc degeneration grade between 2 adjacent discs in AVF group.

DISCUSSION

The success of PKP for OVCF have been confirmed by many clinicians, and this surgery was widely applied as optimal treatment of OVCF. Nonetheless, its complications also aroused great concerns, including respiratory and urinary infection, hematoma, chronic pain, cement embolism, cement leakage, and subsequent neurological deficit (17-21). Of these complications, adjacent vertebrae fracture was frequently observed in OVCF patients after PKP surgery, which led to a sharp decline in surgical outcome and life quality. Its incidence was reported to be up to 52% in patients with PVP (22) and 3%-29% in PKP (11,13,14). In our study, a high incidence of AVF (16.9%) was observed, which might be caused by sample selection bias, surgical technique, and postoperative improvement of BMD after anti-osteoporosis treatment. Although some studies

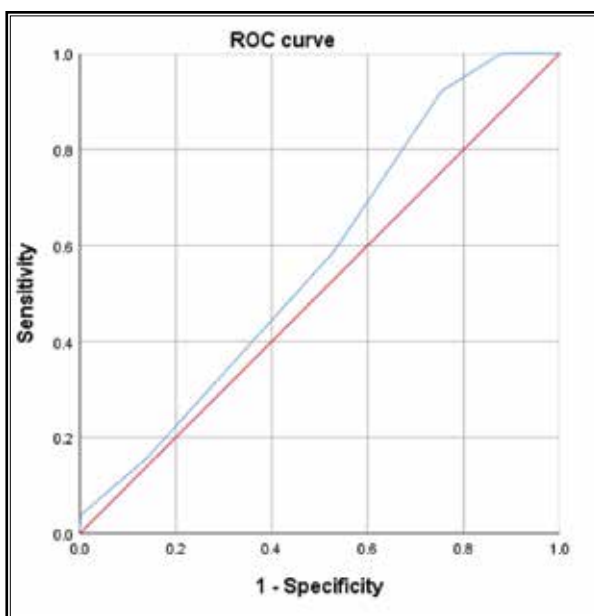


Fig. 2. The ROC curve of kyphosis angle at the last follow-up before second PKP surgery for predicting the occurrence of AVF. ROC, receiver operator characteristic; PKP, percutaneous kyphoplasty; AVF, adjacent vertebral fracture.

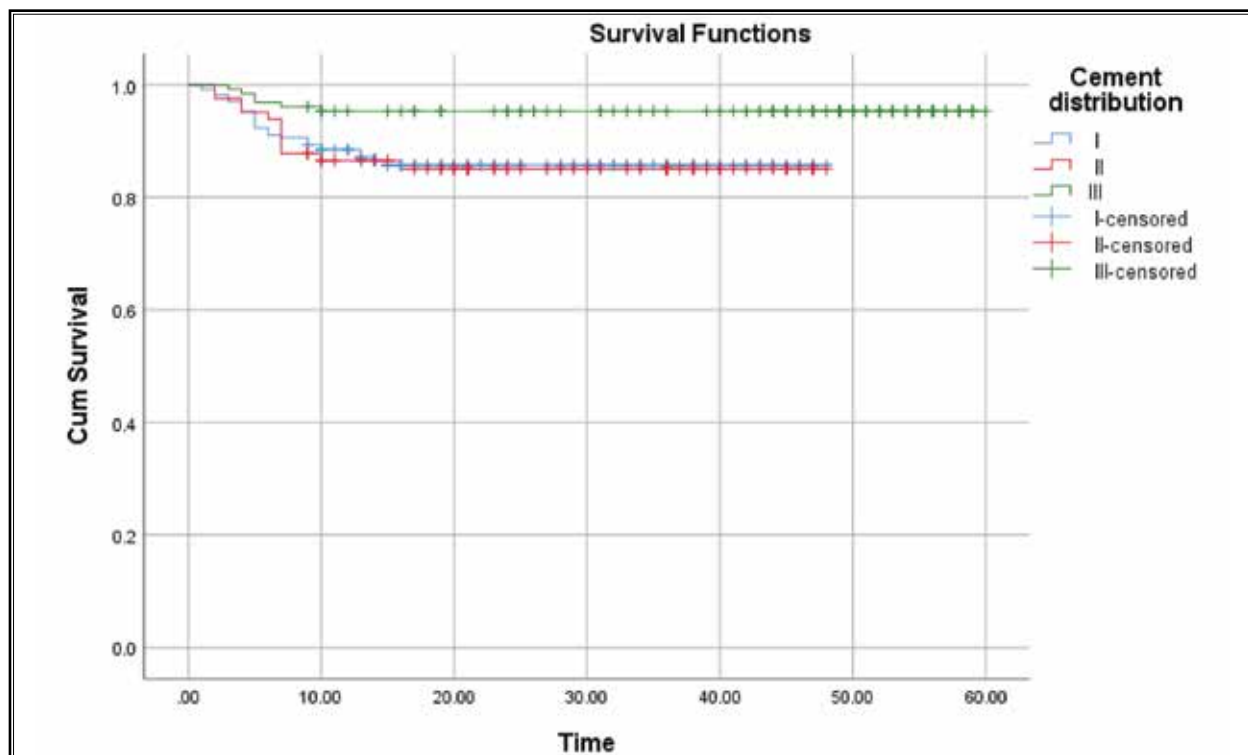


Fig. 3. The Kaplan-Meier plotter assessing the effect of cement distribution on the occurrence of AVF. AVF, adjacent vertebral fracture.

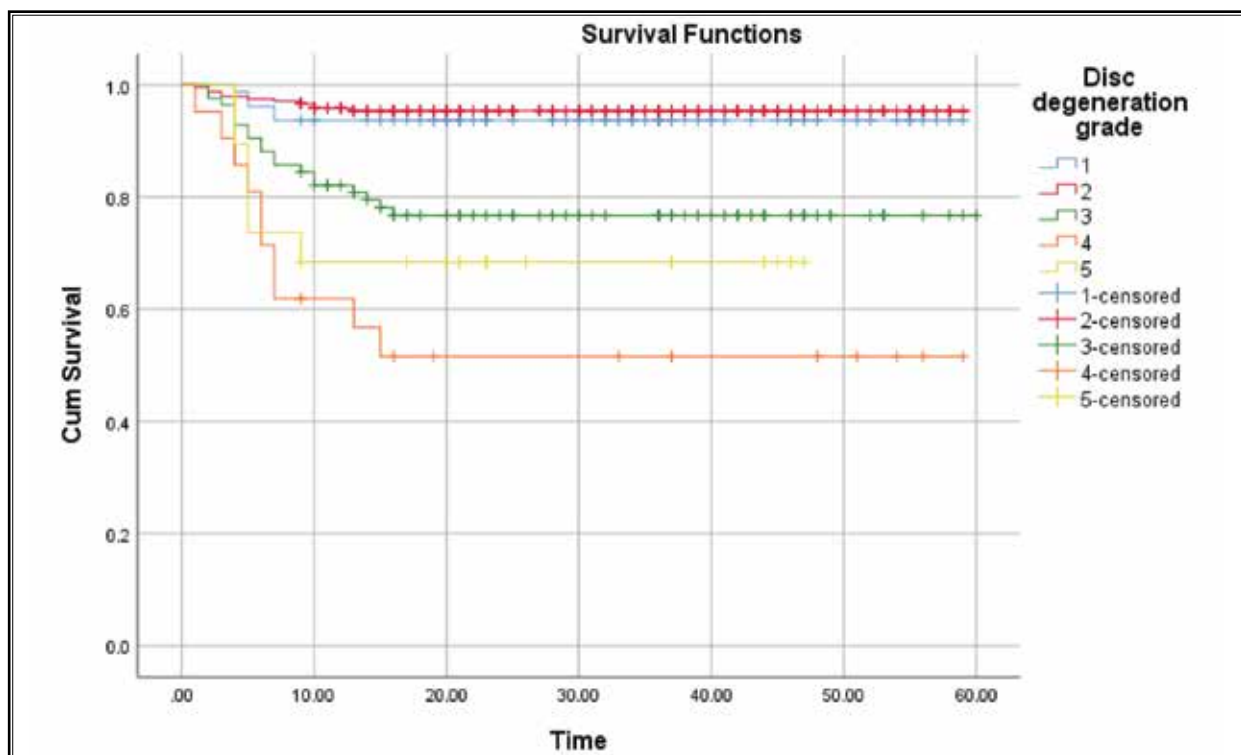


Fig. 4. The Kaplan-Meier plotter assessing the effect of disc degeneration on the occurrence of AVF. AVF, adjacent vertebral fracture.

Table 4. The comparative study of disc degeneration degree between fracture side and nonfracture side.

	I	II	III	IV	V	P value
Fracture	5	11	19	10	6	0
Non-fracture	16	30	5	0	0	

(23,24) demonstrated that neither PVP nor PKP seemed to result in an increased risk of AVF when compared to conservative treatment, more biomechanical studies (25-28) confirmed that conspicuous augmentation of vertebral stiffness due to bone filler materials was considered as main risk factor in developing AVF. Besides change of vertebral stiffness, additional risk factors were identified in previous studies (14,15,29,30), such as age, vertebral kyphosis angle, BMD, modulus of polymethyl methacrylate, cement volume, and so on. It was worthy to note that changes of fractured vertebral body were thoroughly analyzed, but the influence of disc degeneration was ignored in these abovementioned studies. Intervertebral disc, as a compartment of the functional spinal unit, played an important role in transmitting and absorbing mechanical stress onto

the spine (31). Both endplates calcification and dehydration of nucleus pulposus would progress with the exacerbation of disc condition, finally resulting in a notable loss of mechanical absorption ability. Additionally, disc degeneration would also lead to loss of disc height, contributing to regional kyphosis aggravation, and forward stress concentration. Under this situation, it could be deduced that, especially when adjacent to augmented vertebrae, potential risk of AVF would considerably increase. Therefore, we took the influence of disc degeneration into consideration and further find predictors of AVF for OVCF patients receiving PKP.

RESULTS

Results of our study showed that patients in both groups could benefit from PKP surgery, presenting with obvious improvement in symptomatic and radiographical indexes immediately after surgery. Age, gender, surgical approach, surgical time, cement volume, Visual Analog Scale scores, Oswestry Disability Index (ODI) scores, and vertebral height had no influence on the occurrence of AVF in our study. Additionally, BMD, kyphosis angle at last follow-up, cement distribution, and disc degeneration grade were identified to be indepen-

dent predictors of AVF after PKP. Results of ROC curve showed that any patients with bone mineral content ≤ -3.45 or kyphosis angle at last follow-up $\geq 15.5^\circ$ were prone to suffer an AVF after PKP surgery. It could be explained by the fact that porosity of bony trabeculae in patients with lower BMD value would have lower mechanical absorption ability and less strength of vertebral body. Kyphosis deformity would also result in forward stress concentration at vertebral body, further raising potential AVF risk. The above findings were consistent with empirical studies. It could be noted from Fig. 3 that patients with I or II cement distribution were significantly risky to experience an AVF, implying that asymmetrical cement distribution would also lead to lateral stress concentration and finally bring about the risk of AVF. Then it could be observed from curves of Fig. 4 that patients with IV or V degree disc degeneration had more chance to endure an AVF and results of self-control chi-squared test (Table 4) further implied that AVF was prone to take place at the side of more degenerative discs. These findings supported our hypothesis that disc degeneration would lead to loss of mechanical absorption ability and forward stress concentration, and then induce the occurrence of AVF. Although Pfirrmann grades were found to be a potential predictive factor of AVF, it was worthy to note that the performance of PKP would alter the anatomy and spine dynamics, contributing to the changes in the disc

degeneration (32-35). Due to the lack of postoperative MRI in non-AVF group, this issue would be further worked on in the future. Besides, it could be found from Fig. 3 and Fig. 4 that most AVF took place within 10 months after PKP surgery. It might be resulted from anti-osteoporosis treatment that was firstly prescribed immediately after PKP surgery in most OVCF patients, so the obvious effect was not observed in a short time.

There were still several limitations in our study: (1) the retrospective nature would lead to selection bias and reduce power of our results; (2) some potential predictors might be neglected in our study, resulting in bias of our results; (3) limited sample size and short follow-up duration might lead to related bias and failure of observing the potential long-term effects of OVCF; and (4) only one novel finding was found in our study due to ample primary research, but abundant clinical data was provided in this study. Based on abovementioned deficits, more work would be done in the future to fill up these gaps.

CONCLUSIONS

The risk of AVF should be focused, especially when OVCF patients with the following predictors: (1) BMD < -3.45 ; (2) kyphosis angle at last follow-up $> 15.5^\circ$; (3) I or II cement distribution; and (4) IV or V disc degeneration. More prophylactic treatment should be prescribed for these patients to avoid the occurrence of AVF.

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