Retrospective Study

Nomogram for Predicting Intradiscal Cement Leakage Following Percutaneous Vertebroplasty in Patients with Osteoporotic Related Vertebral Compression Fractures

Bin-Yan Zhong, MD, Shi-Cheng He, MD, Hai-Dong Zhu, MD, Tao Pan, MD, Wen Fang, MD, Li Chen, MD, Jin-He Guo, MD, Gang Deng, MD, Guang-Yu Zhu MD, and Gao-Jun Teng, MD, PhD

From: Department of Radiology, Zhongda Hospital, Medical School, Southeast University, Nanjing, China

Address Correspondence: Gao-Jun Teng, MD, PhD Department of Radiology, Zhongda Hospital, Medical School, Southeast University, 87 Dingjiaqiao Rd Nanjing 210009, China Email: gjteng@vip.sina.com

Disclaimer: See pg ... Bin-Yan Zhong, Shi-Cheng He, Hai-Dong Zhu, and Tao Pan contributed equally to the project.
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Background: Intradiscal cement leakage (ICL) is a common complication following percutaneous vertebroplasty (PVP). However, the risk factors for such a complication are under debate and there is no accurate predictive nomogram to predict ICL.

Objectives: To establish an effective and novel nomogram for ICL following PVP in patients with osteoporotic-related vertebral compression fractures (OVCFs).

Study Design: This was a retrospective study approved by the Institutional Review Board of our institution.

Setting: This study consists of patients from a large academic center.

Methods: Patients with OVCFs who underwent their first PVP in our department between January 2007 and December 2013 were included in this study. All the potential risk factors of ICL after PVP were recorded. Univariate and multivariate analyses were used to identify the independent risk factors. The nomogram was then created based on the identified independent risk factors.

Results: A total of 241 patients and 330 vertebrae were included. The mean age of the patients was 73.5 (SD 7.9) years old, and the mean number of treated vertebrae was 1.4 per person. ICL was observed in 93 (28.2%) of the treated vertebrae. Greater fracture severity ($P = 0.016$), cortical disruption of the endplate ($P < 0.0001$), absence of Kummell's disease ($P = 0.010$), and higher computed tomography (CT) values ($P = 0.050$) were the independent risk factors for ICL.

Limitations: The main limitation of this study is that it is a retrospective study.

Conclusion: Greater fracture severity, cortical disruption of the endplate, absence of Kummell's disease, and higher CT values are the independent risk factors for ICL. The novel nomogram gives an accurate prediction of ICL.

Key words: Osteoporotic vertebral compression fracture, percutaneous vertebroplasty, intradiscal cement leakage, risk factors, prediction, nomogram

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Osteoporotic-related vertebral compression fractures (OVCFs) are a common cause of pain and disability, with approximately 1.4 million new fractures occurring annually worldwide (1). First introduced in 1987 by Galibert et al (2), percutaneous vertebroplasty (PVP) has been regarded as an effective treatment approach. It is widely used to treat painful OVCFs. Past debate over the usefulness of this procedure (3-6) has been minimized by more recent and current studies which demonstrate the effectiveness of PVP for painful OVCFs (4,7,8).

As with any invasive procedure, PVP is also associated with asymptomatic and symptomatic complications (9). Severe complications, such as neurologic deficits (10), paraplegia (11), cardiac perforation (12,13), and even death (14) have been reported. Many of these have been restricted to case reports. Cement leakage (CL) is the most frequently occurring complication associated with PVP, having an incidence varying from 5% to more than 80% (8,15-17). With the use of computed tomography (CT), the incidence is estimated at 63% to 87% (8,16,18). Yeom et al (18) divided CL into 3 different types in a typical way, while Tome-Bermejo et al (19) modified it into the following 4 types: through the basivertebral vein (type B), the segmental vein (type S), a cortical defect (type C), and intradiscal leakage (type D). Each type of CL is asymptomatic under most conditions. However, several studies have demonstrated a symptomatic type of CL (20-22).

Intradiscal cement leakage (ICL) has been associated with each of the Tome-Bermejo categories in new adjacent and non-adjacent vertebral compression fractures. Pain with this leakage can reduce the quality of patients' lives (22-26). The risk factors for ICL are still under debate (19,27-29). To date, there has been no effective nomogram to predict the risk of ICL. The purpose of this study is to identify the independent risk factors for ICL following PVP in patients with OVCFs. Our goal is to create a novel and effective nomogram able to accurately predict symptomatic ICLs in post PVP patients.

Methods

Patient Criteria

This retrospective cohort study was approved by the ethical review committees of our hospital. Patients with OVCFs who underwent their first PVP in our department between January 2007 and December 2013 were included in this study. Patients enrolled in this study met the following inclusion criteria: 1) acute VCFs from T5 to L5 based on the results of CT and magnetic resonance imaging (MRI) or CT and nuclear bone scan imaging if an MRI examination was contraindicated; 2) unrelieved, serious, and acute VCF-related focal spinal pain [defined as unrelieved by conservative therapy (analgesics, bed rest, and bracing) for at least 4 weeks]; 3) availability of complete imaging and medical record data; 4) age ≥ 55 years; and 5) compliance with follow-ups after the first treatment with PVP. The exclusion criteria were 1) any previous non-conservative treatments for VCFs; 2) PVP treatment for indications other than simple benign OVCFs; 3) incomplete imaging or medical record data; or 4) history of dementia, malignancy, or stroke (either before or after PVP).

PVP Procedure

All procedures were performed under local anesthesia using 2% lidocaine. PVP was performed under fluoroscopic guidance with a C-arm angiographic unit (Innova3100, GE Healthcare System or FD 20, Philips Medical) by 2 interventional radiologists (Gao-Jun Teng, Shi-Cheng He) using a unilateral transpedicle approach with a Murphy set (Cook, Inc., Bloomington, Indiana). Each of the 2 operators had more than 10 years of experience performing PVP in a standard, reproducible way, assuring consistency in treatment between each of the patients. An additional puncture was performed (bilateral transpedicular approach) if the cement did not distribute as intended. The injected cement was a mixture of 70% polymethylmethacrylate (PMMA) (Corinplast TM3, Corin, Inc., Gloucestershire, United Kingdom) and 30% sterilized barium powder (Dongfeng Chemical, Inc., Qingdao, China). The cement was injected into the vertebral body during the "toothpaste-like" phase to minimize the risks of extravasation. Patients were restricted to absolute bed rest for about 2 hours following the procedure to assure the cement had reached its definitive strength. CT scanning of all patients was performed within 3 days after the PVP procedure to assess the distribution of PMMA and to determine the presence or absence of ICL.

Radiographic Evaluation and Data Collection

All the imaging data were retrospectively reviewed with a PACS system (NEUSOFTPACS/ RIS, Shengyang Neusoft Co., Ltd., China) by 2 radiologists, each having more than 5 years of diagnostic imaging experience (Shi-Cheng He, Hai-Dong Zhu). Disagreements between the 2 radiologists were resolved by consensus. Intradiscal cement leakage was defined as the presence of cement within the intervertebral disc via a vertebral endplate as assessed by post-procedural CT scanning (18).

The following patient data were recorded: age, gender, CT values of the spine, fracture type (wedge, biconcave, or crush), presence of pre-existing OVCFs, number of treated vertebrae, the location (thoracolumbar junction, non-thoracolumbar junction), severity of the vertebral body fracture, the presence of Kummell's disease, preoperative presence of endplate cortical defects, and cemented vertebral body fraction (CVBF,

CVBF = ICV/VBV, where ICV is the volume of cement injected into the fractured vertebra and VBV is the vertebral body volume).

In this study, CT values were used to determine the degree of osteoporosis for each patient. The method of how to measure the CT values was introduced in our previously published study (25). According to Genant et al, (30) the severity of the treated vertebra was divided into 3 types, based on the percentage of vertebral body collapse, as either mild (20% – 25%), moderate (26% – 40%), or severe (> 40%) fractures. Kummell's disease, named as an intravertebral cleft, was identified by the presence of gas within the vertebral body (by CT) or an intravertebral cleft based on plain anteroposterior and lateral radiographs. On MRI, Kummell's disease demonstrates low T1-weighted and high T2-weighted signal (fluid signal) associated with the vertebral cleft, producing the characteristic "double line sign" (31).

Statistical Analysis

Statistical analyses to identify risk factors were performed using SPSS 18.0 for Windows (IBM Corporation, Somers, NY, USA). Each potential risk factor was assessed using univariate logistic regression analysis. Variables that were significantly related to presence of ICL in the univariate analysis ($P < 0.05$) were subsequently included in a multivariate logistic regression analysis. A nomogram was formulated based on the results of multivariate analysis and by the package of rms in R version 3.0.2. A P value of < 0.05 was considered statistically significant.

Results

From January 2007 to December 2013, a total of 241 patients with 330 vertebral body fractures were included in this study. A majority of patients were women (187) and the mean age of the patients was 73.5 (7.9) years old, with mean CT bone mineral density values of 66.1 (34.7), which was an indication of a relative degree of osteoporosis in the majority of patients. Among the 330 treated vertebrae, 208 (63.0%) of them were thoracolumbar vertebra and there were 83 (25.2%), 114 (34.5%), and 133 (40.3%) vertebrae regarded as mild, moderate, and severe fracture, respectively. The detailed characteristics of the patients are described in Table 1.

Based on the post-operative CT, 93 (28.2%) of the 330 treated vertebrae demonstrated an ICL. The clinical and radiological features of the ICL and non-ICL groups are shown in Table 2. After the univariate and multivariate analysis, greater fracture severity ($P = 0.016$), cortical disruption of the endplate ($P < 0.0001$), absence of Kummell's disease ($P = 0.010$), and higher CT values ($P = 0.050$) were demonstrated as the independent risk factors for ICL (Table 3). Based on the 4 identified independent risk factors, a novel nomogram was created to assess the probability of incurring an ICL in a deterministic way (Fig. 1).

Furthermore, we assessed the new OVCFs occurring after PVP and their relationship with ICLs. We found that 85 new vertebral fractures occurred in 66 patients (27.4%) during a follow-up of 924 (SD 654) days after the first PVP. Among them, 48 vertebrae (56.5%) developed new VCFs adjacent to the treated vertebra, more than half of which (26 vertebrae) exhibited ICL. Our previous studies identified ICL as an independent risk factor for new OVCFs following PVP regardless of adjacent or non-adjacent status (25).

Table 1. *Patient characteristics*.

No. patients	241
Gender	
Male	54 (22.4%)
Female	187 (77.6%)
Age (Year)	73.5 (7.9)
CT values (HU)	66.1 (34.7)
No. treated vertebrae	330
TL junction	208 (63.0%)
Non-TL junction	122 (37.0%)
Fracture type	
Wedge	175 (53.0%)
Biconcave	121 (36.7%)
Crush	34 (10.3%)
Pre-existing vertebral fracture	140 (42.4%)
Number treated vertebrae per session	
1	173 (52.4%)
2	104 (31.5)
≥ 3	53 (16.1%)
Fracture severity	
1	83 (25.2%)
2	114 (34.5%)
3	133 (40.3%)
Kummell's disease	53 (16.1%)
Cortical disruption of the endplate	90 (27.3%)
Intradiscal cement leakage	93 (28.2%)

Data are mean (SD) or number (%). CT = computed tomography. HU = Hounsfield unit. TL = thoracolumbar.

Discussion

Cement leakage is the most common complication following PVP and can be divided into 4 types (19). Among them, ICL occurred frequently and is usually clinically asymptomatic. In addition, more and more studies are finding that ICL is associated with new adjacent OVCFs (22-26). Several studies have reported risk factors for ICL. Their findings such as the presence of Kummell's disease however, were inconsistent (19,27,29). In our study, greater fracture severity ($P = 0.016$), cortical disruption of the endplate ($P < 0.0001$), absence of Kummell's disease ($P = 0.010$), and higher CT values ($P = 0.050$) were independent risk factors for ICL following PVP in patients with OVCFs.

Table 2. *Univariate analysis of risk factors for intradiscal cement leakage.*

Characteristic	ICL	No ICL	HR	95%CI	*P*-value *
Gender					
Male	20	54	1		
Female	73	183	0.928	0.520 – 1.659	0.802
Age (Years)					0.445
1st Quartile (< 69)	25	61	1		
2nd Quartile (69 – 73)	25	66	1.460	0.708 – 3.011	0.306
3rd Quartile (74 – 78)	27	53	1.349	0.656 – 2.774	0.415
4th Quartile (≥ 79)	16	57	1.815	0.881 – 3.738	0.106
CT values					0.044
1st Quartile (< 40 HU)	23	61	1		
2nd Quartile (40 – 63 HU)	28	57	1.914	0.892 – 4.110	0.096
3rd Quartile (63 – 83 HU)	29	53	2.494	1.181 – 5.265	0.017
4th Quartile (≥ 83 HU)	13	66	2.778	1.316 – 5.866	0.007
TL junction	66	142	0.611	0.364 – 1.026	0.063
Fracture type					0.469
1	45	130	1		
2	36	85	0.635	0.291 – 1.386	0.254
3	12	22	0.776	0.347 – 1.735	0.537
Preexisting fracture	39	101	1.028	0.633 – 1.671	0.910
Treated vertebra per session					0.418
1	54	119	1		
2	25	79	1.264	0.634 – 2.521	0.506
≥ 3	14	39	0.882	0.413 – 1.882	0.745
Fracture severity					0.001
1	23	60	1		
2	46	68	1.741	0.906 – 3.345	0.096
3	24	109	3.072	1.722 – 5.482	< 0.0001
Kummell's disease	27	26	0.301	0.164 – 0.552	< 0.0001
CVBF					0.941
1st Quartile (< 0.280)	23	65	1		
2st Quartile (0.280 – 0.369)	22	56	0.908	0.461 – 1.786	0.779
3st Quartile (0.370 – 0.481)	25	57	1.008	0.506 – 2.008	0.982
4st Quartile (≥ 0.482)	23	59	1.125	0.574 – 2.206	0.731
Cortical disruption of endplate	47	43	4.610	2.730 – 7.783	< 0.0001

*Univariate logistic regression analysis was used. The grouping of each parameter was based on the statistical meaning. ICL = intradiscal cement leakage. HR = hazard ratio. CI = confidence interval. CT = computed tomography. HU = Hounsfield unit. TL = thoracolumbar. CVBF = cemented vertebral body fraction.

In previous studies, Nieuwenhuijse et al (29) and Ding et al (27) reported that the presence of Kummell's disease was a risk factor for developing an ICL. They suggested that it was due to a frequently present connection between the intervertebral disc space and the intravertebral cleft (27,29). However, Tome-Bermejo et al (19) took the opposite opinion. They concluded that the presence of the Kummell's disease was a protective factor limiting or preventing an ICL (19). They speculated that an intravertebral cleft represented the structure of least resistance within the bone (19,32). Krauss et al (32) reported that the incidence of cement leakage was lower for fractured vertebral bodies with intravertebral clefts than for those without. Interestingly, Tanigawa et al (33) found that there was no statistical significance between the presence of an intravertebral cleft and an ICL. Our study demonstrated that the absence of Kummell's disease was an independent risk factor for development of an ICL. The presence of a necrotic cavity in the vertebral body promotes a more homogeneous and controlled filling of the fractured vertebral body, and the cement can be injected into the fractured vertebral body with lower pressure (19). As such, ICLs occur less often in the presence of Kummell's disease within the treated vertebral body.

Our study identified that cortical disruption of the endplate ($P < 0.0001$) and greater fracture severity ($P = 0.016$) are independent risk factors for ICL. These 2 risk factors have little controversy when referring to the prior published studies. Ding

et al (27) conducted a retrospective study with 292 patients. They explored the risk factors for different types of CL, and found that cortical disruption and greater fracture severity are strong risk factors for ICL (27). Tome-Bermejo et al (19) and Nieuwenhuijse et al (29) also reported similar results. Cortical disruption of the endplate provides a connection between the vertebral body and the intervertebral disc space, thereby providing a path of least resistance for the cement allowing it to leak into the intervertebral disc. The greater the fracture severity, the smaller the volume of the vertebral body. As such, the severely fractured vertebral body volume is insufficient to confine the injected cement. Therefore a severely fractured vertebral body has a greater probability of developing an ICL since it also has a greater chance of cortical disruption of an endplate.

Our study demonstrated that a higher CT value is an independent risk factor for ICL. Xie et al (28) found that patients with higher degree of osteoporosis had a lower chance of ICL. Bone mineral density (BMD) mea-

Table 3. *Multivariate analysis of risk factors for intradiscal cement leakage.*

Variable	B	HR	95%CI	*P*-value*
Cortical disruption of endplate				< 0.0001
0	0	1		
1	1.579	4.852	2.761 – 8.527	
Fracture severity				0.016
1	0	1		
2	0.449	1.567	0.754 – 3.254	0.229
3	0.947	2.578	1.349 – 4.928	0.004
Kummell's disease				0.010
0	0	1		
1	-0.898	0.407	0.206 – 0.806	
CT values (HU)				0.050
< 40	0	1		
40 – 63	0.832	2.297	0.981 – 5.377	0.055
63 – 83	1.024	2.783	1.210 – 6.401	0.016
≥ 83	1.085	2.958	1.307 – 6.695	0.009

*Multivariate logistic regression analysis was used. HR = hazard ratio. CI = confidence interval. CT = computed tomography. HU = Hounsfield unit.

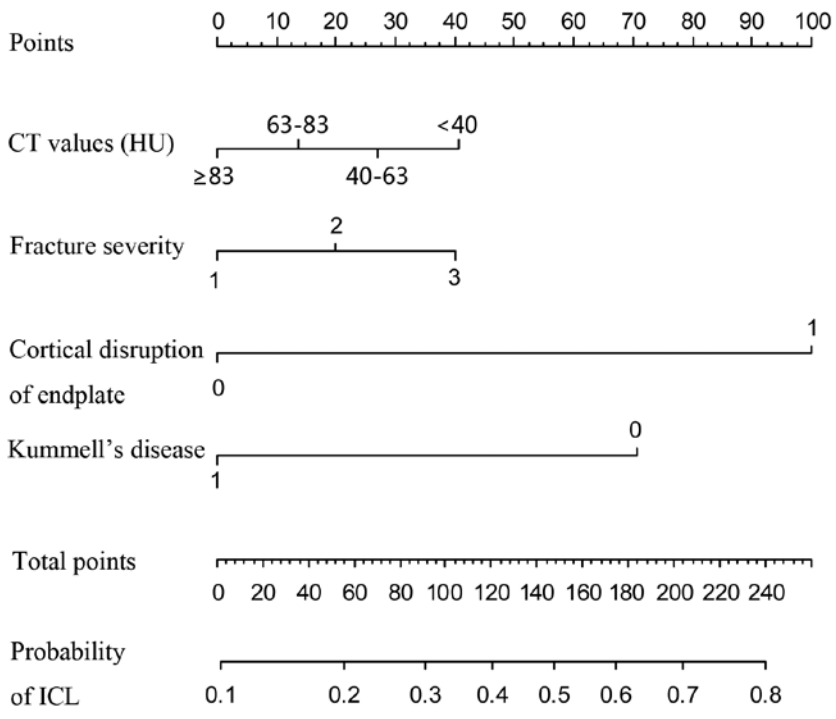

Fig. 1. *Nomogram for ICL following PVP in patients with OVCFs. To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the probability axes to determine the probability of ICL. CT: computed tomography; HU: Hounsfield unit; ICL: intradiscal cement leakage.*

sured by dual energy x-ray absorptiometry is a standard measurement for osteoporosis (34). However, the accuracy of BMD may be affected by several factors, such as spine degeneration and diffuse idiopathic skeletal hyperostosis, and will produce extra costs if additional BMD examinations are required (35,36). Several previous studies showed that the CT values of the vertebrae correlate with BMD in osteoporotic patients (35,37). Higher vertebral body CT values indicate a greater degree of trabecular bone per unit area and smaller spaces between the trabecular. As such, assuming the same dispersion rate and volume of PMMA, the smaller intertrabecular spaces would then require a greater area of cement spread (compared to an osteoporotic patient having larger intertrabecular spaces), thus increasing the risk of ICL (28).

Another frequently debated risk factor is injected cement volume. To assess the relationship between ICL and injected cement volume in treated vertebra with different volumes, we used the cemented vertebral body fraction (CVBF) parameter. In our study, CVBF is not a significant risk factor for ICL following PVP.

To our best knowledge, this study is the first attempt to predict the probability of ICL following PVP in patients with OVCFs by a novel nomogram. This method of creating a nomogram has been demonstrated as a reasonable, feasible approach in several disease models (38,39). Referring to the prior studies, we are unable to calculate the probability of ICL through the identified risk factors. Instead, we can only speculate on the probability of ICL. With this nomogram, we are able to calculate the probability of an ICL with an accurate and easily preformed approach. Through the nomogram, the probability of ICL following PVP ranges from about 10% in patients with none of the independent risk factors to more than 80% in individuals with all 4 of the independent risk factors.

This direct assessment can guide a physician's procedural approach in efforts to prevent ICL. For example, if cortical endplate disruption is seen preoperatively (ICL risk of 35%), the tip of the puncture needle could be directed away from the endplate fracture, or high viscosity cement could be deposited near the base of the fracture, and allowed to solidify, thereby blocking flow of the less viscous cement into the fracture, keeping it out of the disc space. Under circumstances of endplate fracture, physicians should inject the cement slowly and carefully under image guidance. With advanced fracture severity (Grade 3), the probability of ICL is about 40%. A preoperative CT scan with 3-D reconstruction will allow greater identification of area(s) of endplate disruption and allow for better preoperative planning. For those patients with a high probability of ICL, percutaneous kyphoplasty (PKP) could be considered. PKP can provide a lower pressured space for cement deposition, similar to the theory behind Kummell's disease as being a protective factor for ICL.

Our study has a few limitations. First, as a retrospective study, there may be some degree of selection bias. A prospective study is warranted to validate the accuracy of our nomogram and to expound upon ICL risk factors using a stricter approach. Second, since we did not vary the viscosity of our cement (injected in a "tooth-paste" phase), we were not able to assess whether differing cement viscosities could be a risk factor for ICL. From the literature, we know viscosity is crucial for reducing the risk of PMMA cement leakage (27,29,40). But, optimal cement viscosity is subjective, depending in part, on the experience of the surgeon (19). In our study, cement injection was performed during the "toothpaste-like" phase to minimize the risk of ICL.

Conclusion

In conclusion, our study demonstrated that a greater fracture severity, cortical disruption of the endplate, absence of Kummell's disease, and a higher BMD CT value are independent risk factors for developing ICL following PVP in patients with OVCFs. The novel nomogram we created objectively and accurately predicts the probability of an ICL. Further prospective studies are warranted to validate our nomogram.

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