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Research Paper

Epidemiology and detection of cement leakage in patients with spine metastases treated with percutaneous vertebroplasty: A 10-year observational study

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ABSTRACT

Objectives: To investigate the epidemiology of cement leaks and further develop an algorithm to detect the high risk of cement leaks among advanced cancer patients with metastatic spinal disease treated with percutaneous vertebroplasty.
Methods: This study retrospectively analyzed 309 patients with metastatic spinal disease treated with percutaneous vertebroplasty. Patients were randomly divided into a training group and a validation group. In the training group, 13 potential characteristics were analyzed for their abilities to predict cement leaks. Discal cement leakage and paravertebral cement leakage were excluded from the analysis. Those characteristics identified as having significant predictive value were used to develop a predictive algorithm. Internal validation of the algorithm was performed based on discrimination and calibration qualities.
Results: Overall, cement leaks occurred in 61.17% (189/309) patients. Among the 13 characteristics analyzed, younger age (P = 0.03), extravertebral bone metastases (P = 0.02), increased number of treated vertebrae levels (P < 0.01), and cortical osteolytic destruction in the posterior wall (P = 0.01) were included in the algorithm. This algorithm generates a score between 0 and 16 points, with higher scores indicating a higher risk of cement leakage. The area under the receiver operating characteristic curve (AUROC) value for the algorithm was 0.75 in the training group and 0.69 in the validation group. The mean correct classification rates for the training and validation groups were 73.5% and 64.9%, respectively, and the corresponding P-values of the goodness-of-fit test were 0.70 and 0.50.
Conclusions: Cement leaks are common in patients with metastatic spinal disease treated with percutaneous vertebroplasty. The present study proposed and internally validated an algorithm that can be used to screen patients at high risk of cement leakage.

1. Introduction

Metastatic spinal disease is a serious complication that presents in advanced cancer patients, occurring in greater than 30% of all cancer patients [1]. The incidence of metastatic spinal disease is expected to increase over the next 5 years to at least 50% due to improved primary cancer treatments and prolonged survival times [2], and the population of patients presenting with metastatic spinal disease is estimated to reach 15 million globally. Current treatment strategies for this disease include surgery, chemotherapy, and radiation, which are often used in combination [3]. Among existing therapeutic methods, the decompressive surgical treatment of metastatic spinal disease, followed by radiotherapy, was considered a first-line treatment [4]. Radiation causes DNA damage and negatively affects the performance of cancer cell organelles [5], providing developmental control of the metastatic focus. However, patients treated with this technique typically require long recovery periods and suffer from delays in the receipt of subsequent radiation and other systemic cancer treatments. Percutaneous vertebroplasty, which is a minimally invasive surgery, has been shown to be effective for the treatment of patients with severe and intractable back pain, especially among those with relatively short-term life expectancies or who were determined to be unsuitable candi-

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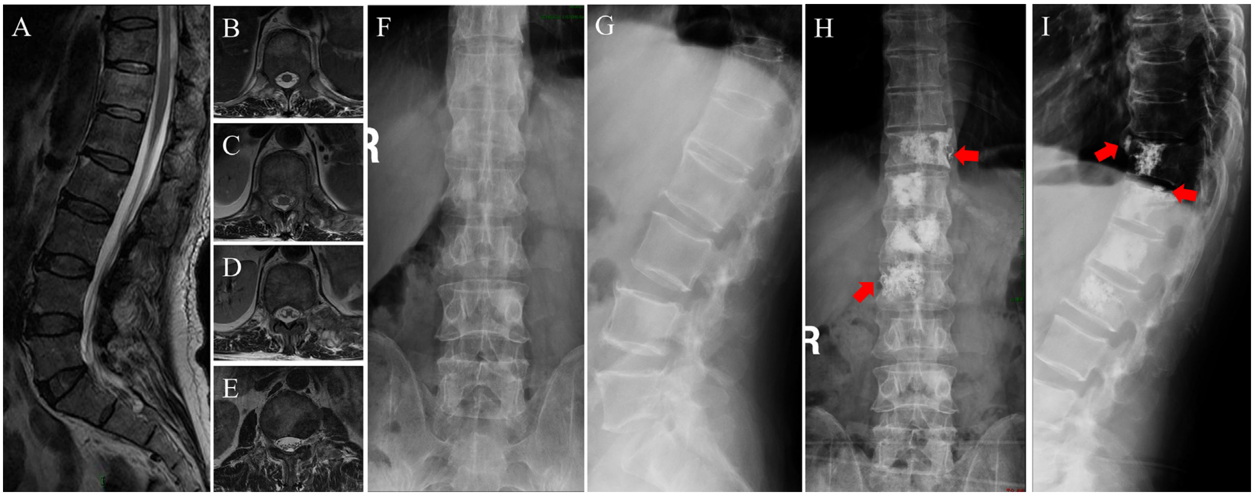

Fig. 1. A 59-year-old man with spine metastases due to urothelial carcinoma: A. Preoperative magnetic resonance imaging (MRI) on the sagittal plane showed spine metastases at T11, T12, L1, and L2. B–E. Preoperative MRI on the transverse plane showed spinal metastasis at T11 (B), T12 (C), L1 (D), and L2 (E). F. Preoperative anteroposterior X-ray. G. Preoperative lateral X-ray. H. Postoperative anteroposterior X-ray showed vascular cement leakage at T11 and L2 (red arrows). I. Postoperative lateral X-ray showed paravertebral cement leakage at T11 and discal cement leakage at T12. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dates for decompressive surgery due to poor overall health. Percutaneous vertebroplasty is less invasive than decompressive surgery, and patients who undergo percutaneous vertebroplasty do not require long recovery times and can receive timely subsequent systemic cancer treatments. Consequently, the treatment paradigm for patients with metastatic spinal disease has shifted toward this minimally invasive technique [6].

However, cement leaks are a common complication of percutaneous vertebroplasty [7]. Most cement leakage, especially discal cement leakage and paravertebral cement leakage, are not associated with the development of serious symptoms. However, some types of cement leakage, such as intraspinal canal cement leakage, can result in devastating neurological deficits [8]. Cement can also leak into blood vessels, which can cause pulmonary embolism or multiple cardiac perforations [9]. Existing studies on cement leaks have primarily focused on patients with osteoporosis vertebral compression fractures. Due to the inadequate investigation of population-specific risk characteristics among patients with metastatic spinal disease, specific recommendations for preventing and reducing cement leakage in this population have not been clearly proposed.

Therefore, this study aimed to investigate the epidemiology of cement leakage and assess the risk characteristics associated with cement leakage in patients with metastatic spinal disease. We further developed and internally validated an algorithm for identifying an increased risk of cement leakage among the population of advanced cancer patients with metastatic spinal disease who are treated with percutaneous vertebroplasty.

2. Patients and methods

2.1. Inclusion and exclusion criteria

We retrospectively analyzed 309 patients with metastatic spinal disease who were treated with percutaneous vertebroplasty at a medical teaching hospital between January 2010 and January 2019. The inclusion criteria were as follows: (1) patients treated with percutaneous vertebroplasty at the orthopedic department in our hospital; (2) patients older than 18 years; (3) patients with mixed or osteolytic lesions in the involved vertebrae; (4) patients with severe or intractable back pain due to metastatic spinal disease; and (5) patients with complete records. The exclusion criteria were as follows: (1) patients treated with conservative treatments or decompressive surgery; (2) patient with intramedullary metastases; (3) patients with vertebral fractures due to primary tumor, trauma, osteoporosis, or angioma at the spine; (4) patients with spinal nerve compression or severe radiculopathy and corresponding declines in Frankel grades; (5) patients with infections of the involved vertebrae and corresponding skin; and (6) patients with uncorrectable coagulation disorders. Radiological tools, including magnetic resonance imaging or myelography, were used to confirm the presence of metastatic spinal disease. Indications for surgery were patients with severe or intractable pain whose symptoms were not significantly relieved after conservative treatments. Patients whose health was too poor to receive open surgery were also considered for percutaneous vertebroplasty treatment. If a patient received multiple rounds of percutaneous vertebroplasty, this study only analyzed the information associated with the first operation. The Ethics Committee Board of the medical teaching hospital approved this study. Patient consent was waived for the review of medical records and images because all data were anonymized and retrospectively analyzed. This study complied with the Declaration of Helsinki.

2.2. Definition of cement leakage

Cement leaks were evaluated using post-procedural computed tomography (CT) examinations, X-ray, or fluoroscopy images recorded at the end of the surgery. Based on the cement leak location, cement leaks were classified into three types, which were developed and revised from those described by Yeom et al. [10]: vascular cement leakage, cortical cement leakage, and intraspinal canal cement leakage. Total cement leakage was defined as all patients with any type of cement leakage that occurred at the involved vertebrae. Vascular cement leakage included cement leaks into veins, such as the anterior external venous plexus or the basivertebral veins. Cement-associated pulmonary embolisms represent a specific type of vascular cement leakage, which were evaluated using chest radiographs or CT examinations following surgery. Cortical cement leakage was divided into discal and paravertebral cement leakage. Intraspinal canal cement leakage was defined as patients with epidural cement leakage. The clinical sig-

Table 1
Patients' basic demographics.

Characteristics	Patients (N = 309)
Age (years)	
<50	11.97% (37/309)
≥50 and < 60	21.68% (67/309)
≥60 and < 70	28.48% (88/309)
≥70 and < 80	24.92% (77/309)
≥80	12.94% (40/309)
Sex	
Male	58.58% (181/309)
Female	41.42% (128/309)
Primary cancer types	
Slow growth	28.80% (89/309)
Moderate growth	14.56% (45/309)
Rapid growth	56.63% (175/309)
Preoperative treatments	
Topical treatments	34.95% (108/309)
Systematic treatments	34.95% (108/309)
No treatment	30.10% (93/309)
Presence of visceral metastasis	
Yes	16.18% (50/309)
No	22.33% (69/309)
Unknown	61.49% (190/309)
Extravertebral bone metastases	
Yes	53.40% (165/309)
No	16.50% (51/309)
Unknown	30.10% (93/309)
Number of treated vertebrae levels	
1	38.83% (120/309)
2	24.92% (77/309)
3	15.86% (49/309)
≥4	20.39% (63/309)
Vertebrae collapse	
No collapse	63.43% (196/309)
Less then 50%	24.27% (75/309)
More than 50%	12.30% (38/309)
Cortical osteolytic destruction in the posterior wall	
Yes	42.72% (132/309)
No	57.28% (177/309)
Vertebral endplate fracture	
Yes	17.15% (53/309)
No	82.85% (256/309)
The Bilsky Scale	
0	77.67% (240/309)
1	10.03% (31/309)
2	10.36% (32/309)
3	1.94% (6/309)
Appearance of spine metastases	
Mixed lesions	16.18% (50/309)
Osteolytic lesions	83.82% (259/309)
Load-bearing lines of the spine	
Normal	89.00% (275/309)
Abnormal	11.00% (34/309)

nificance of cement leakage was observed and recorded, including radicular pain, neurological deficits, or dyspnea. A case report is shown in Fig. 1.

2.3. Potential risk characteristics for predicting cement leakage

We identified potential risk characteristics after carefully reviewing the published literature and the availability of characteristics in medical records and radiographic images. We selected 13 potential characteristics that were screened to predict cement leakage; we did not include the occurrence of discal and paravertebral cement leakage in this analysis in order to improve the clinical meaningfulness and impact of the study. These characteristics include age (<50 years vs. ≥ 50 years; <60 years vs. ≥ 60 years; <70 years vs. ≥ 70 years; and < 80 years vs. ≥ 80 years); sex (male vs. female); primary cancer types (rapid growth, moderate growth, and slow growth) [11]; preoperative treatments (local treatments, systematic treatments, and no treatment); the presence of visceral metastasis (yes, no, and unknown); extravertebral bone metastases (yes, no, and unknown); the number of treated vertebrae levels (1, 2, 3, and ≥ 4); vertebrae collapse (no collapse, <50%, ≥50%) [12]; cortical osteolytic destruction in the posterior wall (yes vs. no); vertebral endplate fracture (yes vs. no); the Bilsky Scale score (0, 1, 2, and 3) [13]; the appearance of spine metastases (mixed lesions vs. osteolytic lesions); and load-bearing lines of the spine (normal vs. abnormal). The evaluated primary cancer types included rapid growth cancers, such as lung, stomach, liver, colon, and unknown cancers; moderate growth cancers, such as kidney and uterus, among others; and slow growth cancers included breast, thyroid, prostate, and others. Local treatments included radiotherapy, and systemic treatments included chemotherapy. The Bilsky Scale is currently used to assess the severity of spinal cord compression due to metastatic cancers [13]. Generally, a higher score indicates more serious spinal cord compression: "0" indicates bone-only disease, "1" indicates epidural involvement without cord compression, "2" indicates spinal cord compression with visible cerebrospinal fluid around the spinal cord, and "3" indicates spinal cord compression without visible cerebrospinal fluid around the spinal cord. In subgroup analyses, we analyzed the potential risk characteristics for predicting vascular cement leakage, discal cement leakage, and intraspinal canal cement leakage across the entire sample, including patients with discal and paravertebral cement leakage.

Table 2
Locations of cement leakage.

Leakage locations	Occurrence rates (n = 309)
Vascular cement leakage	28.48% (88/309) [1]
Cortical cement leakage	
Discal cement leakage	18.45% (57/309)
Paravertebral cement leakage	23.95% (74/309)
Intraspinal canal cement leakage	10.68% (33/309) [2]
Overall cement leakage	61.17% (189/309)

Notes: [1] indicates 1 patient with mild dyspnea; [2] indicates 3 patients with radicular pain or neurological deficits.

2.4. Development of an algorithm to predict overall cement leakage

Patients (n = 309) were randomly divided into a training group (n = 155) and a validation group (n = 154). The training group was used to develop the algorithm, and the validation group was used to validate the algorithm. In the training group, a multiple logistic regression model was generated to identify risk characteristics associated with cement leakage. Among the 13 evaluated risk characteristics, four characteristics that were significantly associated with cement leakage were included in the algorithm based on the multiple logistic regression. A score was assigned to each significant characteristic according to the odds ratios (ORs), which were rounded to the nearest integer. The total score for each patient assessed using the algorithm was the sum of all scores assigned for the four included characteristics. The occurrence rates for cement leakage were calculated for each overall score. Three risk groups were determined based on the occurrence rate of cement leakage associated with each overall score.

2.5. Validation of the algorithm to predict cement leakage

The internal validation of the algorithm was achieved using the validation group. The algorithm was validated according to its discrimination and calibration characteristics. Discrimination was defined as the ability to separate patients who experienced cement leakage from those who did not experience cement leakage. In this study, the area under the receiver operating characteristic curve (AUROC) was evaluated to determine the discrimination ability

Table 3
Univariate and multivariate analysis of risk characteristics for cement leakage in advanced cancer patients with metastatic spinal disease treated with percutaneous vertebroplasty in the training group (n = 155).

Variables	n	Simple logistic regression		Multiple logistic regression	
		OR (95% CI)	P	OR (95% CI)	P
Age (years)	155				
<50	11	0.83 (0.62–1.13)	0.23	0.65 (0.45–0.96)	0.03
≥50 and <60	36				
≥60 and <70	48				
≥70 and <80	42				
≥80	18				
Sex					
Male	93	1.39 (0.71–2.73)	0.33	2.09 (0.83–5.29)	0.12
Female	62				
Primary cancer types					
Slow growth	47	0.89 (0.61–1.29)	0.53	1.10 (0.61–2.00)	0.75
Moderate growth	28				
Rapid growth	80				
Preoperative treatments					
Topical treatments	55	0.91 (0.61–1.35)	0.64	1.05 (0.65–1.71)	0.84
Systematic treatments	47				
No treatment	53				
Presence of visceral metastasis					
Yes	17	1.12 (0.68–1.81)	0.68	0.89 (0.49–1.63)	0.71
No	41				
Unknown	97				
Extravertebral bone metastases					
Yes	80	1.33 (0.92–1.91)	0.13	1.71 (1.08–2.72)	0.02
No	22				
Unknown	53				
Number of treated vertebrae levels					
1	58	1.88 (1.38–2.56)	<0.01	1.93 (1.38–2.71)	<0.01
2	44				
3	20				
≥4	33				
Vertebrae collapse					
No collapse	98	0.92 (0.57–1.51)	0.74	1.73 (0.75–4.00)	0.20
Less then 50%	40				
More than 50%	17				
Cortical osteolytic destruction in the posterior wall					
Yes	67	2.04 (1.04–3.99)	0.04	3.26 (1.26–8.45)	0.01
No	88				
Vertebral endplate fracture					
Yes	31	0.74 (0.32–1.76)	0.50	0.33 (0.09–1.27)	0.10
No	124				
The Bilsky Scale					
0	118	1.05 (0.67–1.65)	0.84	0.88 (0.45–1.72)	0.70
1	22				
2	11				
3	4				
Appearance of spine metastases					
Mixed lesions	28	0.64 (0.28–1.47)	0.29	0.23 (0.05–1.10)	0.07
Osteolytic lesions	127				
Load-bearing lines of the spine					
Normal	136	0.87 (0.31–2.45)	0.80	0.56 (0.14–2.18)	0.40
Abnormal	19				

Abbreviations: OR, odds ratio; CI, confidential interval.

of the algorithm [14]. Generally, a higher AUROC value indicates better discrimination, with values greater than 0.7 indicating a useful algorithm, greater than 0.8 indicating a good algorithm, and greater than 0.9 indicating an excellent algorithm. The calibration was defined as the consistent ability of the algorithm to predict cement leakage risk compared with the observed risk of cement leakage. In the study, the Hosmer-Lemeshow goodness-of-fit test was used to evaluate the calibration. A P-value greater than 0.05 obtained from this test indicates good agreement between the predicted and observed cement leakage risk.

2.6. Statistical analysis

Simple and multiple logistic regression models (with stepwise selection) were generated to screen all risk characteristics for predicting cement leakage. Significant characteristics were included in the algorithm and were used to develop the algorithm. The algorithm was validated by discrimination and calibration analyses. The correct classification rate, sensitivity, specificity, false-positive, and false-negative rates of the algorithm were also calculated. All analyses were performed in SAS 9.2 software**.** A P-value < 0.05 was considered significant.

3. Results

3.1. Patient's basic demographic information

The majority of patients were older than 60 years (66.34%, Table 1). Among the entire patient cohort, 58.58% of patients were men, and 41.42% were women. Rapid growth cancers were the

Table 4
A risk algorithm for predicting cement leakage in advanced cancer patients with metastatic spinal disease treated with percutaneous vertebroplasty.

Included significant characteristics	OR	Assigned scores
Age (years)		
<50	0.65	4
≥50 and <60		3
≥60 and <70		2
≥70 and <80		1
≥80		0
Extravertebral bone metastases		
Yes	1.71	0
No		2
Unknown		4
The number of treated vertebrae levels		
1	1.93	0
2		2
3		4
≥4		6
Cortical osteolytic destruction in the posterior wall		
Yes	3.26	3
No		0

Notes: If a 56-year-old (3 points) patient with extravertebral bone metastases (0 points) and cortical osteolytic destruction in the posterior wall (3 points) is treated with 2 vertebrae levels (2 points), then the total score of the patient was 8 (3 + 0 + 3 + 2).
Abbreviations: OR, odds ratio.

most common type (56.63%), followed by slow growth cancers (28.80%). Among all patients, 69.9% received local or systemic treatments before surgery. The radiological data showed that most patients presented with extravertebral bone metastases (53.40%), one treated vertebrae level (38.83%), no vertebrae collapse (63.43%), no cortical osteolytic destruction in the posterior wall (57.28%), no vertebral endplate fracture (82.85%), a Bilsky Scale score of 0 (77.67%), osteolytic lesions (83.82%), and normal load-bearing lines of the spine (89.00%). Due to incomplete records, nine patients were excluded from the analysis.

3.2. Epidemiology of cement leakage

Among all patients, 61.17% of patients experienced cement leakage (Table 2), including 39.48% with one cement leak, 17.15% with two cement leaks, and 4.53% with at least three cement leaks. Among all patients, vascular cement leakage accounted for 28.48% of cases, discal cement leakage accounted for 18.45%, paravertebral cement leakage accounted for 23.95%, and intraspinal canal cement leakage accounted for 10.68%.

3.3. Analysis of potential risk characteristics for cement leakage

Thirteen potential risk characteristics were used to analyze cement leakages in the training group, excluding discal and paravertebral cement leakage. We found that age (OR: 0.65, 95% confidence interval [CI]: 0.45–0.96, P = 0.03), extravertebral bone metastases (OR:1.71, 95% CI: 1.08–2.72, P = 0.02), number of treated vertebrae levels (OR: 1.93, 95% CI: 1.38–2.71, P < 0.01), and cortical osteolytic destruction in the posterior wall (OR: 3.26, 95% CI: 1.26–8.45, P = 0.01) were significant predictive factors according to the multiple logistic regression analysis (Table 3). Therefore, these four risk characteristics were included in the algorithm.

Across the entire patient cohort, the multiple regression analysis identified the following risk characteristics as being significantly predictive for vascular cement leakage: age (OR: 0.74, 95% CI: 0.58–0.96, P = 0.02), primary cancer type (OR: 1.49, 95% CI: 1.00–2.24, P = 0.05), extravertebral bone metastases (OR: 1.40, 95% CI: 1.01–1.93, P = 0.04), the number of treated vertebrae levels (OR: 1.78, 95% CI: 1.41–2.25, P < 0.01), and the appearance of spine metastases (OR: 0.29, 95% CI: 0.10–0.86, P = 0.03; Supplementary Table 1). The significant risk characteristics associated with intraspinal canal cement leakage included sex (OR: 2.83, 95% CI: 1.09–7.31, P = 0.03), the number of treated vertebrae levels (OR: 1.44, 95% CI: 1.03–2.02, P = 0.03), and cortical osteolytic destruction in the posterior wall (OR: 3.60, 95% CI: 1.40–9.28, P < 0.01; Supplementary Table 2). In the multiple logistic regression analysis, only load-bearing lines of the spine (OR: 3.58, 95% CI: 1.23–10.43, P = 0.02) was found to be a significant predictor of discal cement leakage (Supplementary Table 3), whereas vertebral endplate fracture (OR: 2.56, 95% CI: 0.95–6.92, P = 0.06), which has been associated with discal cement leakage in other studies, approached significance in our study.

3.4. Development of the algorithm to predict overall cement leakage

Scores for the included significant risk characteristics were assigned according to the ORs (Table 4), with all ORs rounded to the nearest integer. The total score for each patient was the sum score of all characteristics included in the algorithm. For example, a 56-year-old (3 points) patient with extravertebral bone metastases (0 points) and cortical osteolytic destruction in the posterior wall (3 points) who was treated at two vertebrae levels (2 points) would receive a total score of 8 (3 + 0 + 3 + 2). The numbers of patients who received each total score value were normally distributed in both the training and validation groups (Fig. 2). The rates of overall cement leakage were calculated for each total score value. Generally, higher scores were associated with higher rates of cement leakage (Table 5 and Fig. 3). Patients were divided into three risk groups according to the risk of total cement leakage: In Group A, which included total scores from 0 to 7, 18.39% of patients experienced cement leaks. In Group B, which included total scores from 8 to 11, 43.18% of patients experienced cement leaks. In Group C, which included total scores from 12 to 16, 75.00% of patients experienced cement leaks.

3.5. Validation of the algorithm to predict overall cement leakage

Internal validation of the algorithm was achieved for both groups. The mean AUROC values for the algorithm were 0.75 in the training group (Fig. 4**A**) and 0.69 in the validation group (Fig. 4**B**). The mean correct classification rates for the training and validation groups were 73.5% and 64.9%, respectively, and the mean P-values obtained from the goodness-of-fit test were 0.70 and 0.50 (Table 6). The sensitivity, specificity, false-positive rate, and false-negative rate are presented in Table 6. Fig. 5 shows the observed and predicted event probabilities for the training and validation groups which demonstrated that the actual cement leakage risk and the predicted cement leakage risk were similar.

4. Discussion

Previously, we proposed an algorithm that could predict cement injection volumes in patients with metastatic spinal disease before being treated with percutaneous vertebroplasty [15]. In addition, other algorithms for predicting survival or functional outcomes in patients with metastatic spinal disease have also been developed [16–19], such as the Tomita scoring system and the Tokuhashi scoring system [16]. Generally, these algorithms have been useful for stratifying patients at different risks of undesirable survival or functional prognosis, and therapeutic strategies have been determined according to the stratification. However, no research has yet developed an algorithm to predict cement leakage in advanced cancer patients with metastatic spinal disease treated with percutaneous vertebroplasty. The identification of cement

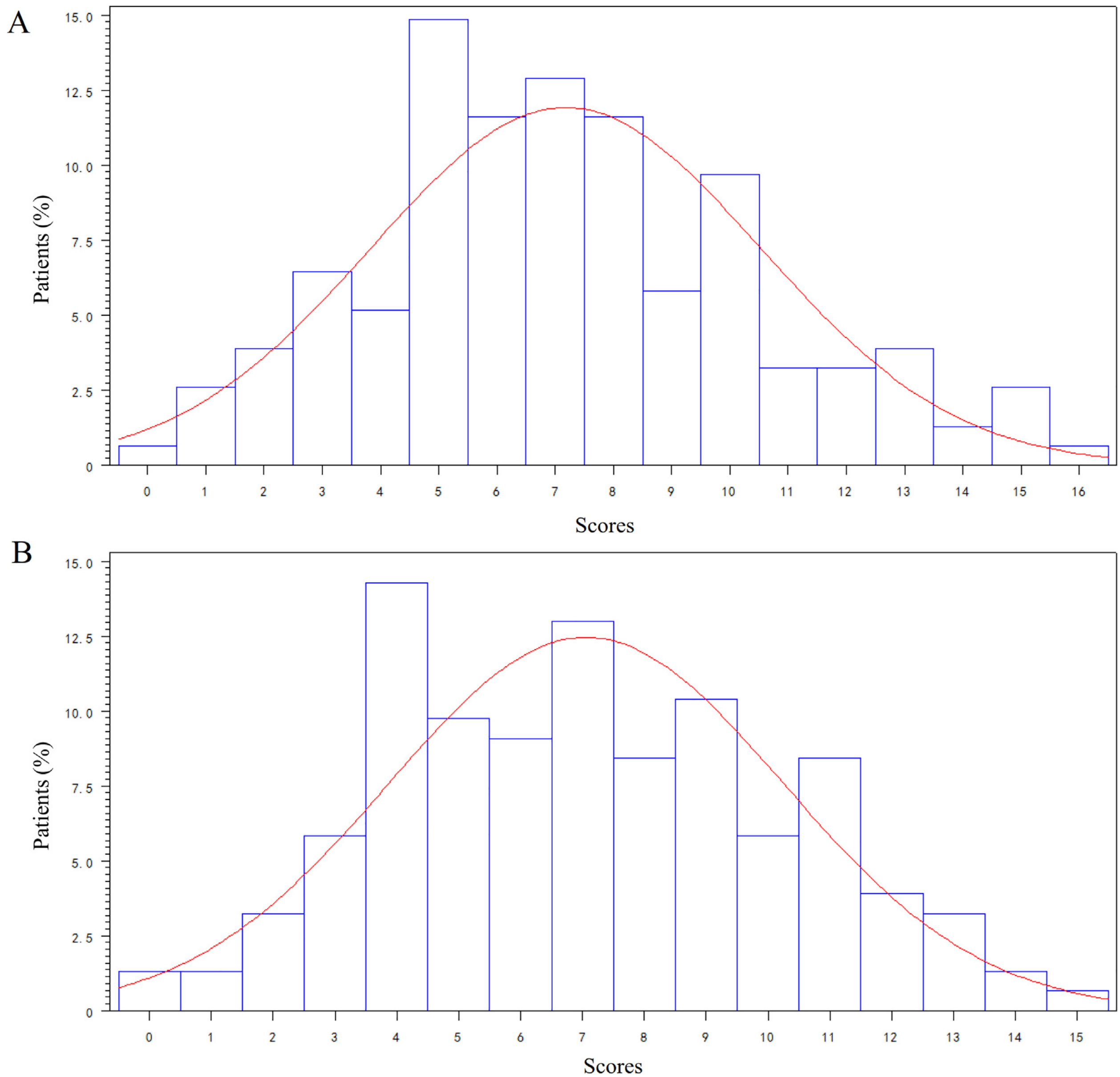

Fig. 2. Histogram plot showing the numbers of patients assigned to each score: A. The training group. B. The validation group. The red line indicates that the numbers of patients with different scores were normally distributed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

leakage risk would facilitate the prevention and reduction of cement leakage occurrence.

A cement leakage prediction algorithm should be developed by including risk characteristics that are clearly associated with cement leakage. A recent *meta*-analysis showed that patients with low cement viscosity, cortical disruption, intravertebral clefts, or high injected cement volumes were more likely to experience cement leakage, based on an analysis of data from 22 studies [20]. Unfortunately, across all 22 studies, only one study specifically enrolled patients with metastatic spinal disease, whereas the remaining studies enrolled patients with osteoporotic vertebral compression fractures, indicating that these studies were initially designed for patients with vertebral fractures due to osteoporosis and were not focused on patients with metastatic spinal disease. The extensive destruction of the vertebral cortex or pedicle caused by metastatic spinal tumors could lead to a higher incidence of cement leakage in metastatic spinal disease compared with the degree of vertebral compression fractures due to osteoporosis [21]. Consequently, the incidence of cement leakage in patients with osteoporotic vertebral compression fractures cannot be considered representative of the incidence of cement leakage in patients with metastatic spinal disease after being treated with percutaneous vertebroplasty. Therefore, the epidemiology of cement leakage in metastatic spinal disease remains unclear due to a lack of uniform evaluations and or large datasets.

In this study, we systematically analyzed the epidemiology of cement leakage, specifically in advanced cancer patients with metastatic spinal disease. We found that the overall occurrence rate of cement leakage was as high as 61.17%. The reported incidence of overall cement leakage due to percutaneous vertebroplasty has varied from 9.94% to 76.83% [22,23], and the reported incidence of pulmonary embolism has ranged from 4.6% to 23.0% [23] in other studies. Intraspinal canal cement leakage was found in 10.68% of patients in our study, which was consistent with the reported incidence in other studies. Mikami et al. [24] reported a 12% incidence of posterior canal cement leakage after analyzing 69 vertebral metastases treated with

Table 5
Distribution of patients, rates of cement leakage, and risk groups across each score in the training group.

Scores	Patients (n = 155)	Cement leakage		Groups	Cement leakage	P
		No (%)	Yes (%)			
0	1	100.00% (1/1)	0.00% (0/1)	A	18.39% (16/87)	<0.01
1	4	100.00% (4/4)	0.00% (0/4)	A		
2	6	66.67% (4/6)	33.33% (2/6)	A		
3	10	100.00% (10/10)	0.00% (0/10)	A		
4	7	85.71% (6/7)	14.29% (1/7)	A		
5	20	85.00% (17/20)	15.00% (3/20)	A		
6	18	77.78% (14/18)	22.22% (4/18)	A		
7	21	71.43% (15/21)	28.57% (6/21)	A		
8	16	56.25% (9/16)	43.75% (7/16)	B	43.18% (19/44)	
9	9	66.67% (6/9)	33.33% (3/9)	B		
10	12	33.33% (4/12)	66.67% (8/12)	B		
11	7	85.71% (6/7)	14.29% (1/7)	B		
12	10	30.00% (3/10)	70.00% (7/10)	C	75.00% (18/24)	
13	5	20.00% (1/5)	80.00% (4/5)	C		
14	3	0.00% (0/3)	100.00% (3/3)	C		
15	5	40.00% (2/5)	60.00% (3/5)	C		
16	1	0.00% (0/1)	100.00% (1/1)	C		
Total	155	102	53	N.A	34.19% (53/155)	N.A.

Abbreviations: N.A., not applicable.

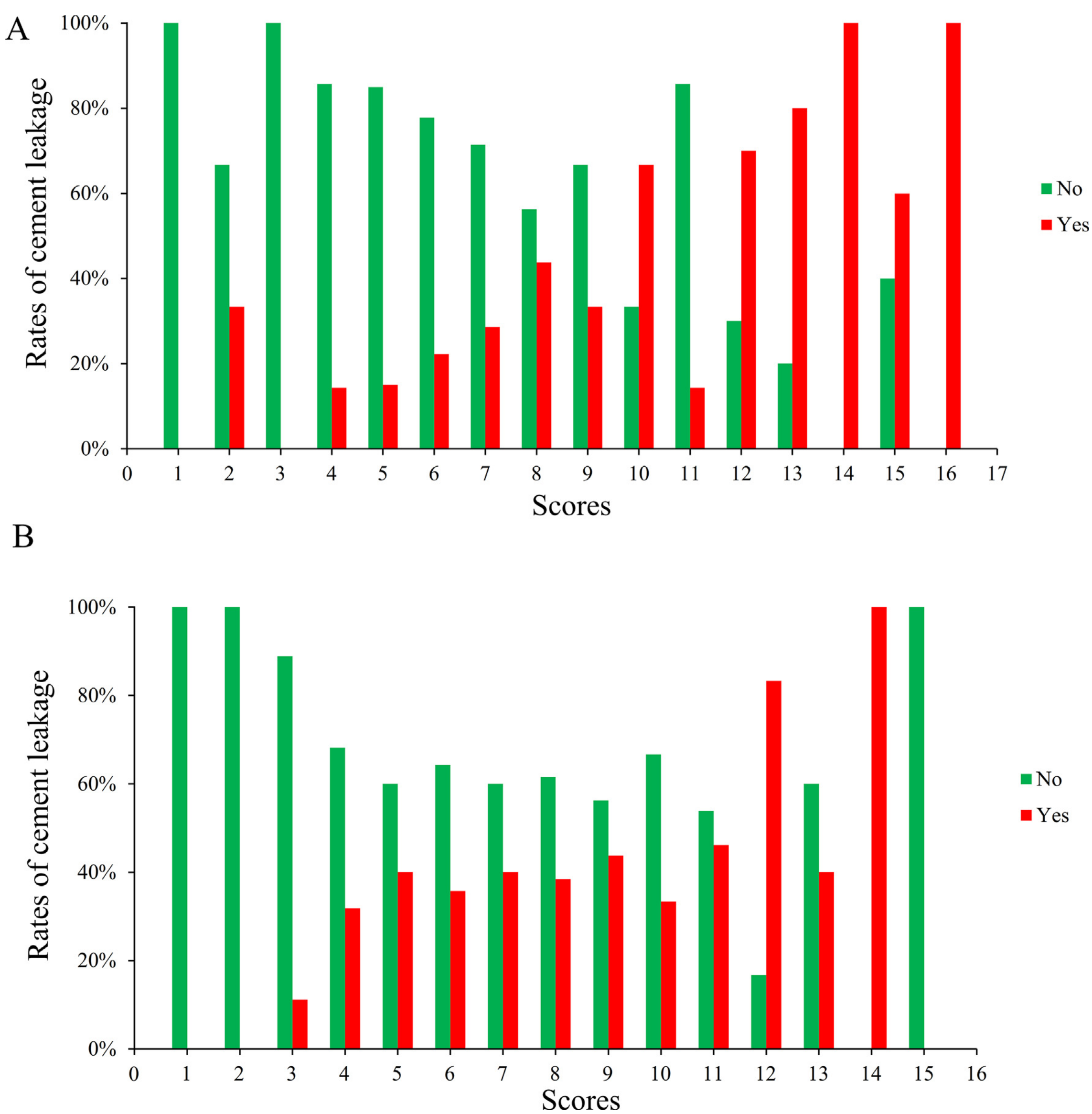

Fig. 3. The rates of overall cement leakage for each score: A. The training group. B. The validation group. The green columns indicate the rates of no cement leakage. The red columns indicate the rates of cement leakage. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

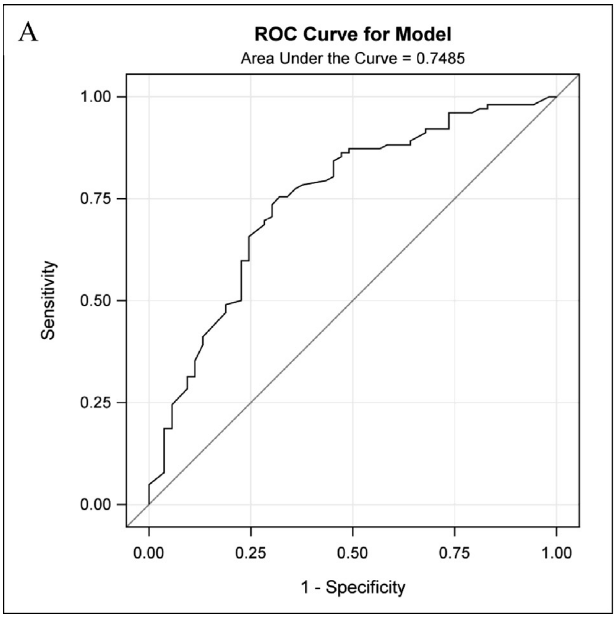

Fig. 4. The receiver operating characteristic (ROC) curve for the algorithm: A. The training group (area under the ROC curve [AUROC] = 0.75); B. The validation group (AUROC = 0.69).

Table 6
The AUROC, CCR, sensitivity, specificity, FPR, and FNR of the algorithm for the training and validation groups.

Evaluation Analysis	AUROC	CCR	Sensitivity	Specificity	FPR	FNR	Goodness-of-Fit Test
Training group	0.75	73.5%	52.8%	84.3%	36.4%	22.5%	0.70
Validation group	0.69	64.9%	54.4%	71.1%	47.5%	27.4%	0.50

Abbreviations: AUROC, area under the receiver operating characteristic curve; CCR, correct classification rate; FPR, false-positive rate; FNR, false-negative rate.

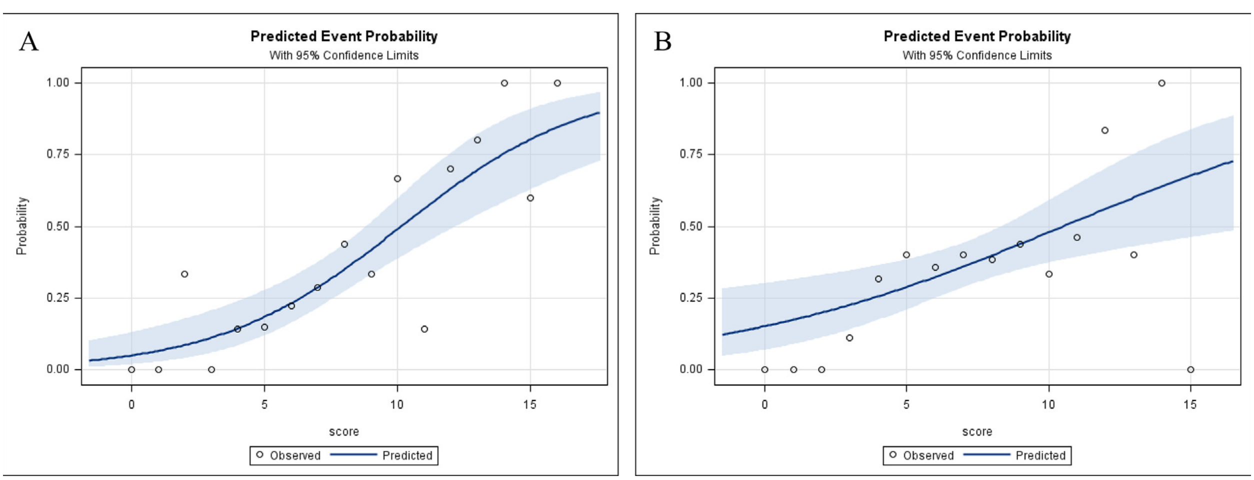

Fig. 5. The observed versus predicted event probability, according to the algorithm: A. The training group. B. The validation group. The blue line indicates the predicted probability of cement leakage. The black hollow dots indicate the observed probability of cement leakage for each score. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

percutaneous vertebroplasty. Tumor invasion and extensive bone destruction might be able to predict the rate of spinal canal cement leakage among patients with spine metastases. These results indicated that cement leakage was common among advanced cancer patients with metastatic spinal disease who were treated with percutaneous vertebroplasty; however, the clinical manifestations of this complication were primarily asymptomatic. In the present study, three patients presented with radicular pain or neurological deficits. In previous studies that have reported the occurrence rates of cement leakage among cancer patients with spine metastases, the reported incidence has ranged from 14.8% to 65.0% [25–29]. However, the sample sizes included in these studies have been limited, ranging from 30 to 153 [25,27–30]. Insufficient sample sizes can result in epidemiology outcomes that are not representative of the whole population, and the statistical power to obtain underlying answers would also be limited. To our knowledge, our 10-year observational study is the first to enroll a large, specific population of patients with metastatic spinal disease.

We analyzed 13 risk characteristics that are potentially associated with cement leakage, including the patients' basic and clinical information and radiological data. In the training group, we identified four risk factors that were significantly associated with cement leakage, excluding discal and paravertebral cement leakage. Some studies have focused on analyzing risk factors for predicting cement leakage in patients with osteoporotic vertebral compression fractures [23,31,32] or mixed types of compression fractures (including osteoporotic, malignant, or other causes combined) [22,33]. These studies have reported that cement viscosity [31], age [32], sex [32], bone mineral density [32], the interval from injury to surgery [32], injection routes [23,32], intravertebral vacuum clefts [23], operation using C-arm fluoroscopy [23], fracture severity grade [22,31], and the presence of Kummell avascular necrosis [22] were associated with cement leakage. However, limited data regarding associations between patients' potential risk variables and cement leakage has been reported, especially for cancer patients after being treated with percutaneous vertebroplasty. A study conducted by Gabriel et al. [12] showed that vertebral collapse and cortical destruction were risk factors for cement leakage, but the history of prior treatment was found to be a protective factor after analyzing 56 cancer patients and 81 vertebrae. Age has been reported as a nonsignificant factor for cement leakage in some studies [20]. However, in the present study, we found that younger age tended to be associated with an increased incidence of cement leakage. The outcome difference may be explained by study sample heterogeneity. Previous studies analyzed risk factors for predicting overall cement leakage, whereas our study assessed the risk factors for predicting cement leakage but excluded discal cement leakage and paravertebral cement leakage. In the supplementary material, we also demonstrated that age was significantly associated with vascular cement leakage.

In the present study, we further developed and validated an algorithm to predict cement leakage, excluding discal and paravertebral cement leakage. This algorithm produced a score ranging from 0 to 16 points, with higher scores indicating higher rates of cement leakage. Patients were divided into three risk groups: low, moderate, and high risk of cement leakage. Patients in the high cement leakage risk group had a cement leakage rate of 75.00%. Therefore, we recommend that careful surgical plans be developed for patients in Group C to prevent cement leaks and the serious complications associated with cement leakage.

This study has some limitations. First, this was a retrospective study, and patients with incomplete records were excluded from the study; therefore, selection bias was unavoidable. Second, some potential risk characteristics, including cement viscosity and operations performed with C-arm fluoroscopy, were not analyzed due to unavailable data, which may also lead to bias. Third, although the algorithm was validated and reproducible, we should not rely only on this algorithm when planning and implementing treatments. Overall, the findings of this study remain to be validated in prospective studies based on large populations.

5. Conclusions

Cement leaks are common among patients with metastatic spinal disease treated with percutaneous vertebroplasty. The present study proposed and internally validated an algorithm that can be used to screen patients at a high risk of experiencing cement leakage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Author's contributions

SDX and YPC designed the study. YXP, BW, and MXL wrote the manuscript. SDX, YPC, YXP, BW, and MXL revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets of the current study are available under reasonable request.

Ethics approval and consent to participate

All analyses of human data conducted in this study were approved by the Ethics Committee Board of the Peking University First Hospital and were performed in accordance with the ethical standards of the institutional and national research committees and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was exempted due to the retrospective nature of this study.

Consent for publication

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2021.100365.

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