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Research article

Hidden blood loss and its influencing factors after cement augmentation for vertebral metastasis

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ABSTRACT

Introduction: Few studies have focused on the risk factors for hidden blood loss (HBL) during cement augmentation surgery for pathologic vertebral compression fraction (PVCFs).

Method: From January 2014 to December 2020, the clinical data of 169 PVCF patients (283 levels) who underwent cement augmentation were retrospectively analysed. HBL was calculated according to the linear Gross formula using the patient's average Hct during the perioperative course and PBV. Multivariate linear regression analysis was performed to evaluate the independent factors associated with HBL.

Results: The mean HBL was 448.2 ± 267.2 ml, corresponding to 10.8% ± 6.2% of the patient blood volume (PBV). There were significant differences between pre- and postoperative haematocrit (Hct) ($P < 0.001$) and Hb ($P < 0.001$), and 132 patients developed anaemia postoperatively, while 79 patients had anaemia preoperatively ($P < 0.001$). Multivariate linear regression revealed that bone lesion quality ($p = 0.028$), number of PVCFs ($p = 0.002$), amount of bone cement ($p = 0.027$), bone cement leakage ($p = 0.001$), and percentage of vertebral height loss (VHL) ($p = 0.011$) were independent risk factors for HBL.

Conclusion: In conclusion, patients with lytic vertebral destruction, larger amounts of bone cement, greater amounts of bone cement leakage, more PVCF(s), and greater percentages of VHL may be more prone to HBL.

1. Introduction

Currently, although the incidence of cancer is increasing, life expectancy is also increasing due to the use of systemic and local therapies for malignant tumour patients [1]. Metastatic bone disease (MBD), especially spinal metastases, is becoming increasingly common in patients with metastatic cancer, and serious skeletal-related events (SREs), including pain, hypercalcaemia, pathologic fracture, and spinal cord or nerve root compression, drastically diminish quality of life [2,3]. The most common site of involvement in patients with bone metastases is the spine, and spine metastasis may cause serious pain and lead to permanent neurological disability if pathologic vertebral compression fractures (PVCFs) occur and involve the spinal cord and/or nerve root [1,4]. Cement augmentation,

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including percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP), is an effective approach and can provide temporary local control and pain relief for PVCFs. Radiofrequency ablation (RFA) is an effective cytoreductive surgery that induces a good therapeutic response [5,6].

Hidden blood loss (HBL) is the decrease in blood volume and haemoglobin concentration caused by blood penetrating into tissues or retained in a dead space and blood haemolysis; these conditions are often disregarded by spine surgeons. HBL was first described by Sehat et al. [7] in 2000 and has become the focus of attention in assessing blood loss in PKP/PVP for osteoporotic vertebral compression fractures (OVCFs) [8–10]. However, these analyses of HBL have focused mainly on surgery for OVCFs, and few studies have focused on the risk factors for HBL after cement augmentation surgery in patients with PVCFs. For patients with PVCFs, due to the invasion and destruction of bone, the poor blood supply for metastatic tumours and poor physical fitness, HBL has a more significant influence on the postoperative outcomes of cement augmentation, especially with adjuvant RFA therapy. However, there are still no published studies dedicated to exploring the causes of HBL during cement augmentation with or without RFA.

Hence, this retrospective study was founded to calculate the HBL amount during the perioperative period, given the measured visible blood loss. The variables that may prevent HBL and predict the amount of HBL were analysed.

2. Methods and materials

2.1. Patients

This was a retrospective analysis of the clinical data of 169 patients with PVCFs who underwent cement augmentation from January 2014 to December 2020. This study protocol was reviewed and approved by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. All the included patients were diagnosed with PVCFs through their previous cancer history and clinical manifestations, and the most important imaging examinations included X-ray, CT and MRI.

The inclusion criteria were complete medical record materials, specific diagnosis of PVCFs, clear surgical indications, cement augmentation, and signed informed consent form. The exclusion criteria were a specific diagnosis of OVCFs, cement augmentation combined with pedicle screw fixation, and coagulation disorders. Clinical information, including sex, age, BMI, hypertension status, diabetes status, duration of pain, bone metastasis type, vertebral location, bone lesion quality, number of PVCF(s), VAS score, Tomita grade, Tokuhashi grade, preoperative radiotherapy, surgery type, surgical duration, amount of bone cement, bone cement leakage, postoperative pathology, percentage of VHL, and percentage of VHR, was extracted from medical records.

2.2. Surgical technique and postoperative therapy

All of the operations were primary procedures performed by the same surgical team under local anaesthesia under the guidance of conventional C-arm fluoroscopy. PKP, PVP and RFA surgeries were conducted in accordance with a standard published technique, namely, the bilateral pedicle approach [11–13]. All the vertebral specimens were subjected to histopathological examination to confirm the clinical diagnosis. All patients received denosumab or zoledronic acid to inhibit the progression of bone metastasis.

2.3. Calculation of patient blood volume (PBV) and HBL

No haemostatic material or drainage tube was used, and no blood transfusions were performed. In this study, low visible blood loss could not be assessed clearly and was always overlooked. HBL can be calculated by deducting the amount of visible loss from the calculated total blood loss (TBL). Therefore, the HBL was approximated to the TBL in this article. All the patients underwent complete blood count testing before surgery and 2–3 days after surgery to compare the changes in Hct and Hb. The patients' haemodynamics were stable, and there were no additional fluid shifts at this time in Sehat and Newman's [14] article.

According to the weight and height of the patients, the patient's blood volume (PBV) was calculated using Nadler's formula [15]:

$$PBV\ (L) = K_1 \times \text{height}\ (m)^3 + K2 \times \text{weight}\ (kg) + K3$$

(male: $K_1 = 0.3669$, $K_2 = 0.03219$ and $K_3 = 0.6041$; female: $K_1 = 0.3561$, $K_2 = 0.03308$ and $K_3 = 0.1833$)

TBL was calculated according to the linear Gross formula [16] using the patient's average Hct during the perioperative course and PBV.

$$TBL\ (L) = PBV \times (Hct_{pre} - Hct_{post})/Hct_{ave\sim HBL\ (L)}$$

(Hct_{pre} is the initial preoperative Hct, Hct_{post} is the Hct on postoperative day two or three, and Hct_{ave} is the average of the Hct_{pre} and Hct_{post}).

2.4. Calculation of the percentages of vertebral height loss and restoration

The vertebral height (VBH) was determined by plain radiography according to the average of the first, middle and last three parts of the vertebral body. The percentages of vertebral height loss (VHL, %) and vertebral height restoration (VHR, %) were computed according to the following formulas:

$VBH_{ave} = (VBH_{upper} + VBH_{lower})/2$

$VHL\ (\%) = (VBH_{ave} - VBH_{pre})/VBH_{ave} \times 100\%$

$VHR\ (\%) = (VBH_{post} - VBH_{pre})/VBH_{ave} \times 100\%$

(VBH_{upper} and VBH_{lower} represent the upper and lower adjacent vertebral heights, respectively, of malignant vertebral fractures. VBH_{ave} is the average height of VBH_{upper} and VBH_{lower} and represents the predicted height of the fractured vertebra. VHL% and VHR% represent the percentage of vertebral height loss and restoration, respectively. VBH_{pre} and VBH_{post} represent the preoperative and postoperative fracture vertebral heights, respectively.)

2.5. *Additional measurements*

The Hb concentration was used to define anaemia. According to the World Health Organization/National Cancer Institute, anaemia is characterized by Hb levels <120 g/L for women and <140 g/L for men [17]. BMI was confirmed by the World Health Organization criteria.

2.6. *Statistical analysis*

The mean ± SD for the descriptive statistics was used to present the data. Independent sample Student's *t*-test was used to test for significant differences in two quantitative variables. One-way ANOVA was performed to identify significant differences in three or more quantitative variables. Pearson product-moment correlation analysis was used to determine the degree of linear correlation between two quantities. t, F and r are special symbols for the independent samples Student *t*-test, one-way ANOVA, and Pearson product-moment correlation analysis, respectively. A positive coefficient indicated a positive influence, whereas a negative coefficient denoted a negative influence on the dependent variable (HBL). The closer the absolute value is to 1, the stronger the correlation (negative or positive correlation). Significant variables with a P value < 0.05 in the above analysis were included in the multivariate linear regression analysis, which was performed to evaluate the independent factors associated with HBL. The data analyses were performed with SPSS version 19.0 and GraphPad Prism 8. A P value < 0.05 indicated significant differences.

3. Results

A total of 169 patients—79 males and 90 females—with a mean age of 58.5 ± 9.9 years and a mean BMI of 24.1 ± 3.9—were included in this study. The demographic information and clinical results are summarized in Table 1 and Table 2. A total of 27.2% (46/

Table 1
Patient Demographics.

Parameters	Statistics
Total patients	169
Sex	
Male	79
Female	90
Hypertension	46
Diabetes	12
Bone metastases type	
Single	43
Multiple	126
Bone lesion quality	
Lytic	112
Blastic	16
Mixed lytic/blastic	41
Preoperative radiotherapy	26
Postoperative pathology	
Lung cancer	73
Breast cancer	32
Digestive system tumour	29
Urinary system tumour	19
Other tumours	16
Age, years	58.5 ± 9.9
BMI, kg/m^2	24.1 ± 3.9
Duration of pain, day(s)	117.5 ± 112.7
VAS score	5.8 ± 1.7
Tomita grade	5.9 ± 1.9
Tokuhashi grade	8.6 ± 2.9

BMI, body mass index; VAS, visual analogue scale.

169) and 7.1% (12/169) of patients suffered from hypertension and diabetes, respectively. A total of 25.4% (43/169) and 74.6% (126/169) of the patients had single and multiple bone metastases, respectively. In this study, the bone metastases were predominantly osteolytic, osteoblastic or mixed osteolytic/osteoblastic, which accounted for 66.3% (112/169), 9.5% (16/169), and 24.3% (41/169), respectively. In conclusion, a total of 169 patients with 283 levels were reviewed retrospectively. A total of 14.8% (25/169), 71% (120/169) and 14.2% (24/169) of patients underwent PVP, PKP and PKP plus RFA, respectively, for PVCFs.

The mean preoperative Hct and Hb levels were 38.1 ± 5.4 and 127.6 ± 19.1 g/L, respectively. The mean postoperative Hct and Hb levels were 34.2 ± 4.9 and 114.8 ± 17.6 g/L, respectively. There were significant differences between pre- and postoperative Hct ($P < 0.001$) and Hb ($P < 0.001$), and 132 patients developed anaemia postoperatively, while 79 patients suffered from preoperative anaemia ($P < 0.001$; Table 3). The mean PBV was 4.17 ± 0.69 L, and the mean HBL was 448.2 ± 267.2 ml, for a percentage of 10.8% ± 6.2%.

To analyse the correlation between HBL and the 26 risk factors, the independent samples Student *t*-test, one-way ANOVA and Pearson product-moment correlation analysis were used. We found the following parameters with a $P < 0.05$ (Table 4): bone metastases type ($t = -2.374$, $p = 0.019$), RFA ($t = 2.305$, $p = 0.022$), bone cement leakage ($t = -3.777$, $p < 0.01$) (Fig. 1C), bone lesion quality ($F = 4.097$, $p = 0.018$) (Fig. 1B), number of PVCFs ($F = 3.407$, $p = 0.035$) (Fig. 1D) , Tokuhashi ($r = -0.159$, $p = 0.039$), the amount of bone cement ($r = 0.304$, $p < 0.01$) (Fig. 1E) , percentage of VHL ($r = 0.321$, $p < 0.01$) (Fig. 1F) , percentage of VHR ($r = 0.337$, $p < 0.01$), preoperative Hct ($r = 0.246$, $p = 0.001$), preoperative Hb ($r = 0.228$, $p = 0.003$), PBV ($r = 0.176$, $p = 0.022$). Multivariate linear regression showed that bone lesion quality ($p = 0.028$), number of PVCFs ($p = 0.002$), amount of bone cement ($p = 0.027$), bone cement leakage ($p = 0.001$), and percentage of VHL ($p = 0.011$) were found to be independent risk factors for HBL (Table 5).

4. Discussion

The few studies of HBL after cement augmentation surgery have focused on PKP/PVP for the treatment of OVCFs [8–10]. However, no research has explored hidden blood loss and its influencing factors after cement augmentation for vertebral metastasis in patients with PVCFs. The main findings of the present study were that the HBL was 448.2 ± 267.2 ml, accounting for 10.8% ± 6.2% of the PBV, and that the mean Hb loss was 12.8 g/L during the perioperative period. The findings in our study were worse than those of previous studies on OVCFs; for example, Cao et al. [8] and Wu et al. [10] reported that 279 ± 120 ml of HBL was accompanied by 8.2 ± 3.9 g/L Hb loss and that a mean of 282 ml of HBL was accompanied by 8.7 g/L Hb loss during the perioperative period. Additionally, 53 patients with normal preoperative Hb levels developed anaemia, which implied that the 46.7% preoperative anaemia rate increased to 78.1% after the operation (Fig. 1 A). Patients with PVCFs and advanced malignant tumours are at high risk for bleeding during the perioperative period. Massive blood loss prolongs the postoperative recovery time due to the potential adverse effects of anaemia, which delays comprehensive treatment. However, no study has focused on the risk factors for HBL during cement augmentation with or without RFA for the treatment of PVCFs. Hence, confirming the extent of HBL and its related influencing variables is crucial for patients with PVCFs.

To date, HBL is reportedly the result of blood penetrating tissues or being retained in a dead space and blood haemolysis [18,19].

Table 2
Clinical results related to surgery.

Parameters	Statistics
Number of PVCF(s)	
One level	102
Two levels	36
Three or more levels	31
Vertebral location	
Thoracic vertebra	41
Lumbar vertebra	90
Thoracic and lumbar vertebra	38
Surgery type	
PVP	25
PKP	120
PKP + RFA	24
Bone cement leakage	41
Amount of bone cement, ml	5.7 ± 3.2
Surgical duration, min	100.6 ± 50.8
Percentage of VHL, %	17.7 ± 12.4
Percentage of VHR, %	15.3 ± 11.5
PBV, l	4.17 ± 0.69
HBL, ml	448.2 ± 267.2
HBL/PBV, %	10.8 ± 6.2

PVCF, pathologic vertebral compression fraction; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; RFA, radiofrequency ablation; VHL, vertebral height loss; VHR, vertebral height restoration; HBL, hidden blood loss; PBV, patient blood volume.

Table 3
Perioperative blood changes in patients and Results of Pearson or Spearman correlation analysis for hidden blood loss.

Parameters	Preoperative (n = 169)	Postoperative (n = 169)	Statistical significance
Hct, %	38.1 ± 5.4	34.2 ± 4.9	**P < 0.001**
Hb, g/l	127.6 ± 19.1	114.8 ± 17.6	**P < 0.001**
Anaemia	79	132	**P < 0.001**

Hct, haematocrit; Hb, haemoglobin.

Table 4
Results of the Pearson or Spearman correlation analysis for hidden blood loss.

Parameters	检验值	*P*
Sex	t = 1.870	0.063
Hypertension	t = -0.345	0.731
Diabetes	t = 1.217	0.225
Preoperative anaemia	t = 1.407	0.161
Bone metastases type	t = −2.374	**0.019**
Preoperative radiotherapy	t = 1.740	0.084
RFA	t = 2.305	**0.022**
Bone cement leakage	t = -3.777	**< 0.01**
Bone lesion quality	F = 4.097	**0.018**
Number of PVCF(s)	F = 3.407	**0.035**
Vertebral location	F = 0.254	0.776
Surgery type	F = 2.736	0.068
Postoperative pathology	F = 1.034	0.391
Age	r = −0.018	0.817
BMI	r = 0.135	0.080
Duration of pain	r = 0.027	0.729
VAS score	r = 0.134	0.082
Tomita grade	r = 0.075	0.330
Tokuhashi grade	r = −0.159	**0.039**
Amount of bone cement	r = 0.304	< 0.01
Surgical duration	r = 0.059	0.445
Percentage of VHL	r = 0.321	< 0.01
Percentage of VHR	r = 0.337	< 0.01
Preoperative Hct	r = 0.246	**0.001**
Preoperative Hb	r = 0.228	**0.003**
PBV	r = 0.176	**0.022**

RFA, radiofrequency ablation; PVCF, pathologic vertebral compression fraction; BMI, body mass index; VAS, visual analogue scale; VHL, vertebral height loss; VHR, vertebral height restoration; Hct, haematocrit; Hb, haemoglobin; PBV, patient blood volume.

However, no factors influencing the HBL volume were clearly identified for patients with PVCFs treated with cement augmentation with or without RFA. In our study, multiple linear regression analysis was employed to investigate the related influencing factors. The study showed that patients with lytic bone destruction, more PVCF(s), a greater percentage of VHL, more bone cement, and more bone cement leakage were more likely to have HBL.

Our study demonstrated that lytic bone destruction was related to more HBL than was blastic or mixed lytic/blastic lesions during the perioperative period (Fig. 1B). Compared with blastic and mixed lytic/blastic spinal metastases, lytic spinal metastases are associated with greater vertebral bone reduction and loss of vertebral structural stability. Vertebral reduction causes the vertebral body to become an “empty shell'' [20], which may be a source and reason for more HBL in patients with severe VHL [10]. Loss of vertebral structural stability is apt to occur in the bone with VHL, which was also positively related to HBL in our study ($p = 0.011$, Table 5). In a previous study, HBL was also shown to be positively correlated with the number and severity of vertebral fractures [8–10].

In the analysis of the relationship between bone cement leakage and HBL, multivariate linear regression analysis showed that bone cement leakage was positively correlated with HBL in our study, which was also confirmed in another article [8–10]. Bone cement leakage most commonly occurred due to a cortical defect in the fracture gap [21], which can worsen due to lytic bone destruction. Cortical defects lead to persistent bleeding of the vertebra [8,10] and cause bone cement leakage during the perioperative period of cement augmentation. Moreover, a large bone cement volume was found to be a strong predictor of bone cement leakage [22]. In addition, there was significant evidence that the amount of bone cement was positively associated with HBL in our study. Polymethylmethacrylate (PMMA), the most commonly used bone cement, can restore the stability of vertebrae and also induce tumour cells due to its exothermic effects on the solidification process and cell toxicity [10]. In a previous study, thermal necrosis was found to indicate haemolysis during PKP [10], which was not confirmed by us. In our study, the temperature during RFA reached a maximum of 103 °C, which was higher than the 55 °C temperature needed for the bone–cement interface. However, no association was found between RFA and HBL ($p = 0.413$; Table 5). In summary, thermal necrosis may not be a risk factor for HBL, so further studies should explore the correlation between cement and HBL.

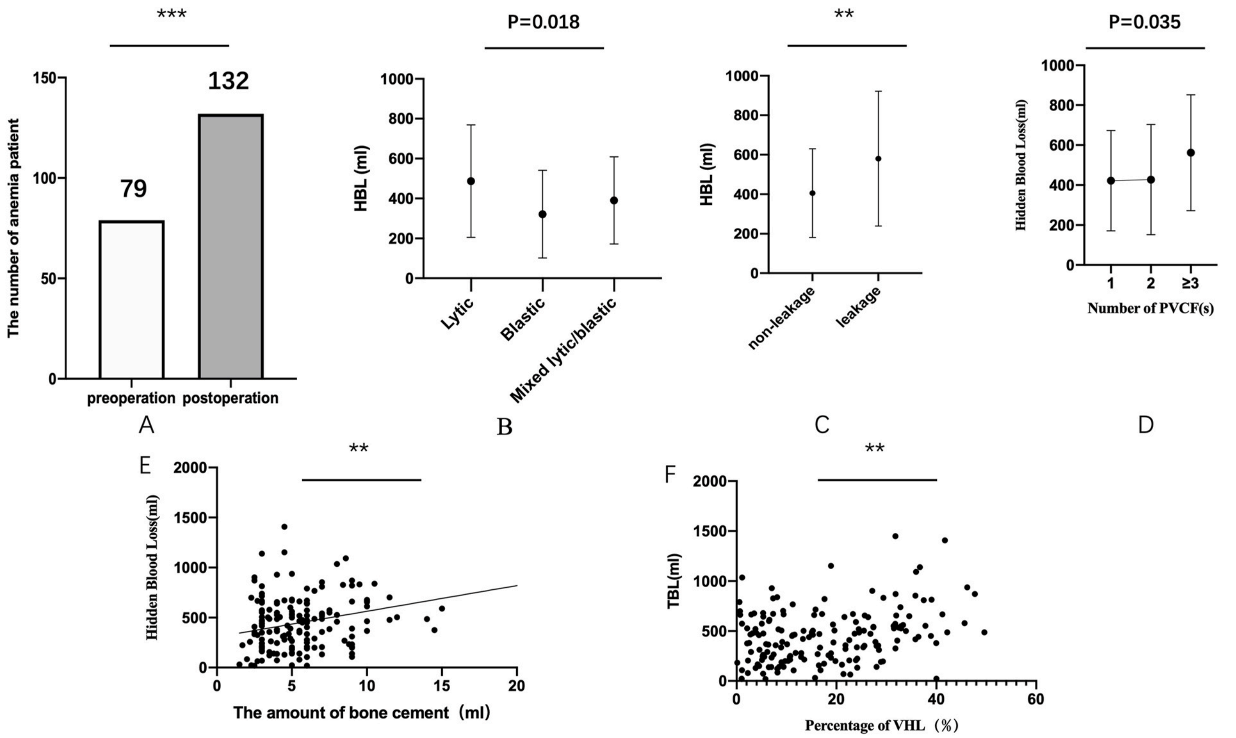

Fig. 1. A. Number of anaemia patients pre- and postoperation. (***P < 0.001); B. Differences in HBL according to vertebral destruction grade. C. Difference in HBL with or without bone cement leakage. (p < 0.01). D. Difference in HBL with different number of PVCFs. (p = 0.035). E. The relationship between the HBL and the amount of bone cement (**p < 0.01). F. The relationship between the HBL and Percentage of VHL (**p < 0.01). HBL, hidden blood loss; PVCF, pathologic vertebral compression fraction; VHL, vertebral height loss.

Table 5
Results of multivariate linear regression for hidden blood loss.

Coefficients[a]	Unstandardized		Standardized		
	β	SE	β	t	P
Constant	−526.941	184.366		−2.858	0.005
Bone metastases type	81.249	46.405	0.134	1.751	0.082
RFA	−40.464	49.294	−0.055	−0.821	0.413
Bone cement leakage	146.860	41.515	0.235	3.538	0.001
Bone lesion quality	−43.891	19.784	−0.141	−2.218	0.028
Number of PVCF(s)	83.938	27.205	0.244	3.085	0.002
Tokuhashi	−1.348	6.572	−0.015	−0.205	0.838
The amount of bone cement	12.969	5.824	0.153	2.227	0.027
Percentage of VHL	5.216	2.033	0.244	2.565	0.011
Percentage of VHR	3.356	2.148	0.145	1.562	0.120
Preoperative Hct	2087.208	1320.678	0.422	1.580	0.116
Preoperative Hb	−2.266	3.720	−0.163	−0.609	0.543
PBV	16.798	25.842	0.044	0.650	0.517

RFA, radiofrequency ablation; PVCF, pathologic vertebral compression fraction; VHL, vertebral height loss; VHR, vertebral height restoration; Hct, haematocrit; Hb, haemoglobin; PBV, patient blood volume.
[a] Dependent variable: HBL (ml).

Based on the research findings, effective management of occult blood loss during cement augmentation surgery for vertebral metastasis necessitates tailored strategies. An individualized approach to anemia management should be implemented, considering the patient's preoperative condition and minimizing transfusion-related risks. Employing real-time monitoring with advanced technologies such as hemodynamic monitoring and intraoperative ultrasound allows dynamic adjustments during surgery to minimize blood loss and address potential complications promptly. It is crucial to optimize cement application techniques, including minimally invasive procedures and navigation system assistance, particularly in patients with lytic bone destruction. Emphasizing preventive measures to avoid cement leakage involves careful patient selection, precise cement calculations, and advanced surgical techniques. Multidisciplinary collaboration, encompassing spine surgeon, hematologists, and anesthesiologists, is indispensable for formulating comprehensive treatment plans tailored to individual needs. Postoperative monitoring of hematological parameters and clinical conditions is imperative, with interventions, including judicious transfusion decisions and rehabilitation plans, ensuring stability and optimal treatment outcomes. This integrated and nuanced approach aims to enhance surgical success, minimize complications, and facilitate a positive postoperative recovery for patients undergoing this procedure.

As a retrospective study, there are still many limitations, despite being well designed and appropriately implemented. First, the research results should be verified in a multicentre study to compensate for data limitations inherent to a single-centre retrospective study. Second, HBL was falsely estimated. One reason is that the postoperative Hct was evaluated at 2 or 3 days after surgery when more fluid shifts were expected [14]. Another reason is that intravenous fluid infusion during the perioperative period leads to haemodilution. Third, a more specific and detailed method for measuring the degree of vertebral destruction, especially for evaluating osteolysis, should be used.

5. Conclusion

In conclusion, the present study indicates that HBL in patients with PVCFs is much greater than generally considered in patients with OVCFs. Spine surgeon should remain vigilant in preventing lytic vertebral destruction, reducing the amounts of bone cement used to reduce the likelihood of bone cement leakage, and appropriately assess the number of PVCFs and the percentages of VHL. Further in-depth clinical research should be performed, especially for patients with preoperative anaemia, to assure the safety of patients during the perioperative period of cement augmentation.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Ethics approval statement

This investigation was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (NCC2537) and was conducted in accordance with the Declaration of Helsinki. The patients in the validation cohort signed their written agreement.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Zhenguo Zhao: Writing – original draft, Data curation. **Shuguang Zhang:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Libin Xu:** Software, Methodology. **Songfeng Xu:** Software, Methodology, Investigation. **Xinxin Zhang:** Supervision, Formal analysis, Data curation. **Ting Liu:** Methodology, Investigation. **Xuan Liu:** Software, Data curation. **Shengji Yu:** Writing – review & editing.

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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Appendix A. Supplementary data

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