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CHAPTER 4

Cement leakage in percutaneous vertebroplasty for osteoporotic vertebral compression fractures

Identification of risk factors

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Abstract

Background. Percutaneous VertebroPlasty (PVP) is a common treatment modality for painful Osteoporotic Vertebral Compression Fractures (OVCFs). Its complication rate is low, but cement leakage occurs in up to 90% of the treated levels. Recent evidence suggests sequelae of cement leakage may be more common and clinically relevant than previously thought. Preoperative appreciation of risk factors would therefore be helpful, but has not been thoroughly investigated.

Objective. Identification of preoperative risk factors for occurrence of cement leakage in PVP for painful OVCFs.

Methods. The effect of all known risk factors and other parameters potentially influencing the occurrence of cement leakage was retrospectively evaluated in 89 patients with 177 OVCFs treated with PVP. Cement leakage was assessed on postoperative CT scans of the treated levels. Besides cement leakage in general, three fundamentally different leakage types (cortical, epidural and anterior venous), with different possible clinical sequelae, were discerned and their respective risk factors were assessed.

Results. In 130 of 173 (75.1%) treated OVCFs cement leakage was detected. Leakage incidence was found to increase approximately linear with advancing semiquantitative severity grade (1-4). High fracture severity grade and low bone cement viscosity were strong risk factors for occurrence of cement leakage in general (adjusted per grade Relative Risk (RR) 1.14, 95%CI: 1.05 – 1.24, $p = 0.002$ and medium versus low viscosity: adjusted RR 0.73, 95%CI: 0.61 – 0.87, $p < 0.001$). For occurrence of cortical leakage (95% intradiscal), presence of cortical disruption and presence of an intravertebral cleft on the preoperative MRI scan were additional strong risk factors (adjusted RR 1.62, 95%CI: 1.16 – 2.26, $p = 0.004$ and adjusted RR 1.43, 95%CI: 1.07 – 1.77, $p = 0.017$).

Conclusion. High fracture severity grade and low viscosity of PMMA bone cement are general, strong and independent risk factors for occurrence of cement leakage. Presence of cortical disruption and presence of an intravertrebral cleft are additional strong risk factors for occurrence of cortical cement leakage, potentiating anticipation.

4.1 Introduction

Percutaneous VertebroPlasty (PVP) has gained widespread acceptance and implementation, mainly as a treatment modality for painful Osteoporotic Vertebral Compression Fractures (OVCFs) [1–5]. Its benefit over conservative treatment has been proven in a large, high-quality randomized clinical trial [6]. However, results of recently published, long-awaited placebo-controlled randomized trials call this belief into question [7, 8]. With discussion regarding the generalizability of these results and the subsequent position of PVP ongoing [9–19], it is likely patient selection criteria should be individually optimized and a careful benefit versus risk analysis for each individual patient is warranted.

The complication rate of PVP is low, with 1.6 – 3.8% reported by meta-analyses [20, 21]. Severe complications of PVP are rare, restricted to case reports and mainly comprise sequelae of excessive cement leakage, like paraplegia [22], neurologic deficits [23, 24], cardiac perforation [25, 26] and even death [27].

The rate of occurrence of cement leakage itself appears variable, however, and reported incidences range from less than 5% to well over 80% [28–31]. When assessed on postoperative Computed Tomographic (CT) scans, known to be substantially superior to assessment on intra-operative fluoroscopy or on postoperative radiographs [31, 32], the incidence of cement leakage is found to be 63 to 87% [29–32].

Due to its generally asymptomatic character, cement leakage is commonly considered of minor importance and regarded as a procedure inherency rather than a true complication. However, besides the aforementioned severe sequelae, recent evidence suggests that certain sequelae of cement leakage may be more common and clinically relevant than previously thought. The first two prospective studies on the occurrence of pulmonary cement emboli after PVP in OVCFs, which are concomitantly also the first studies to use routine CT scanning of the thorax for examination, reported an unexpectedly high incidence: in 18 of 78 (23%) and 14 of 54 (26%) patients one or more cement emboli were detected [33, 34]. Furthermore, several studies found an association between intradiscal cement leakage and occurrence of new, adjacent OVCFs [35–38]. Although this association has not been found unanimously [39–42], avoidance of intradiscal cement leakage therefore seems advisable and further research is necessary.

With the benefit of PVP questioned and possible high incidences of cement leakage and clinically relevant sequelae, preoperative identification of risk factors for occurrence of cement leakage, preferably on standard PVP work-up methods, would be helpful in order to make a balanced treatment decision. Moreover, appreciation of risk factors allows preoperative anticipation and intraoperative minimization with early detection of cement leakage.

We assessed the preoperative characteristics of 177 OVCFs in 89 patients treated with PVP and identified several significant risk factors for occurrence of cement leakage.

4.2 Materials and Methods

4.2.1 Patients

Between August 2002 and October 2008, 177 patients received primary PVP. One-hundred-and-four patients received PVP for one or more OVCFs, of whom 89 were under clinical follow-up at our institution and were included in the present study (table 4.1, figure 4.1). All patients met the following criteria: (I) Osteoporotic VCF confirmed by biopsy, (II) focal back pain in the midline refractive to at least eight weeks of appropriate conservative treatment, (III) back pain related to the location of the VCF on spinal radiographs, (IV) the presence of bone marrow edema on Magnetic Resonance Imaging (MRI) Short-Tau-Inversion-Recovery (STIR) sequences in the corresponding collapsed vertebral body.

Table 4.1: Group characteristics (values as mean with range or count with proportion)

Characteristics of patient group	
Number of patients	89
Male	20 (22.5%)
Female	69 (77.5%)
Mean age in years (range)	73.2 (41.7 – 90.8)
Fractures	
Mean pre-existing per patient	4.4
(range, group total)	(1 – 13, 388)
Mean treated per patient	2.0
(range, group total)	(1 – 5, 177)
Mean fracture age (range, months)	5.9 (2.0 – 17.4)
Mean spinal deformity index (range)	8.6 (1 – 26)
Type according to Genant *et al*.*	
Wedge	
Mild (grade 1, 20-25%)	19
Moderate (grade 2, 25-40%)	47
Severe (grade 3, 40-67%)	16
Very severe (grade 4, >67%)	23
Biconcave	
Mild (grade 1, 20-25%)	16
Moderate (grade 2, 25-40%)	29
Severe (grade 3, 40-67%)	11
Very severe (grade 4, >67%)	14
Crush	
Severe (grade 3, 40-67%)	2
Intravertebral cleft on MRI scan	32 (18.1%)
Cortical disruption on MRI scan	31 (17.6%)
Viscosity	
Low	30 (33.7%)
Medium	59 (66.3%)

*Using modified semiquantitative severity grade, see text for details

4.2.2 Procedure

Vertebroplasty was performed on a biplane angiography unit using conscious sedation. A 10G vertebroplasty needle was gently hammered into the anterior third of the vertebral body and a bone biopsy was obtained, followed by injection of PolyMethyl-MethAcrylate (PMMA) bone cement until I) a satisfactory distribution of the cement, i.e. symmetrical filling of the central and anterior parts of the vertebral body, was

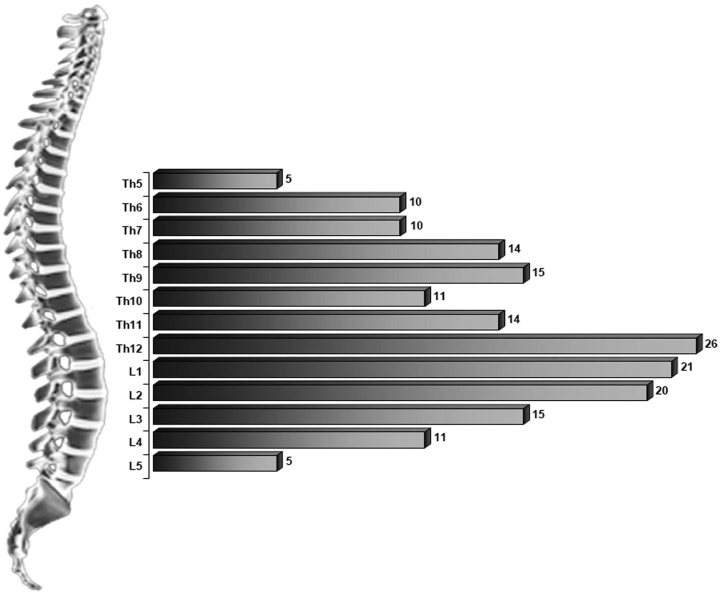


Figure 4.1: Distribution of 177 OVCFs treated with PVP.

obtained or II) when cement leakage was noted, in which case injection was temporarily halted and upon reoccurrence of leakage terminated. When necessary, a second needle was advanced into the vertebral body through the contralateral pedicle, followed by injection of cement.

Different types of PMMA bone cement were used: the first 30 patients were treated using low (injection) viscosity PMMA (OsteoPal-V®, Hereaus Medical, Germany) and, at availability, we changed to medium viscosity PMMA for the next 39 (Disc-O-Tech®, Disc-O-Tech Medical Technologies Ltd. Israel) and 20 (Spineplex®, Stryker Spine, Switzerland) patients.

Bone cement was strictly prepared as stated by the manufacturer. The injection timeframe was between 4 and 8 minutes after mixing.

4.2.3 Detection of cement leakage

On a direct postoperative CT scan of the treated levels, presence of cement leakage was assessed. Cement leakage was defined as the presence of any extravertebral cement. Patterns of cement leakage are described using the classification proposed by Yeom *et al.*[32], which identifies three types of leakage sites (figure 4.2): I) via the basivertebral vein (B-type), II) via the segmental vein (S-type) and III) through a cortical defect (C-type).

4.2.4 Fracture classification

Fracture morphology was denominated according to the semiquantitative classification of Genant *et al.* [43]. This classification identifies three types of fractures, wedge, biconcave and crush, and concomitantly characterizes fracture severity on the basis of the percentage of vertebral body collapse as mild (20-25%), moderate (25-40%) and severe (>40%) fractures. This classification serves as a fast and proven reliable surrogate for quantitative morphometry in assessment of vertebral body collapse [43].

However, the authors believe PVP in OVCFs with vertebral body collapse of (for example) 80% is technically more complicated and poses increased procedure-related risks compared to PVP in OVCFs with vertebral body collapse of (for example) 45%, although both classify as 'severe'. Moreover, during and after PVP we noted more frequent occurrence of cement leakage in more severely collapsed vertebrae. Therefore, an additional fourth semiquantitative grade of severity was added: Termed 'very severe', this grade comprises vertebral body collapse of over two-thirds (67%) of its original height and classifies, among others, the so-called vertebra plana [44]. The grade 'severe' then consists of fractures with vertebral body collapse between 40% and 67%. Since a relation between fracture severity and occurrence of cement leakage has not been investigated before, this relation will be assessed separately.

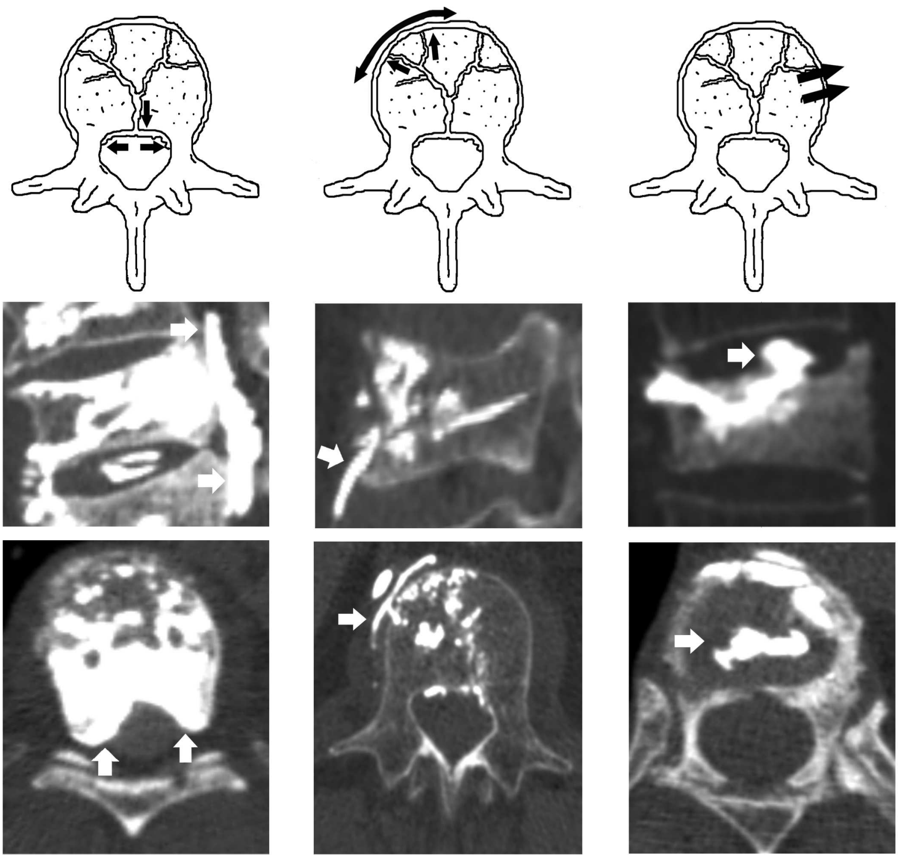


Figure 4.2: Sketch (upper row) and reformatted sagittal (middle row) and transverse (lower row) postoperative CT images illustrating the three leakage types discerned (white arrows): B-type (left), S-type (middle) and C-type (right).

4.2.5 Model factors

In order to provide a more complete and general model for the prediction of occurrence of cement leakage and to control for possible confounders, all known factors influencing occurrence of cement leakage and all remaining parameters potentially influencing occurrence of cement leakage were added. The complete model includes the following parameters: patient age and sex, patient spinal deformity index (the summed severity

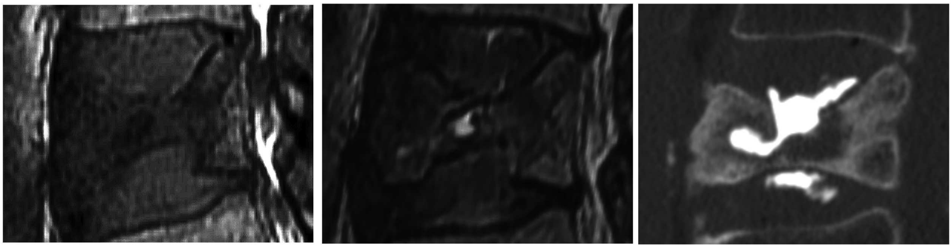


Figure 4.3: Vertebral fracture with an intravertebral cleft on MRI T1-weighted (left) and STIR sequences (middle) which communicates with the intervertebral disc space and with subsequent cement leakage after PVP on the postoperative CT scan (right).

grade of all vertebral deformities present [43, 45]) as assessed on preoperative radiographs, fracture level, fracture age (defined as the time between the onset of new back pain related to a radiological confirmed fracture and the time of PVP), fracture type and modified semiquantitative severity grade (both assessed on preoperative radiographs), presence of an intravertebral cleft on preoperative MRI scans, presence of cortical disruption on preoperative MRI scans and viscosity of bone cement used.

An intravertebral cleft was defined an abnormal, well-demarcated, linear or cystic hypointensity similar to air on MRI T1-weighted sequences and/or hyperintensity similar to cerebrospinal fluid on MRI STIR sequences (figure 4.3) [46–50].

Cortical disruption was defined as the evident discontinuation of cortical hypointensity on preoperative MRI scans (figure 4.4) [49, 50].

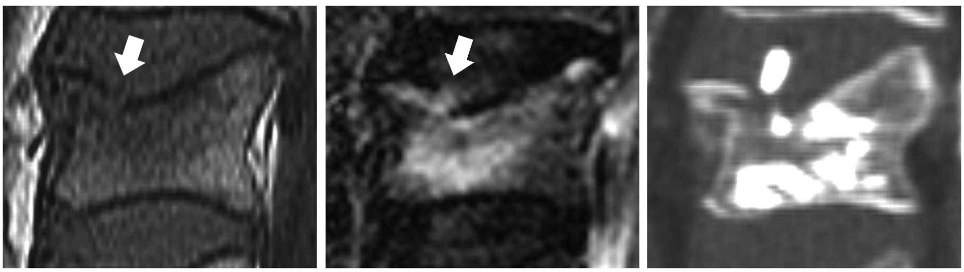


Figure 4.4: Evident cortical disruption (white arrow) on MRI T1-weighted (left) and STIR sequences (middle) with subsequent cement leakage after PVP through the cortical disruption as detected on the postoperative CT scan (right).

4.2.6 Outcome models

For practical purposes, since preoperative MRI is not used routinely in every institution, one model with and one model without MRI characteristics was analyzed with respect to the occurrence of cement leakage in general.

Since the three different leakage types discerned represent fundamentally different leakage patterns, with different potential sequelae, analysis of only occurrence of cement leakage in general will not make optimal usage of the available data and risk factors may be incorrectly attributed to all leakage types, whereas other risk factors may not be detected at all. Also, identification of risk factors for occurrence of the three different types of cement leakage allows one to more specifically anticipate leakage in the presence of particular risk factors. Therefore, additional analysis regarding risk factors for occurrence of specific leakage types was carried out.

4.2.7 Statistical analysis

Relative risks (RRs) were estimated using a log-binomial distribution analyzed with a Poisson regression approach with robust error variance according to Zou [51].

The linear effect of the adjusted semiquantitative severity grade in the analysis was assessed by comparison with an identical model which makes no assumption of linearity (i.e. categorized variable) and by incorporation of quadratic terms. No superior model was identified and no evidence against a linear effect was found.

Interaction terms of variables physically plausible to interact (severity grade, presence of cortical disruption, presence of an intravertebral cleft, cement viscosity) were assessed by successive incorporation in regression models and assessment of the likelihood ratio statistic. No superior model with interaction terms was identified.

A p-value of less than 0.05 was considered significant (SPSS statistical software 16.0, SPSS Inc, Chicago, IL).

4.3 Results

4.3.1 Incidence of cement leakage

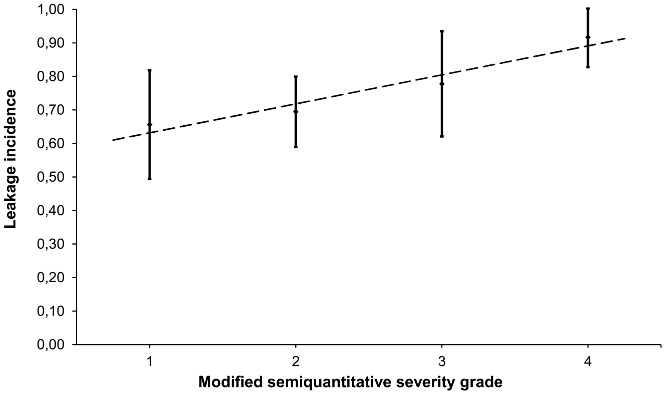
In 130 of 173 (75.1%) treated OVCFs cement leakage was detected (table 4.2). For two treated OVCFs, postoperative CT scans were unavailable for evaluation. Only two of 177 (1.1%) OVCFs were of the crush type and due to their small number excluded from further analysis. Hence, only the wedge and biconcave fracture type are present in our analysis.

Leakage incidence was found to increase in an approximately linear fashion with advancing severity grade (figure 4.5). Moreover, univariate analysis identified a per grade RR for occurrence of cement leakage of 1.12 (95%CI: 1.04 – 1.21, $p = 0.002$, table 4.2).

All three leakage types (B-type, S-type and C-type) were relatively common (table 4.2) and approximately linear relations between incidence and severity grade were found (figure 4.5, table 4.2). They vary directionally though: The incidence of B- and S-type leakages *decreased* with advancing severity grade (per grade RR 0.70, 95%CI: 0.53 – 0.93, $p = 0.012$ and per grade RR 0.69, 95%CI: 0.50 – 0.87, $p = 0.004$), whereas the incidence of cortical leakage *increased* with advancing severity grade (per grade RR 1.71, 95%CI: 1.49 – 1.97, $p < 0.001$). Since C-type leakage is in >95% of the cases intradiscal cement leakage (table 4.2), the latter will not be reported separately in further analysis.

4.3.2 Risk factors for occurrence of cement leakage in general

In order to control for confounding, multivariate analysis was performed. In both the model without and with relevant MRI characteristics, severity grade remained an independent predictor of occurrence of cement leakage (adjusted per grade RR 1.14,



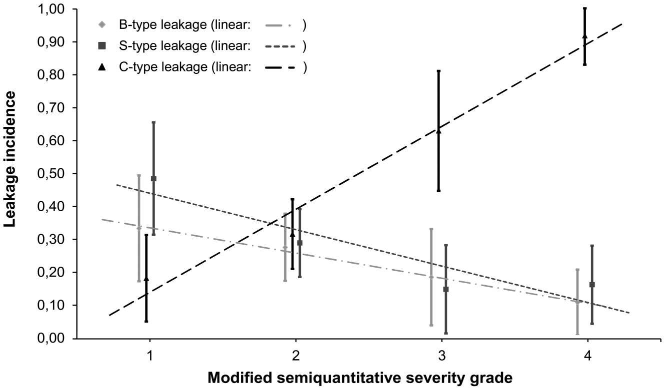


Figure 4.5: Incidence of cement leakage in general (upper) and of specific leakage types (lower) per modified semiquantitative severity grade (mean and 95%CI). Estimated trend lines are shown.

95%CI: 1.05 – 1.24, p = 0.002 and adjusted per grade RR 1.10, 95%CI: 1.01 – 1.20, p = 0.039, table 4.3).

Besides severity grade, both models identified the treated level and cement viscosity as independent risk factors. The influence of treated level was minor (adjusted RR 0.96, 95%CI: 0.94 – 0.99, p = 0.006 and adjusted RR 0.96, 95%CI: 0.94 – 0.99, p = 0.005) but lower levels appear to be at a slightly lower risk for occurrence of cement leakage. Viscosity of bone cement was found to be a major influential factor regarding

Table 4.2: Leakage characteristics

Presence of leakage	Overall	B-type	S-type	C-type	Intradiscal
Overall (n = 173)	130 (75.1%)	41 (23.7%)	48 (27.1%)	81 (46.8%)	78 (45.1%)
Grade 1 (n = 33)	22 (66.7%)	11 (33.3%)	16 (48.5%)	6 (18.2%)	6 (18.2%)
Grade 2 (n = 76)	53 (69.7%)	21 (27.6%)	22 (28.9%)	24 (31.6%)	22 (28.9%)
Grade 3 (n = 27)	21 (77.8%)	5 (18.5%)	4 (14.8%)	17 (63.0%)	17 (63.0%)
Grade 4 (n = 37)	34 (91.9%)	4 (10.8%)	6 (16.2%)	34 (91.9%)	33 (89.2%)
Univariate per grade Relative Risk [95% CI]	1.12 [1.04 – 1.21] $p = 0.002$	0.70 [0.53 – 0.93] $p = 0.012$	0.69 [0.50 – 0.87] $p = 0.004$	1.71 [1.49 – 1.97] $p < 0.001$	1.73 [1.49 – 2.01] $p < 0.001$

occurrence of cement leakage: usage of medium instead of low viscosity cement was found to reduce the risk of occurrence of leakage by more than 25% (adjusted RR 0.73, 95%CI: 0.61 – 0.87, $p < 0.001$ and adjusted RR 0.72, 95%CI: 0.61 – 0.86, $p < 0.001$).

Value of MRI assessment in the preoperative estimation of the risk of occurrence of cement leakage in general lies in the presence of cortical disruption of levels to be treated, which can be added as an additional risk factor: the presence of cortical disruption increased the risk of occurrence of cement leakage with almost 25% (adjusted RR 1.24, 95%CI: 1.05 – 1.46, $p = 0.012$).

4.3.3 Risk factors per leakage type

Results of multiple regression analysis for occurrence of the three leakage types are shown in table 4.4. In B-type leakage, only cement viscosity was identified as an independent, but strong, predictor of occurrence of cement leakage (adjusted RR 0.48, 95%CI: 0.29 – 0.81, $p = 0.006$). Fracture severity grade was not a significant risk factor.

For occurrence of S-type cement leakage, fracture severity and fracture type were identified as strong risk factors (per grade adjusted RR 0.69, 95%CI: 0.52 – 0.91, $p = 0.009$ and adjusted OR 1.72, 95%CI: 1.04 – 2.84, $p = 0.034$ respectively).

Table 4.3: Results of multivariate analysis for occurrence of cement leakage in general

Modified Poisson regression analysis: Occurrence of cement leakage		**Model without MRI characteristics**			**Model with MRI characteristics**		
	Characteristic	**Relative Risk [95%CI]**	***p***		**Relative Risk [95%CI]**	***p***	
Patient	Patient age (years)	1.00 [0.99 – 1.01]	0.692		1.00 [0.99 – 1.01]	0.507	
	Patient sex (♀/♂)	1.04 [0.84 – 1.29]	0.729		1.06 [0.85 – 1.31]	0.623	
	Spinal deformity index	0.99 [0.97 – 1.00]	0.140		0.99 [0.97 – 1.01]	0.301	
Fracture (radio-graphy)	Fracture level	0.96 [0.94 – 0.99]	0.006	*	0.96 [0.94 – 0.99]	0.005	*
	Fracture age (months)[§]	1.01 [0.98 – 1.04]	0.560		1.01 [0.98 – 1.04]	0.634	
	Fracture type	1.17 [0.97 – 1.39]	0.094		1.15 [0.97 – 1.38]	0.117	
	Fracture severity	1.14 [1.05 – 1.24]	0.002	*	1.10 [1.01 – 1.20]	0.039	*
Fracture (MRI)	Intravertebral cleft on MRI scan	-			1.11 [0.92 – 1.34]	0.276	
	Cortical disruption on MRI scan	-			1.24 [1.05 – 1.46]	0.012	*
Pre-procedural	Cement viscosity (medium/low)	0.73 [0.61 – 0.87]	< 0.001	*	0.72 [0.61 – 0.86]	< 0.001	*

** Statistically significant parameter*
[§] *Anamnestically*

Regarding occurrence of C-type cement leakage, strong dependence was found on fracture severity (per grade adjusted RR 1.61, 95%CI: 1.36 – 1.91, $p < 0.001$), presence of cortical disruption on the preoperative MRI scan (adjusted RR 1.62, 95%CI: 1.16 – 2.26, $p = 0.004$), presence of an intravertebral cleft on the preoperative MRI scan (adjusted RR 1.43, 95%CI: 1.07 – 1.77, $p = 0.017$) and bone cement viscosity (medium versus low: adjusted RR 0.61, 95%CI: 0.45 – 0.83, $p = 0.002$). Fracture level was a significant but weak predictor of occurrence of cortical cement leakage (adjusted RR 0.94, 95%CI: 0.90 – 0.99, $p = 0.015$).

Table 4.4: Results of multivariate analysis for occurrence of specific leakage types

Modified Poisson regression analysis: Occurrence of specific types of cement leakage

Occurrence	Characteristic	Relative Risk [95%CI]	*p*	
B-type cement leakage				
Patient	Patient age (years)	1.01 [0.98 – 1.05]	0.411	
	Patient sex (♀/♂)	0.65 [0.36 – 1.17]	0.148	
	Spinal deformity index	0.98 [0.93 – 1.03]	0.423	
Fracture (radiography)	Fracture level	0.97 [0.89 – 1.05]	0.412	
	Fracture age (months) §	1.05 [0.96 – 1.14]	0.303	
	Fracture type	0.92 [0.50 – 1.69]	0.789	
	Fracture severity	0.84 [0.63 – 1.12]	0.237	
Fracture (MRI)	Intravertebral cleft on MRI scan	0.38 [0.10 – 1.45]	0.157	
	Cortical disruption on MRI scan	0.72 [0.26 – 2.04]	0.540	
Procedural	Cement viscosity (medium/low)	0.48 [0.29 – 0.81]	0.006	*
S-type cement leakage				
Patient	Patient age (years)	0.98 [0.95 – 1.02]	0.297	
	Patient sex (♀/♂)	0.99 [0.55 – 1.77]	0.969	
	Spinal deformity index	0.98 [0.92 – 1.04]	0.420	
Fracture (radiography)	Fracture level	0.93 [0.96 – 1.00]	0.064	
	Fracture age (months) §	0.95 [0.88 – 1.02]	0.157	
	Fracture type	1.72 [1.04 – 2.84]	0.034	*
	Fracture severity	0.69 [0.52 – 0.91]	0.009	*
Fracture (MRI)	Intravertebral cleft on MRI scan	0.77 [0.34 – 1.74]	0.523	
	Cortical disruption on MRI scan	1.14 [0.55 – 2.39]	0.721	
Procedural	Cement viscosity (medium/low)	1.00 [0.61 – 1.64]	0.992	
C-type cement leakage				
Patient	Patient age (years)	1.00 [0.98 – 1.02]	0.929	
	Patient sex (♀/♂)	1.05 [0.73 – 1.52]	0.781	
	Spinal deformity index	1.01 [0.99 – 1.04]	0.367	
Fracture (radiography)	Fracture level	0.94 [0.90 – 0.99]	0.015	*
	Fracture age (months) §	1.03 [0.97 – 1.09]	0.364	
	Fracture type	1.09 [0.81 – 1.46]	0.585	
	Fracture severity	1.61 [1.36 – 1.91]	< 0.001	*
Fracture (MRI)	Intravertebral cleft on MRI scan	1.43 [1.07 – 1.77]	0.017	*
	Cortical disruption on MRI scan	1.62 [1.16 – 2.26]	0.004	*
Procedural	Cement viscosity (medium/low)	0.61 [0.45 – 0.83]	0.002	*

** Statistically significant parameter*
§ *Anamnestically*

4.4 Discussion

With the benefit of PVP called into question, a more rigorous and individually optimized benefit versus risk analysis for each patient should be made. As the incidence of cement leakage appears considerable and evidence regarding the incidence of its sequelae is emerging or conflicting, preoperative appreciation of risk factors would be helpful and facilitate in the reduction of (occurrence of) cement leakage.

We performed a detailed analysis of potential risk factors for occurrence of cement leakage, all of which can be easily assessed from routine examinations. High fracture severity, according to the modified semiquantitative severity classification, and low PMMA bone cement viscosity were two strong independent predictors of occurrence of cement leakage in general. When a preoperative MRI scan is available, presence of cortical disruption is an additional risk factor.

4.4.1 Cement viscosity

The identification of viscosity of PMMA bone cement as an independent predictor of occurrence of cement leakage is in agreement with experimental results [52–54]. Lower viscosity cements are hypothesized to favor interdigitation of cement into the trabecular bone but increase the risk of extravertebral leakage, whereas cements of higher viscosity form a more clump-like intracorporal distribution with trabecular disruption, but reduce leakage incidence [53]. Viscosity of PMMA bone cement increases with time and is readily assessable immediately before commencement of injection. Therefore, viscosity of bone cement is one of the (peroperative) factors with notable potential for reduction of (occurrence of) cement leakage. We, in agreement with others [55, 56], recommend usage of cement with a doughy consistency which, when tested in 'open-air' immediately before injection, does not dissociate from the cement in the syringe tip under its own weight. Moreover, when additional risk factors for occurrence of cement leakage are present, e.g. high fracture severity grade or cortical disruption, usage of higher viscosity bone cement may be the only method to achieve an acceptable preoperative risk of occurrence of cement leakage.

4.4.2 Fracture severity

The association found between occurrence of cement leakage and fracture severity grade is intuitively plausible and in agreement with morphological expectations, but has, to the authors' best knowledge, not been published before. The linear dependence of the incidence of cement leakage on fracture severity implicates relevance for the modification of the severity grading system of Genant *et al.*[43] in case of preoperative (clinical) estimation of the risk of occurrence of cement leakage and establishes the additional fourth category 'very severe' as an independent category with its own (ratio of) complication risks. The classification of Genant *et al.* is easily clinically applicable and more practical than quantitative vertebral morphometrics, yet at the same time proven to be robust and reliable [43]. Since we only added a fourth semiquantitative severity grade, these benefits are likely to be maintained.

4.4.3 Specific leakage types

Because the three leakage types discerned by Yeom *et al.*[32] are fundamentally different with different possible clinical sequelae, we assessed risk factors for occurrence of the three different leakage types as well and identified specific (combinations of) risk factors per leakage type.

B-type cement leakage

Cement leakage type B represents cement leakage following the basivertebral vein and anterior internal venous plexus into the epidural space. Leakage into the epidural space is not rare and occurs in over 20% of treated fractures, as has been demonstrated by us (23.7%) and others [31, 32, 57], and has the potential for dramatic sequelae [22–24]. We identified bone cement viscosity as an independent risk factor for occurrence of this leakage type: Usage of low viscosity PMMA bone cement increased the risk of occurrence of B-type leakage by approximately a factor two compared to usage of medium viscosity PMMA bone cement. Fracture severity was not a risk factor for occurrence of B-type leakage, which is not surprising since in our population, and in OVCFs in general, the posterior cortex is usually largely intact and fractures are usually of the wedge or biconcave type.

S-type cement leakage

The second venous leakage type, the S-type, comprises cement leakage via the segmental vertebral veins and anterior external vertebral venous plexus. This type of cement leakage is related to occurrence of pulmonary cement emboli [33]. Fracture severity grade and fracture type were identified as risk factors for occurrence of S-type cement leakage. It should be emphasized that the risk of occurrence of S-type cement leakage *decreases* with advancing severity grade and has its highest incidence in less deformed fractures, which is concomitantly higher than the incidence of B- and C-type leakages. This is likely to be the result of the increased destruction of the venous system with higher fracture severity and concurs with the fact that the risk of ocurrence of S-type cement leakage in biconcave fractures is 70% higher compared to wedge-shaped fractures, the latter probably having a more destructed anterior venous system. This makes it very likely that the risk of venous cement leakage associated sequelae, e.g. cement emboli [33, 58], also *decreases* with advancing severity grade. Cement viscosity was, surprisingly, not identified as a risk factor for occurrence of S-type cement leakage.

C-type cement leakage

For occurrence of C-type leakage, and hence intradiscal leakage which comprises over 95% of the C-types leakages, multiple strong risk factors were identified. Both one increase in modified semiquantitative severity grade and the presence of cortical disruption on a preoperative MRI scan were associated with a RR of 1.6. Both are likely to be a result of more pronounced cortical destruction with advancing severity grade, but remained independent predictors in multivariate analysis. Presence of an intravertebral cleft on a preoperative MRI scan was also identified as an independent risk factor, probably due to the frequently present connection with the intervertebral disk space. This association is in accordance with some studies [45–47, 55], but not all [49, 50]. Usage of bone cement with medium viscosity compared to usage of low viscosity was found to reduce the risk of occurrence cortical cement leakage with around 40%. By positioning the needle tip away from the cortical disruption and careful, slow filling of the usually low-pressure intravertebral clefts, there is considerable potential for avoidance of C-type cement leakage and hence its potential sequelae, e.g. induction of new, adjacent OVCFs.

4.4.4 Current knowledge

Despite frequent occurrence of cement leakage, the number of reports studying its predictors is small: only 3 studies were identified [49, 50, 55].

Hiwatashi *et al.*[49] and Koh *et al.*[50] assessed the association between preoperative MRI characteristics and occurrence of cement leakage as detected on postoperative CT scans. They identified cortical disruption and absence of an intravertebral cleft as risk factors for occurrence of cement leakage. Fracture severity as assessed in the midsaggital plane of MRI scans was not found to be a risk factor. Although both studies are substantially smaller than this study, another explanation might be that measurement of vertebral dimensions on one selected (midsagittal) slice might compromise appreciation of the overall deformity of the vertebrae. In addition, Hiwatashi *et al.* considered only intradiscal cement leakage and in the study of Koh *et al.* the mean loss of vertebral body height was only 20%.

Mirovsky *et al.*[55] also assessed predictors of occurrence of intradiscal cement leakage only. Fracture severity was graded (mild/moderate/severe) on preoperative radiographs but not found to be a risk factor, whereas a fractured endplate and presence of an intravertebral cleft were. However, this study was relatively small, no multivariate analysis was performed and cement leakage was not assessed on postoperative CT scans.

To the authors' best knowledge, the present assessment of risk factors for occurrence of cement leakage in PVP for painful OVCFs is the largest and most comprehensive to date. Moreover, we are the first to analyze risk factors for occurrence of all different leakage types, which is relevant since they are associated with different sequelae. All known risk factors were included and potential ones were added, all of which are easily assessable on standard methods for PVP work-up in order to facilitate usage for standard clinical practice.

4.4.5 Study limitations

A limitation of our study was the subsequent usage of different types of bone cement instead of randomized usage. Therefore, we are unable to cancel out the effect of a possible operator learning curve. However, the operators had substantial PVP experience. Also, we did not objectively measure pre-injection bone cement viscosity, although the difference in viscosity was readily apparent and a standardized injection protocol was used. Despite performed strictly as described, one crucial parameter regarding occurrence of cement leakage, and PVP in general, which cannot be accounted for is operator expertise.

4.5 Conclusion

High fracture (modified semiquantitative) severity grade and low viscosity of PMMA bone cement are strong and independent risk factors for occurrence of cement leakage in general. Appropriate cement viscosity in particular provides a means to reduce occurrence of cement leakage, especially in the presence of additional risk factors. On preoperative MRI scans, presence of cortical disruption and presence of an intravertebral cleft were identified as additional strong risk factors for occurrence of cortical (intradiscal) cement leakage, thereby potentiating anticipation.

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