Retrospective Study

Minding the Gap in Vertebroplasty: Vertebral Body Fracture Clefts and Cement Nonunion

Caroline Tomas, MD[1], Alexandria Jensen, MS[2], Farres Ahmed, MD[3], Corey K Ho, MD[1], and MK Jesse, MD[1]

From: [1]Department of Radiology, University of Colorado School of Medicine, Aurora, CO; [2]Department of Biostatistics & Informatics, Colorado School of Public Health, Aurora, CO; [3]Tahoe Carson Radiology, Carson City, NV

Address Correspondence: Caroline Tomas, MD Department of Radiology, University of Colorado Denver - Anschutz Medical Campus 12631 E 17th Ave, MS 8200 Aurora, Colorado 80045 E-mail: caroline.tomas@cuanschutz.edu

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Background: Vertebroplasty and kyphoplasty are leading treatments for patients with vertebral body compression fractures. Although cement augmentation has been shown to help relieve pain and instability from fractures containing a cleft, there is some controversy in the literature regarding the procedure's efficacy in these cases. Additionally, some of the literature blurs the distinction between clefts and cement patterns (including cement nonunion and cement fill pattern). Both clefts and cement patterns have been mentioned in the literature as risks for poorer outcomes following cement augmentation, which can result in complications such as cement migration.

Objectives: This study aims to identify the prevalence of fracture clefts and cement nonunion, the relationship between them as well as to cement fill pattern, and their association with demographics and other variables related to technique and outcomes.

Study Design: Retrospective cohort study.

Setting: Interventional radiology department at a single site university hospital.

Methods: This retrospective cohort study assessed 295 vertebroplasties/kyphoplasties performed at the University of Colorado Hospital from 2008 to 2018. Vertebral fracture cleft and cement nonunion were the main variables of interest. Presence and characterization of a fracture cleft was determined on pre-procedural imaging, defined as an air or fluid filled cavity within the fractured vertebral body on magnetic resonance or computed tomography. Cement nonunion was evaluated on post-procedural imaging, defined as air or fluid surrounding the cement bolus on magnetic resonance or computed tomography or imaging evidence of cement migration. Cement fill pattern was assessed on procedural and/or post-procedural imaging. Pain improvement scores were based on a visual analog score immediately prior to the procedure and during clinical visits in the short-term follow-up period. Additional patient demographics, medical history, and procedure details were obtained from electronic medical chart review.

Results: Pre-procedural vertebral fracture clefts were demonstrated in 29.8% of our cases. Increasing age, secondary osteoporosis, and thoracolumbar junction location were associated with increased odds of clefts. There was no significant difference in pain improvement outcomes in patients following cement augmentation between clefted and non-clefted compression fractures. Clefts, especially large clefts, and cleft-only fill pattern were associated with increased odds of cement nonunion. Procedure techniques (vertebroplasty, curette, and balloon kyphoplasty) demonstrated similar proportion of cement nonunion and distribution of cement fill pattern.

Limitations: Cement nonunion was observed in only 6.8% of cases. Due to this low proportion, statistical inference tends to have low power. Multiple levels were treated in nearly half of the study's patients undergoing a single vertebroplasty/kyphoplasty session; in these cases, each level was treated as independent rather than spatially correlated within the same study patient.

Conclusions: Vertebral body fracture clefts are not uncommon and are related to (but distinct from) cement nonunion and cement fill patterns. Our study shows that, although patients with clefts will benefit from cement augmentation just as much as patients without a cleft, the performing provider should take note of cement fill and take extra steps to ensure optimal cement fill. These providers should also identify cement nonunion and associated complications (such as cement migration) on follow-up imaging.

Key words: Kyphoplasty, vertebroplasty, compression fracture, cement nonunion, vertebral fracture cleft, spine, cement augmentation

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Vertebroplasty is a common treatment for compression fractures, first introduced in France in 1984 and adapted for widespread use in the US in the 1990s. This minimally invasive procedure involves administering polymethylmethacrylate cement percutaneously into a fractured vertebral body and has been proven to be superior to conservative medical management for pain relief and functionality improvements (1-22). Osteoporosis is the most common etiology behind compression fractures, with over 700,000 cases a year resulting in over 100,000 hospitalizations in the US (23-25).

Since the introduction of the procedure, despite the continuous overwhelming literature illustrating its overall benefits and superiority over conservative therapy (1-18,26-39), occasionally a study will arise challenging its widespread use, including the recent ASMBR task force report published in January 2019 (40). It is increasingly important to reaffirm benefits of procedures and treatments and strive to optimize benefit-risk ratios for patients. In this context, we aim to explore covariates that may be associated with a successful outcome following vertebroplasty and kyphoplasty. We focus on 2 such covariates that we suspect are related to each other: cleft fractures and cement filling patterns.

Described as osteonecrosis, avascular necrosis, or non-united fracture, clefts demonstrate poor revascularization and, therefore, poor healing and instability (41-44). Although clefts are known to respond poorly to conservative therapy (45) and cement augmentation has been shown to be beneficial (46), there is nevertheless controversy in the literature as to how cleft patients compare to noncleft patients following cement augmentation (47-54). In addition to exploring this as it relates to pain outcomes, we surmised if cement patterns and clefts — and their relationship with one another — may contribute to the inconsistent results and nonsignificant trends in many of these studies. Several studies focusing on clefts and cement pattern have blurred the distinction between the 2 (50,55) or mention in passing that clefts and cement patterns are related (49).

We question if cement nonunion may play a role here.

The aim of our single site, retrospective study is to evaluate vertebral fracture clefts and cement nonunion in compression fractures following cement augmentation, demographic associations with these variables, and their relationship to each other. We hypothesize that fracture clefts and cement nonunion are separate but related entities and that these variables are important considerations when performing or recommending cement augmentation.

Methods

This retrospective cohort study assessed vertebroplasties and kyphoplasties performed on 295 patients at the University of Colorado Hospital between 2008 and 2018, following Institutional Review Board approval. Inclusion criteria encompassed patients presenting with acute pain from vertebral body compression fracture/s, with magnetic resonance imaging (MRI) or computed tomography (CT) findings consistent with an acute timeline. Exclusion criteria disqualified patients lost to follow-up, patients without preprocedural cross-sectional imaging (for cleft analysis), patients without post-procedural cross-sectional imaging (for cement nonunion analysis), and patients without documented pain scores (for pain outcome analysis).

Preprocedural cross sectional imaging (MR or CT) was evaluated to identify the presence of a cleft (an air or fluid filled cavity within the vertebral body), and then subsequently categorized by morphology: small linear/triangular cleft as < 20% vertebral body height, moderate cleft as 20% – 50% of vertebral body height, and large cleft as > 50% of vertebral body height (Fig. 1). Intra-procedural or post-procedural images were analyzed to describe cement fill within vertebral bodies containing a cleft, categorized as no-cleft fill (only trabecular fill), cleft-only fill, and combination of both cleft and trabecular fill (Fig, 2). Post-procedural cross-sectional images (MR or CT), typically performed one to 3 months following the procedure, were then analyzed to determine presence of cement nonunion, defined in our study as air or fluid along the periphery of the cement bolus and/or evidence of cement migration (Fig. 3). Additional patient demographics, medical history, and procedure details were obtained from electronic medical chart review. Covariates of interest included patient age at the time of the procedure, gender, underlying etiology of fracture, number of levels treated by cement augmentation, spinal level of fracture, cleft presence, cleft morphology, and procedure technique.

Pain scores were recorded immediately prior to the procedure and then during short-term clinic follow-up, with average follow-up of 5 to 9 days after the procedure. Pain scores were based on the standard visual analog scale (VAS) via patient subjective reporting, with no pain defined as 0 and the worst pain possible defined as 10. Pain improvement was categorized as follows: complete resolution as 100% reduction in VAS, near-completion resolution as 75% – 99% reduction in VAS, partial resolution as 25% – 75% reduction in VAS, relatively unchanged as 0% – 25% reduction in VAS, and worsened pain.

Statistical Analysis

Descriptive statistics were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. To assess whether an association existed between cleft presence and procedure nonunion, a logistic regression was utilized with procedure nonunion the outcome, cleft presence the covariate of interest, and other demographic variables included as potential confounders. Ordinal logistic regressions were fit to understand the associations between pain outcome with cleft presence and procedure nonunion, respectively; pain response was the outcome of interest and demographic variables included as additional covariates of interest. As a secondary analysis, cleft morphology, cleft fill pattern, and procedure method were examined for their possible influence on procedure nonunion using Fisher's exact tests in a subset of patients with vertebral cleft. Descriptions of potential relationships between cleft fill pattern and both procedure method and pain score were summarized. From the regression models, odds ratios, their accompanying 95% confidence intervals (CI), and *P*-values were calculated. Analyses were conducted in R version 3.6.0 (Vienna, Austria) and statistical significance determined at the standard $P < 0.05$ level.

Results

Over the 2008 – 2018 period, 295 patients who underwent vertebroplasty and/or kyphoplasty were included in the study sample. Ninety-one patients were excluded overall, 63 from the pain analysis because of incomplete VAS pain documentation and 28 from the cleft analysis due to the lack of adequate preprocedural cross-sectional imaging. Table 1 provides a summary of the study sample's demographics. There were more women than men in the sample (58.3% to 41.7%), with the most common underlying etiology primary osteopenia/osteoporosis (51.9%).

The majority of patients had a single fracture on presentation (51.5%) with the most common location in the lumbar spine (63.4%). A vertebral cleft was present in 29.8% of analyzed fractures, of which a small cleft was the most dominant type (45.5% of all clefts). Cement nonunion was identified in 20 (6.8%) cases.

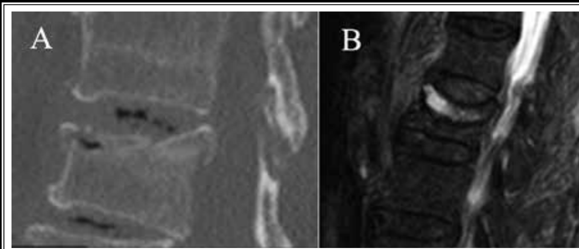

Fig. 1. *Fracture cleft morphology. Small gas-containing cleft within T12 on sagittal CT (A), and large fluid filled cleft within L1 on sagittal STIR MR (B).*

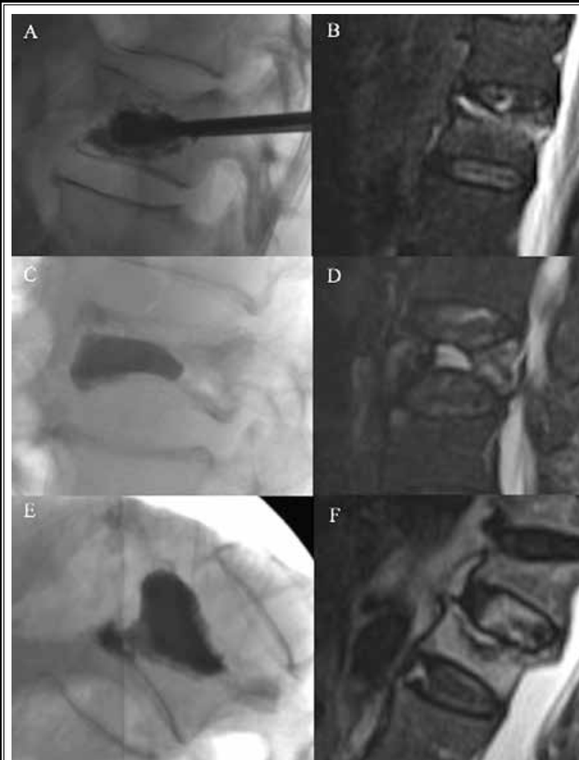

Fig. 2. *Cement fill patterns during fluoroscopy, with MR images of the corresponding cleft. Vertebral body only cement pattern (A and B), cleft-only cement fill pattern (C and D), and combined vertebral body and cleft cement fill pattern (E and F).*

To understand the association between procedure nonunion and cleft presence, a logistic regression was fit. Fig. 4, provides a forest plot summary of the regression results. As can be seen, a patient with a vertebral cleft had 5.5 (95% CI: 1.47 – 21.74) higher odds of procedure nonunion than one without a cleft, all else

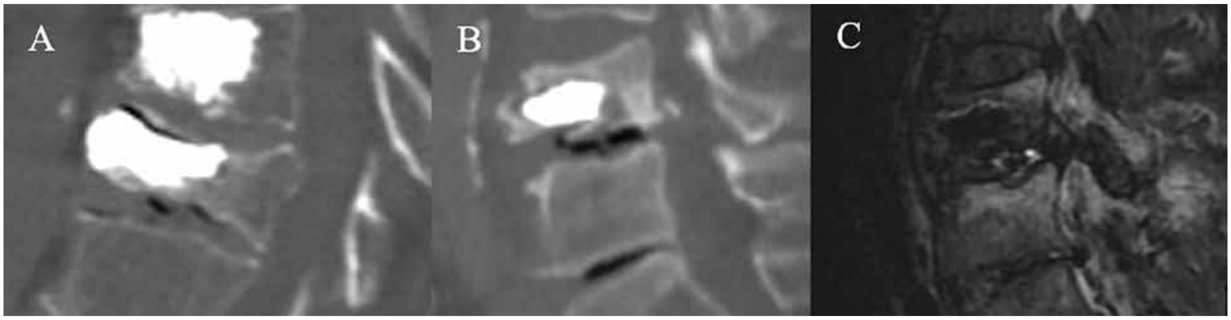

Fig. 3. *Cement nonunion. Gas along the cement bolus on sagittal CT (A). Fluid along the cement bolus within L4 on sagittal CT (B) with corresponding sagittal STIR MR (C).*

Table 1. *Descriptive characteristics of sample, mean ± SD or N (%).*

Age (yrs)	68.4 ± 12.6
Gender	
Female	172 (58.3%)
Male	123 (41.7%)
Underlying medical condition	
Primary osteopenia/osteoporosis	153 (51.9%)
Secondary osteopenia/osteoporosis	46 (15.6%)
Malignancy	92 (31.2%)
Trauma	26 (8.8%)
Degeneration	2 (0.7%)
Number of fractures	
1	152 (51.5%)
2	74 (25.1%)
3	49 (16.6%)
4	19 (6.4%)
5	1 (0.3%)
Location of fracture(s)	
Upper thoracic	26 (8.8%)
Lower thoracic	153 (51.9%)
Lumbar	187 (63.4%)
T12 or L1	139 (47.1%)
Presence of vertebral cleft	88 (29.8%)
Vertebral cleft morphology (n = 88)	
Small (< 20% VB height)	40 (45.5%)
Moderate (20% – 50% VB height)	25 (28.4%)
Large (> 50% VB height)	23 (26.1%)
Cleft fill pattern (n = 88)	
No cleft filling	5 (5.6%)

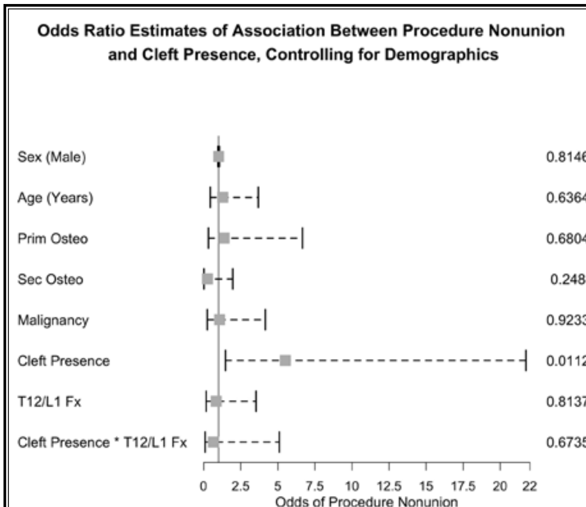

Fig. 4. *Forest plot of the odds ratio estimates for the association between procedure nonunion and cleft presence, controlling for demographics. The gold boxes represent the odds ratio estimate for the covariate while the dashed lines represent the 95% confidence limits for the estimates.*

equal. The other variables of gender, age, etiology, and fracture location were not significantly associated with nonunion. To assess whether any relationships between cleft presence and demographics existed, a secondary logistic regression was fit for the outcome of cleft presence. Age (OR 1.04, 95% CI: 1.01 – 1.06), secondary osteoporosis (OR 3.48, 95% CI: 1.46 – 8.50), and a fracture occurring at the T12/L1 junction (OR 2.17, 95% CI: 1.27 – 3.78) were all significantly associated with higher odds of cleft presence. The interactions between cleft presence and age as well as secondary osteoporosis resulted in the variance inflation factor for the main effect of cleft presence to spike. Therefore, only the interaction between cleft presence and T12/L1 fracture

Table 2. *Relative pain improvement scores overall and stratified by cleft presence.*

	Overall (n = 232)	Vertebral Cleft Present (n = 72)	Vertebral Cleft Absent (n = 132)
Worsened	6 (2.59%)	1 (1.39%)	5 (3.79%)
No Improvement	36 (15.51%)	11 (15.28%)	21 (15.91%)
Little Improvement (1% – 49%)	55 (23.71%)	14 (19.44%)	34 (25.76%)
Partial Improvement (50% – 74%)	47 (20.26%)	16 (22.22%)	28 (21.21%)
Near Complete Improvement (75% – 90%)	31 (13.36%)	10 (13.89%)	18 (13.64%)
Complete Improvement (> 90%)	57 (24.57%)	20 (27.78%)	26 (19.70%)

location was included in the final model, presented in Fig. 4.

Vertebral cleft presence's relationship to categorical pain outcome is presented in Table 2, below. Little and partial improvement categories were most common both overall and stratified by cleft presence. Near complete and complete improvement was found to be more frequent in patients with a cleft than for those without (41.7% versus 33.3%).

To fully assess the association between these 2 variables, an ordinal logistic regression was fit for the outcome of categorical pain outcome. The 6 categories of pain outcome seen in Table 2 were collapsed into 3 broad classifications, to help with model convergence: none/worse improvement, partial improvement, and (near) complete improvement. The proportional odds assumption was tested and met for the model. The results of the ordinal logistic regression are summarized in Table 3, below. No variables were found to be significantly associated with an increase in pain improvement category. Similarly, an ordinal logistic regression fit to assess the potential association between procedure nonunion and categorical pain outcome, controlling for the same set of demographics as in Table 3, did not find any statistically significant results.

As a secondary analysis, cleft morphology and cleft fill pattern were examined for their possible influence on procedure nonunion using a subset of patients who had a vertebral cleft. Both Fisher's exact tests comparing procedure nonunion and cleft morphology and cleft fill pattern, respectively, were significant ($P = 0.0456$ and $P < 0.001$, respectively), suggesting that neither one of these cleft-based variables is independent of procedure nonunion. The highest proportion of procedure nonunion occurs with a cleft-only fill (9/18, 50%), with few or no nonunion occurring in either a cleft and trabecular fill (3/65, 4.6%) or a no cleft fill (0/5, 0%). In other words, out of the 12 cement nonunion cases observed in this analysis, 9 (75%) demonstrated cleft-only

Table 3. *Results of ordinal logistic regression testing association between categorical pain outcome and cleft presence, controlling for demographics.*

Covariate	Odds Ratio Estimate	95% CI	*P* Value
Cleft presence	1.11	(0.64, 1.95)	0.7030
Gender (male)	1.35	(0.80, 2.26)	0.2605
Age (yrs)	1.01	(0.99, 1.03)	0.4189
Primary osteopenia/ osteoporosis	1.62	(0.79, 3.34)	0.1899
Secondary osteopenia/ osteoporosis	0.94	(0.42, 2.15)	0.8905
Malignancy	0.99	(0.52, 1.91)	0.9876
T12/L1 fracture location	0.82	(0.49, 1.36)	0.4426

cement fill pattern during the procedure and 3 (25%) demonstrated combined cleft and vertebral body fill.

When a secondary logistic regression was performed to compare moderate and large cleft morphology on the rate of nonunion, using small morphology as the reference level, patients with a large cleft morphology had a 5.25 higher chance of nonunion (95% CI 1.28 – 26.87, $P = 0.0276$) while patients with a moderate cleft morphology had a nonsignificant association (1.04 higher odds of nonunion, 95% CI 0.13 – 6.76, $P = 0.9643$). Fig. 5 summarizes the distribution of nonunion cases among cleft morphologies.

Finally, the relationships between nonunion and procedure method (Table 4), cleft fill pattern and procedure method (Table 5), and cleft fill pattern and categorical pain score were explored. Procedure method appears to be unrelated to nonunion; balloon procedures are the most common with vertebroplasty the next most common; all other methods were relatively rare. The curved needle procedure method has the lowest proportion of cleft and trabecular fill pattern and the highest of no cleft fill patterns. All other procedure methods have comparable proportions of fill patterns. Additionally, patients who experienced cleft-only fill patterns all reported at least some level of pain improvement, while those with no cleft fill or cleft and trabecular fill patterns had a proportion of patients reporting no pain improvement or worse pain levels compared to preprocedure. Despite identifying patterns, formal statistics did not demonstrate significant associations, and the inherent analysis format and smaller sample sizes precluded meaningful conclusions from these analyses.

Discussion

As suspected, the fracture cleft is not an uncommon occurrence following vertebral body compression fracture, occurring in 29.8% of our study patients. Certain patient demographics were significantly associated with the presence of a cleft, including increasing age, secondary osteoporosis, and fracture location at the thoracolumbar junction. We believe that the increased mechanical stress at the thoracolumbar junction inhibits healing, increasing the risk of cleft formation. This has been described in previous literature (47,56,57), which also postulates that the poor healing potential is the main underlying mechanism leading to cleft formation. This may explain why increasing age and secondary osteoporosis were also significantly associated with cleft formation in our study, as these conditions likely contribute to impaired healing.

Our review of the current literature regarding vertebral fracture clefts revealed mixed results, some clearly demonstrating the benefit of cement augmentation in treating clefts (45,46), while other articles suggest the opposite. Wu et al 2013 (47) summarizes multiple studies highlighting either significant pain relief after vertebroplasty and kyphoplasty for patients with clefted fractures, or lackluster pain improvement as compared to non-clefted groups. While many studies have not discovered a significant difference in clinical outcomes following the procedure, specifically with mobility and pain scores (48,49), some authors suggest a nonsignificant trend of worse outcomes with clefts (48) while others suggest a nonsignificant trend in better outcomes with clefts (50). Wu et al (47) also summarizes multiple studies on rates of cement leakage, finding conflicting results that conclude either increased or decreased cement leakage rates between cleft and non-cleft groups (51-54).

In the context of this unclear literature, our study provides some relevant clarity regarding cement augmentation and clefts. One of the most clinically important results regarding clefts is one without statistical significance: there is no significant difference in pain improvement scores between patients with clefts and patients without clefts. Therefore, providers should not hesitate to perform or recommend cement augmentation based on the presence or absence of a cleft, provided that the patient otherwise is a good candidate for the procedure.

This is a similar conclusion that Tanigawa et al (58) published in 2007, describing similar pain improvement

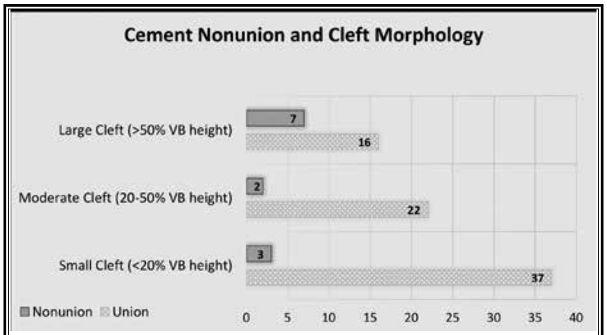

Fig. 5. *Number of cement nonunion cases within each cleft morphology category, where VB = vertebral body.*

Table 4. *Procedure nonunion by method.*

	Union	Nonunion
Balloon	41 (83.7%)	8 (16.3%)
Curette	5 (83.3%)	1 (16.7%)
Curved	7 (77.8%)	2 (22.2%)
Mixed/Other	6 (100.0%)	0 (0.0%)
Vertebroplasty	15 (93.8%)	1 (6.3%)

Table 5. *Procedure method by cleft fill pattern.*

	Balloon	Curette	Curved	Mixed/Other	Vertebroplasty
No Cleft Fill	4 (8.2%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
Cleft Only Fill	10 (20.4%)	1 (16.7%)	3 (33.3%)	1 (16.7%)	3 (18.8%)
Cleft and Trabecular Fill	35 (71.4%)	5 (83.3%)	5 (55.5%)	5 (83.3%)	13 (81.3%)

in patients with "cleft" and "trabecular" fills. Our study elaborates on these findings by confirming cleft presence on preprocedural imaging, separating clefts from cement patterns, and further subsegmenting cleft morphology. We found the dominant morphology to be the "small cleft," with large clefts most significantly associated with cement nonunion.

We defined cement nonunion on post-procedural imaging as a rim of high T2 signal representing fluid or rim of gas on CT along the cement periphery, with residual bone marrow edema. These findings represent development of an undesirable fibrous connection between the non-united cement bolus and the adjacent bone, the latter of which has become dense and sclerotic. Cement nonunion may have been termed many different things in the literature, including non-trabecular filling, cleft pattern filling, fracture pattern filling, solid lump, cystic, confluent reservoir, and non-interdigitation (49,50,55,58-62), although some of these terms do not seem to distinguish nonunion from intra-procedural cement fill patterns. The lack of term consistency can make it difficult for providers to appreciate the significance of cement nonunion, and certain terms (such as "cleft pattern filling") can be misleading. Furthermore, some studies assume that this type of cement pattern/nonunion is synonymous with cleft presence despite no preprocedural confirmation or despite conflicting preprocedural imaging (50,58,61). However, no study to date has shown that cement nonunion only occurs in the setting of a cleft. For this reason, we separated the parameters of cement nonunion, cement fill pattern, and clefts. Additionally, our study adds power to this analysis, as the vast majority of the literature referencing nonunion and cement fill pattern are based on small cohorts or case reports, or did not complete a meaningful analysis (49,60).

In our study, cement nonunion was observed in 6.8% of cases. Variables significantly associated with cement nonunion were the presence of a cleft (especially a large cleft morphology, as described above) and cement fill pattern. Specifically, cleft-only cement filling was significantly associated with cement nonunion, and 75% of patients with cement nonunion demonstrated cleft- only cement fill pattern during the procedure. These results indicate that clefts, cement nonunion, and cement fill pattern are related but are distinct entities.

What is the significance of these results regarding cement filling patterns and nonunion? Both in our clinical anecdotal experience and in limited published articles, cement nonunion has been associated with refracturing at the treated level, refracturing at adjacent levels, and cement bolus migration (58-62). By identifying cement nonunion on follow-up imaging, providers can take extra precautions in monitoring for associated complications. Although no difference was seen in nonunion rate between different techniques (vertebroplasty, curette, balloon, etc.), strong conclusions from this result should be avoided given the lower power in these subsets. Future studies with larger sample sizes should be evaluated for trends regarding nonunion and technique. In the meantime, our results indicate that providers can continue using their preferred technique without fear of increasing the rate of nonunion. Variables of gender, age, and compression fracture etiology were not significantly associated with cement nonunion, and therefore these parameters should not deter physicians from recommending or performing cement augmentation in qualifying patients.

Finally, failure to fill a cleft with cement has been observed to result in diminished pain improvement outcomes (50). By identifying clefts on preprocedural imaging, providers can take care in filling the cleft with cement. Because our study demonstrated a significant association between clefts and cement nonunion (especially between large cleft morphology and cement nonunion), as well as cleft-only fill and nonunion, providers can identify these cases before nonunion occurs, taking extra care to properly fill the trabeculae and monitor the patient on follow-up.

Limitations

Nearly half of our patients had multiple levels treated during the procedure, which may have confounded associations between fracture level, specific fracture characteristics, and outcomes. Although 295 patients qualified for our study, a portion of our analysis demonstrated low power because of the inherent comparison and, therefore, may have missed associations that would have otherwise been significant. For instance, analyses between nonunion and procedure method, cleft fill pattern and procedure method, and cleft fill pattern and categorical pain score contained lower sample sizes, which was further diminished by their distribution among multiple arms and categories inherent to these specific analyses. On a similar note, although 88 patients were included in the cleft analysis, only 20 of those cases had cement nonunion. However, these 20 nonunion cases were nonetheless more numerous than any of the articles we came across discussing nonunion, aside from Tanigawa et al with

34 patients (described as "cleft type" cement filling, presumably similar to our definition of either cleft-only fill or nonunion) (58).

Conclusion

Vertebral fracture clefts and cement nonunion are important variables to consider for providers performing or recommending cement augmentation. Vertebral fracture clefts are common, occurring in nearly 30% of our cases, and were associated with secondary osteoporosis, increasing age, and location at the thoracolumbar junction; many of these associations can be theoretically explained by poor fracture healing. Presence of a vertebral fracture cleft did not significantly alter pain relief outcomes when compared to patients without a cleft; therefore, providers should not hesitate to recommend or perform the procedure for a clefted fracture in a qualifying patient.

Vertebral body fracture cleft, cement nonunion, and cement fill pattern in a clefted vertebral fracture are separate entities, although related. Clefts, and especially large clefts, were associated with cement nonunion, and cement nonunion was associated with cleft-only cement fill.

Therefore, it could be suggested that performing providers take care to achieve as much trabecular fill as possible to reduce nonunion risk and inform the patient of nonunion risk in the setting of large cleft morphology. Cement nonunion should be avoided due to risk of cement migration and refracturing as discussed in previous published articles and as demonstrated in our own experiences.

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