ORIGINAL RESEARCH

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Mortality in the Vertebroplasty Population

BACKGROUND AND PURPOSE: Vertebroplasty is an effective treatment for painful compression fractures refractory to conservative management. Because there are limited data regarding the survival characteristics of this patient population, we compared the survival of a treated with an untreated vertebral fracture cohort to determine whether vertebroplasty affects mortality rates.

MATERIALS AND METHODS: The survival of a treated cohort, comprising 524 vertebroplasty recipients with refractory osteoporotic vertebral compression fractures, was compared with a separate historical cohort of 589 subjects with fractures not treated by vertebroplasty who were identified from the Rochester Epidemiology Project. Mortality was compared between cohorts by using Cox proportional hazards models adjusting for age, sex, and Charlson indices of comorbidity. Mortality was also correlated with pre-, peri-, and postprocedural clinical metrics (eg, cement volume use, RDQ score, analog pain scales, frequency of narcotic use, and improvement in mobility) within the treated cohort.

RESULTS: Vertebroplasty recipients demonstrated 77% of the survival expected for individuals of similar age, ethnicity, and sex within the US population. Compared with individuals with both symptomatic and asymptomatic untreated vertebral fractures, vertebroplasty recipients retained a 17% greater mortality risk. However, compared with symptomatic untreated vertebral fractures, vertebroplasty recipients had no increased mortality following adjustment for differences in age, sex, and comorbidity (HR, 1.02; 95% CI, 0.82–1.25). In addition, no clinical metrics used to assess the efficacy of vertebroplasty were predictive of survival.

CONCLUSIONS: Vertebroplasty recipients have mortality rates similar to those of individuals with untreated symptomatic fractures but have worse mortality compared with those with asymptomatic vertebral fractures.

ABBREVIATIONS: CI = confidence interval; HR = hazard ratio; RDQ = Roland-Morris Disability Questionnaire; VAS = visual analog scales

Osteoporotic fractures of the spine are extremely common,[1] and the lifetime risk of a symptomatic vertebral compression fracture has been estimated at 18% for women and 11% for men.[2] Painful compression fractures result in considerable morbidity and mortality,[3,4] accounting for more morbidity in the population younger than 75 years of age than hip fractures,[5] and are comparable with serious chronic diseases such as heart disease and diabetes with respect to the negative impact on quality of life.[6] In addition to the disability resulting from vertebral fractures, there is an enormous financial burden: National health care expenditures for vertebral fracture care were estimated at $746 million in 1995 or >$1.4 billion in 2011 dollars.[7] Because osteoporosis is primarily a disease of the elderly and the population of individuals aged 65 and older is growing rapidly, the cost of caring for vertebral fractures could increase 53% by 2025.[8]

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Most osteoporotic compression fractures are self-limited cases amenable to conservative management with short-term courses of analgesics and bed rest.[9] However, some within this group will be disabled by severe pain lasting >2–3 months.[10-12] The vertebroplasty procedure was initially developed in Europe in the 1980s as a means to better treat this refractory subset of patients who failed conservative management.[13,14] This procedure emerged in the United States in the late 1990s as the preferred long-term palliative treatment for refractory painful compression fractures of osteoporotic origin.[10,14-16] Vertebroplasty gained widespread clinical favor due to numerous observational studies demonstrating immediate, significant, and durable improvements in pain, mobility, and narcotic use.[15-19] However, more recent randomized controlled clinical trials failed to show a beneficial effect over sham therapy.[20,21]

The origin of pain improvement notwithstanding, the mobility and narcotic dependence of these patients favorably improves following vertebral augmentation, and such changes are expected to reduce morbidity and mortality.[22-25] Despite favorable clinical outcomes that might be presumed to confer a survival advantage, there remain little data on mortality among vertebroplasty recipients.[26] In an effort to better define the effect of vertebroplasty on survival in the osteoporotic fracture population, we retrospectively compared the postprocedural mortality of a cohort of vertebroplasty recipients (treated) with the mortality of a population-based cohort of Rochester, Minnesota residents with vertebral compression fractures identified between 1985 and 1994 (untreated), before the introduction of vertebroplasty.[27] Additionally, we

sought to retrospectively identify pre-, peri-, and postoperative outcome variables in the treated cohort that might be correlated with survival and thus be predictive of individuals who would experience the greatest benefit from vertebroplasty.

Materials and Methods

Study Population

A retrospective study design was implemented that involved 2 separate patient populations: The treated cohort comprised patients who underwent vertebroplasty for osteoporotic compression fractures at our institution between February 1999 and February 2007. Many of these vertebroplasty recipients have been included in several publications investigating short- and long-term outcomes and subsequent fracture,[17-19,28] but none of those reports addressed mortality. For this analysis, the vertebroplasty cohort was limited to patients with benign compression fractures of the vertebral body between T1 and L5 in the setting of clinical symptoms and radiologic evidence of osteoporosis. All of these subjects provided informed consent. Patients with vertebral compression fractures arising from metastatic disease, multiple myeloma, or traumatic fracture in the absence of osteopenia/osteoporosis were excluded to limit confounding effects in the survival analysis.

To better understand the natural history and correlates of this disease, we compared survival outcomes in the vertebroplasty cohort with those among the "untreated" Rochester residents with vertebral compression fractures documented in the comprehensive medical records linkage system of the Rochester Epidemiology Project.[29] Through institutional review board–approved access to outpatient and inpatient records,[30] all 820 patients with clinically diagnosed and radiographically confirmed fractures of the thoracic or lumbar vertebral bodies (excluding fractures of posterior elements or transverse processes) that occurred in the Rochester population in 1985–94 could be identified, whether or not they presented symptomatically.[27] This system allowed more complete ascertainment of vertebral fractures than was possible in other settings on the basis of symptomatic fracture cases alone. Nonetheless, 80% of this population had vertebral deformities that were classified as severe,[31] the type of fracture most likely to be symptomatic.[32] Exclusion of nonosteoporotic fracture etiologies reduced this population-based untreated cohort to 589 individuals. Overall mortality in a subset of the untreated cohort was reported previously.[33]

Vertebroplasty Procedure and Clinical Follow-Up

Vertebroplasty was performed by 1 of 7 experienced interventional neuroradiologists by using previously described techniques.[17,34] Contraindications to treatment included improvement with conservative management, technical contraindication, and noncorrelating pain. Quantitative and qualitative clinical outcome metrics were collected pre-, peri-, and postoperatively by trained nursing staff. Quantitative clinical outcome metrics included the modified RDQ, graded 0–23,[35] and the VAS, scored 0–10 for "pain at rest" and "pain with activity." Qualitative measures, including changes in pain, frequency of narcotic use, and mobility, were graded as complete improvement (+2), improvement (+1), no change (0), or worse than preprocedural status (−1) as assessed for each patient by trained nurses pre- and perioperatively in person and via telephone postoperatively at specified intervals of 1 week, 1 month, 6 months, 1 year, and 2 years to determine the efficacy of vertebroplasty. Ninety-five percent of patients had both quantitative (RDQ and VAS) and qualitative (change in mobility, change in narcotic drug use, change in pain with rest, and pain with activity) outcome data available at the 1-month end point.

Table 1: Characteristics of treated vertebroplasty and untreated vertebral fracture cohorts

	Treated Cohort (n = 524)	Untreated Cohort[a]	
		Asymptomatic (n = 371)	Symptomatic (n = 201)
Age (yr) (mean)	75.3 ± 10.5	76.9 ± 11.6	73.1 ± 12.0
Male (%)	155 (29.6)	68 (18.3)	17 (8.5)
Caucasian (%)	481 (97.6)	363 (98.1)	199 (99.0)
Charlson index (mean)	3.1 ± 3.2	2.2 ± 2.6	1.6 ± 2.4
0	111 (21.2%)	117 (31.5%)	95 (47.3%)
1–3	249 (47.5%)	177 (47.7%)	72 (35.8%)
4+	164 (31.3%)	77 (20.8%)	34 (16.9%)

[a] Seventeen of the 589 untreated subjects had unknown back pain and were excluded from the table.

Medical Record Data

Following institutional review board approval at Mayo Clinic and the Olmsted Medical Center, demographic data (including age, sex, ethnicity, and place/state of residence) and associated comorbidities were collected from archived medical records. Treated patients had provided informed consent for medical record review, but histories of untreated patients who declined use of their medical records for research were not reviewed.[30] The level of disability[1-4] was adopted from the modified Rankin Scale[36,37] and classified in ascending order as bedridden, restricted, able to walk <1 block, and able to walk >1 block. Comorbidity data reflecting all documented clinical diagnoses were recorded for each patient, and a weighted score was generated for each patient by using the Deyo modification of the Charlson comorbidity index.[38,39] Individual comorbidity scores were categorized as 0, 1–3, or ≥4. The vital status of both groups was determined through review of medical records at our institution and other local providers,[29] as well as active follow-up of the vertebroplasty cohort.

Statistical Methods

Categoric variables were summarized by using frequencies and percentages, and continuous variables were summarized by using means and SDs. Survival was estimated by using the Kaplan-Meier method with expected survival rates based on US White decennial life tables.[33] Point estimates at 5 years are reported from the survival curves, and the overall curves were compared by using the logrank test statistic. Survival was estimated from the date of intervention among the treated cohort and from the date of fracture diagnosis among the untreated cohort. To account for possible survivor bias as a result of the delay between fracture and vertebroplasty, we also evaluated survival among the untreated patients starting at 6 weeks following their vertebral fracture. Cox proportional hazards models by using an age scale were used to compare survival between the treated and untreated cohorts. These models were run overall by subsets of Charlson index scores and were also used to assess the impact of various covariates on death within the treated group.

Results

Demographic and Clinical Data

As shown in Table 1, the treated group comprised 524 study participants (mean age, 75.3 ± 10.5 years; 30% men; 98% white) meeting inclusion/exclusion criteria who underwent

vertebroplasty for chronic severe back pain in 1999–2007, whereas the untreated group comprised 589 Rochester residents meeting inclusion/exclusion criteria who were diagnosed with vertebral compression fractures (mean age, 75.5 ± 11.8 years; 15% men; 98% white) in 1985–1994. However, only 63% of the latter group presented with back pain (77% of men and 60% of women), akin to those seen in the treated cohort. Among the symptomatic Rochester residents, 45% had fractures only in the thoracic spine; 40%, only in the lumbar spine; and 16%, at both sites. Corresponding data for the treated patients were 43%, 38%, and 19%, respectively.

Relative Survival Outcomes

The vertebroplasty cohort was observed for a total of 1927 person-years (mean, 3.7 ± 2.7 years per person), during which time 30 (6%) patients died within 6 months of the procedure, and 182 (35%), within 5 years, including 110 (30%) women and 72 (46%) men. Ultimately, 224 (43%) vertebroplasty patients died by the end of follow-up. Three patients died within 30 days of their first vertebroplasty, yet the causes of death were unrelated to the procedure and included lacunar infarct, sepsis from cellulitis, and congestive heart failure secondary to pulmonary hypertension arising from primary biliary cirrhosis. The untreated cohort was observed for a total of 3178 person-years (mean, 5.4 ± 3.0 years per person), during which time 24 (4%) patients died within 6 months of fracture, and 175 (30%), within 5 years, including 130 (26%) women and 45 (51%) men. By the end of follow-up, 247 (42%) of these patients had died. The estimated survival for the treated cohort was 56% (43% in men and 61% in women) at 5 years compared with 73% expected for the US white population of the same age and sex at baseline (relative survival, 0.77; $P < .001$, On-Line Fig 1*A*). In contrast, the estimated survival of the patients with untreated vertebral fractures was 68% (44% in men and 72% in women) at 5 years compared with an expected 72% (relative survival, 0.94; $P = .045$).

Adjustments for Differences in Follow-Up

Because the untreated cohort had more extensive follow-up than the treated cohort, the vital status of the treated cohort was less certain, and we sought to determine whether the observed differences in survival could be attributed to follow-up bias. Among the 524 vertebroplasty recipients, 86 (16%) were local residents who had comparably extensive follow-up to the untreated cohort. Survival analysis performed on this subset of local treated patients mirrored the findings of the full treated cohort. At 5 years, the estimated survival of the treated Olmsted County residents was 49% (41% in men and 51% in women) compared with 67% for the US white population of the same age and sex (relative survival, 0.73; $P = .011$), 68% compared with all Rochester residents with untreated vertebral fractures (44% in men and 72% in women) (relative survival, 0.72; $P = .002$), and 61% compared with patients with untreated symptomatic vertebral fractures in the community (40% in men and 66% in women) (relative survival, 0.80; $P = .157$).

Because the duration of survival was measured differently between the treated and untreated cohorts, we sought to correct for this potential survival bias by evaluating the survival of the untreated patients who had lived for at least 6 weeks following their vertebral fracture. On the basis of our institutional clinical practice guidelines, 6 weeks represented the average delay between fracture date and intervention within the treated cohort. This alternative analysis excluded 8 of 589 (2%) untreated patients, 7 of whom had died. The estimated survival of the patients with untreated vertebral fractures who survived 6 weeks following fracture was 68% (45% in men and 72% in women) at 5 years compared with an expected 72% (relative survival, 0.94; $P = .068$, On-line Fig 1*A*). Estimated survival at 6 months was 96% (89% in men and 98% in women) in this group compared with an expected 97%. The comparable figure for the treated cohort at 6 months was 94% (93% in men and 95% in women) versus 97% expected for the US white population of the same age and sex. Collectively, these results suggest that the treatment delay introduced no significant survival bias in our data, and the remainder of the survival analysis discussed below was conducted by using the 581 untreated patients who survived at least 6 weeks following fracture.

Exclusion of Subjects with Asymptomatic Fracture

Only 367 of 581 untreated patients (63%) presented with back pain, compared with 100% of the patients undergoing vertebroplasty. The 5-year survival among asymptomatic untreated patients was not significantly different from that expected for the US white population (estimated survival, 79%; expected survival, 77%; relative survival, 1.03; $P = .146$), but it was significantly higher compared with the symptomatic subgroup (estimated survival, 61%; relative survival, 1.30; $P < .001$). The symptomatic subgroup (mean age, 76.8 ± 11.6 years; 18% men; 98% white) was observed for a total of 1801 person-years (mean, 4.9 ± 2.9 years per person); 131 (36%) patients had died by the 5-year point, and a total of 179 patients died overall. The estimated survival for the untreated patients who were symptomatic was 61% (40% in men and 66% in women) at 5 years compared with 69% expected for the US white population of the same age and sex at baseline (relative survival, 0.88; $P < .001$). Because only symptomatic patients undergo vertebroplasty, we limited the comparison to symptomatic fractures to interrogate the survival impact of the procedure. As shown in On-Line Fig 1*B*, men had worse overall survival, and survival was slightly better for treated men ($P = .315$), while it was somewhat worse for treated women ($P = .100$).

Influence of Comorbidity on Mortality

Using the patients with untreated vertebral fractures as the reference group afforded control, not only for the underlying condition but for significant comorbid conditions that are independently associated with an increased risk of death. The mean Charlson comorbidity score in the vertebroplasty cohort was 3.1 ± 3.2 compared with 1.9 ± 2.5 in the untreated cohort considered as a whole (Table 1). Thirty-eight percent of the untreated patients had a Charlson index score of zero compared with just 21% of treated patients. Conversely, 31% of treated patients, compared with only 19% of Rochester residents, had ≥4 of the serious conditions considered in the Charlson index. Comparable proportions of patients in the treated and untreated cohorts (48% versus 44%) had comorbidity scores of 1–3. Adjustment for the greater proportion of

Table 2: HRs with 95% CIs comparing risk of death after adjusting for age in treated-versus-untreated cohorts

Subgroup	HR (95% CI)
All subjects: treated-vs-untreated cohort	
Univariate	1.62 (1.35–1.96)
Sex adjustment	1.41 (1.17–1.71)
Sex + Charlson score adjustment	1.17 (0.96–1.42)
Charlson index = 0	
Univariate	1.50 (0.86–2.61)
Sex adjustment	1.46 (0.84–2.55)
Charlson index = 1–3	
Univariate	1.09 (0.83–1.43)
Sex adjustment	1.00 (0.76–1.32)
Sex + Charlson score adjustment	0.94 (0.71–1.24)
Charlson index >3	
Univariate	1.35 (0.99–1.83)
Sex adjustment	1.26 (0.91–1.73)
Sex + Charlson score adjustment	1.20 (0.87–1.66)
All subjects: treated vs symptomatic untreated cohort	
Univariate	1.32 (1.08–1.62)
Sex adjustment	1.20 (0.98–1.48)
Sex + Charlson score adjustment	1.02 (0.82–1.25)
Charlson index = 0	
Univariate	1.22 (0.68–2.19)
Sex adjustment	1.22 (0.68–2.19)
Charlson index = 1–3	
Univariate	0.97 (0.72–1.30)
Sex adjustment	0.92 (0.68–1.24)
Sex + Charlson score adjustment	0.86 (0.64–1.16)
Charlson index >3	
Univariate	1.07 (0.76–1.51)
Sex adjustment	1.02 (0.72–1.45)
Sex + Charlson score adjustment	1.00 (0.71–1.42)

men (with their worse survival) in the vertebroplasty cohort reduced the overall excess risk of death from an HR of 1.63 (95% CI, 1.35–1.96) in the univariate analysis to an HR of 1.41 (95% CI, 1.17–1.71), whereas further adjustment for greater comorbidity in the vertebroplasty cohort reduced the HR to 1.17 (95% CI, 0.96–1.42) compared with the untreated cohort (Table 2).

As also shown in Table 2, however, differences were reduced or disappeared altogether when the treated patients were compared with the more comparable symptomatic untreated patients. Thus, the mean Charlson comorbidity score in the subgroup of untreated patients who were symptomatic was 2.1 ± 2.6. The univariate relative risk of death among symptomatic vertebroplasty recipients compared with the symptomatic untreated subgroup was found to be 1.32 (95% CI, 1.08–1.62), and this was reduced to an HR of 1.02 (95% CI, 0.82–1.25) following adjustment for the differences in sex and comorbidity distributions (On-Line Fig 1*C*). Among symptomatic patients with none of the conditions included in the Charlson index, the univariate relative risk of death in the vertebroplasty cohort compared with the untreated group was an HR of 1.22 (95% CI, 0.68–2.19). Similar results were seen in the group with 1–3 such conditions (HR, 0.97; 95% CI, 0.72–1.30) or with ≥4 conditions (HR, 1.07; 95% CI, 0.76–1.51). None of these latter comparisons were statistically significant (Table 2).

Clinical Predictors of Survival

We also examined the extent to which clinical improvement 1 month following vertebroplasty was associated with a reduced risk of death (On-Line Table 1). Compared with preoperative scores, mean improvements in the pain at rest (1.3 ± 0.9), pain with activity (1.0 ± 0.7), mobility (0.7 ± 0.5), and medication use (0.6 ± 0.6) were consistent with those in previous reports. Despite these favorable outcomes among the treated cohort, neither the raw scores nor the improvements were associated with a significant change in mortality risk (On-Line Table 1).

Discussion

Vertebroplasty has enjoyed widespread success as a means of achieving immediate and durable reductions in pain, disability, narcotic use, and immobility among patients with osteoporotic vertebral compression fractures refractory to conservative management.[40] Recent randomized controlled studies, however, suggest that the observed clinical improvements may be attributable to a placebo effect.[20] Regardless of the mechanisms of efficacy, we assumed that survival would, in turn, also show a benefit following vertebroplasty. Instead, our initial analysis revealed that vertebroplasty recipients had only 77% of the survival at 5 years relative to that expected for persons of like age and sex in the general US white population. This was not entirely unexpected because reduced survival has been observed among patients with vertebral fractures treated only with conservative measures.[33,41-47] However, our findings suggest that the well-established improvements in mobility and narcotic dependence do not translate into improved survival relative to patients treated with conservative measures, and the causes for this failure to enhance longevity remain unclear. Consistent with this observation, our analysis failed to identify a demographic or clinical metric during the pre-, peri-, or postprocedural period that was predictive of survival outcome among vertebroplasty recipients.

Because the associated comorbidities commonly seen among patients with vertebral fractures can adversely influence their long-term survival,[27,45] we compared the survival of our treated cohort with that of an untreated cohort of patients with vertebral fractures to better control for these variables. Even compared with untreated patients, the risk of death remained 17% greater among the patients with vertebroplasty after adjusting for the greater percentage of men, whose survival is worse, and the higher average comorbidity scores in the treated group. However, recent data suggest that symptomatic fractures portend worse outcomes[48] and are thus more like those in the vertebroplasty candidates who present exclusively with symptomatic fractures. Exclusion of the asymptomatic fractures from the untreated comparison group resulted in similar mortality rates between groups, suggesting that the vertebroplasty procedure itself does not carry an increased risk of mortality. Instead, our findings suggest that vertebroplasty candidates represent the subpopulation of vertebral compression fractures with the highest mortality risk due to associated comorbid conditions and the intrinsic severity of their osteoporotic disease.

To date, there are limited reports detailing survival following vertebroplasty, though larger studies of survival following kyphoplasty have been reported.[26,49] Among vertebroplasty

studies that tangentially report survival, most feature limited numbers of patients and short follow-up. In 1 Australian trial, for example, 2 of 38 patients randomized to vertebroplasty died within 6 months (including 1 from a chest infection deemed unrelated to the procedure) compared with 1 of 40 assigned to the placebo intervention.[21] In our treated cohort, 3 of 524 patients died within 30 days of their first osteoporosis vertebroplasty; however, none of these deaths were a result of procedural complications. Instead, there was a steady increase in mortality with time following vertebroplasty, also seen among unselected patients with vertebral fractures in Rochester.[31] The relative increase in late mortality contrasts with that in patients with hip fractures, in whom a 10-fold increase in the relative risk of death occurs in the first weeks following fracture and declines thereafter.[50]

It is generally held that only severe vertebral fractures directly contribute to death through complications such as respiratory restriction.[43] Additionally, reduced survival following vertebral fracture may be confounded by the significant diseases and treatments (eg, corticosteroid therapy) that also cause the fractures.[45] Adjusting for differences in underlying comorbidity did reduce by a third the apparent excess of deaths following vertebroplasty, but the hazard of death was still significantly increased. However, when we limited our age-, sex-, and comorbidity-adjusted analysis to those individuals with symptomatic fractures within the untreated cohort, we found that vertebroplasty recipients had similar survival rates. These findings reveal that clinical selection criteria for the vertebroplasty procedure seem to favor those patients with a higher risk of mortality compared with the entire pool of patients with symptomatic and asymptomatic vertebral fractures combined. The relatively greater mortality overall is unexplained, as indeed is the case for reduced survival following vertebral fractures generally.[44,51]

The strengths of this study lie in the large number of patients with vertebroplasty evaluated and in the duration of follow-up relative to other studies. In addition, our analysis is unique insofar as we retrospectively compared the survival of a treated cohort enrolled in our institutional treatment data base (1999–2007) with that of an untreated cohort of Rochester residents with vertebral fractures identified in 1985–1994. This latter cohort was diagnosed in the decade preceding the advent of vertebroplasty within the United States in the late 1990s and thus did not have the opportunity to receive this treatment. The availability of the extensive data resources of the Rochester Epidemiology Project facilitated this comparison, which would otherwise have been impossible to conduct in light of current ethical and clinical practice guidelines.

Limitations of this analysis reside largely in the use of a parallel nonconcurrent retrospective study design, because comparison of 2 independent cohorts has the potential to introduce unwanted error via confounding variables. Although our data suggest similar survival following statistical adjustment, our cohorts were dissimilar, with the treated group possessing significantly higher Charlson indices, indicative of more severe comorbid conditions. Despite the fact that we adjusted for this disparity in our survival analysis, the treated cohort may have had additional important comorbid conditions not accounted for in the Charlson comorbidity index. It is also possible that changes in standards of care subsequent to the management of the untreated cohort in the 1980s to 1990s may have been inadvertently contributing to a reduced lifespan. However, modern standards of care should have led to earlier detection and more rigorous management and follow-up, all of which would be expected to improve survival following vertebral fracture. Finally, long-term follow-up was more complete among the untreated Rochester cohort, and it is possible that this follow-up bias could lead to erroneous conclusions in relative survival ratios. Accordingly, we studied the subgroup of treated local patients and found no appreciable changes in relative survival compared with the treated cohort, suggesting that our analyses of the larger treated group are valid.

Conclusions

Our analysis suggests that recipients of vertebroplasty have mortality rates similar to those of individuals of similar age, sex, and comorbid burden with untreated but symptomatic osteoporotic vertebral fractures. These results suggest that the increased mortality risk seen among vertebroplasty recipients compared with the general US population or among the asymptomatic fracture population simply represents a selection bias because the medical community is treating with vertebroplasty the patients with the most severe vertebral fractures. Among treated individuals, no clinical metric used to assess the efficacy of vertebroplasty was predictive of survival.

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