Review Article

The statistical fragility of vertebroplasty outcomes: A systematic review of randomized controlled trials

ABSTRACT

Randomized clinical trials (RCTs) on vertebroplasty are crucial for guiding the treatment of vertebral compression fractures, but their overlooked statistical fragility can undermine clinical reliability. Minor outcome changes may overturn significant findings, risking unreliable evidence, and impacting patient care. This study assessed the fragility of significant outcomes in vertebroplasty RCTs, hypothesizing high sensitivity to such changes. PubMed, Embase, and MEDLINE were searched for RCTs on vertebroplasty reporting dichotomous outcomes. The fragility index (FI) and reverse FI quantified the number of outcome reversals needed to change statistical significance for significant and nonsignificant results, respectively. The fragility quotient (FQ) was calculated as the FI divided by the study sample size. Subgroup analysis was conducted by outcome category. A total of 276 outcomes from RCTs were analyzed. The median FI was 5 (interquartile range [IQR]: 4–5), with a FQ of 0.053 (IQR: 0.019–0.088). Statistically significant outcomes (n = 36) had a median FI of 3 (IQR: 2–4) and FQ of 0.034 (IQR: 0.018–0.051), whereas nonsignificant outcomes (n = 240) showed a median FI of 5 (IQR: 4–5) and FQ of 0.062 (IQR: 0.021–0.088). Fracture-related outcomes were the most robust (FI: 5, FQ: 0.088), whereas cement leakage was the most fragile (FI: 3, FQ: 0.041). Pain outcomes had an FI of 5 (FQ: 0.062), and complications and vertebroplasty versus kyphoplasty outcomes were more robust (FI: 5, FQ: 0.013). Patients lost to follow-up exceeded the FI in 79% of outcomes. The statistical findings in vertebroplasty RCTs are fragile and warrant cautious interpretation. A small number of outcome reversals or consistent postoperative follow-up can shift the significance of the results. Standardized reporting of P values alongside FI and FQ metrics is recommended to help clinicians evaluate the robustness of study findings.

Keywords: Spine surgery, statistical fragility, vertebral compression fracture, vertebroplasty

INTRODUCTION

Vertebroplasty for the treatment of vertebral compression fractures (VCFs) is a common surgical intervention in which bone cement is injected into a fractured vertebra to stabilize the vertebra and relieve pain.[1] Stabilizing the vertebra minimizes the risk of developing spine deformities or further vertebral collapse.[2] The utilization of vertebroplasty for the treatment of VCFs has declined by 73% between 2004 and 2017.[3] The general trend of spine surgeons moving away from vertebroplasty for the treatment of VCFs can be attributed to a variety of causes, including concerns about efficacy and safety, evolving clinical guidelines for the treatment of osteoporotic fractures, and more promising

Alexander Yu, Kareem S. Mohamed, Mark Kurapatti, Junho Song, Jonathan J. Huang, Prabhjot Singh, Yazan Alasadi, Abhijeet Grewal, Avanish Yendluri, Nikan Namiri, John Corvi, Jun S. Kim, Samuel K. Cho

Department of Orthopaedic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Address for correspondence: Dr. Junho Song, Department of Orthopaedic Surgery, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029, USA. E-mail: junhosong96@gmail.com

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outcomes from alternative treatments.[4,5] Regardless, there remains debate about the efficacy of this procedure in comparison to alternative surgical interventions such as balloon kyphoplasty.

Randomized controlled trials (RCTs) have been the gold standard in assessing vertebroplasty outcomes and have played a crucial role in guiding physicians' decisions to pursue vertebroplasty versus alternative treatments.[6-8] However, ongoing concerns about the statistical robustness of RCT outcomes have prompted further scrutiny.[9,10] Although *P* values do serve to indicate statistical significance in RCTs, overreliance on this singular metric can be misleading when incorporating the results of such studies into clinical decision-making.[11,12] Metrics such as the fragility quotient (FQ), fragility index (FI), and reverse FI (rFI) help elucidate the statistical reliability of the data used to formulate *P* values in research studies. These metrics calculate the number of reversals that would need to occur in a binary variable data set to alter the result from statistically significance to statistically nonsignificant or vice versa. Prior fragility studies have revealed the statistical fragility and limited robustness of various RCTs in spine surgery and the broader orthopedic literature.[13-18]

With continued controversy on the efficacy of vertebroplasty procedures, it is important to analyze the robustness of the results reported in RCTs. However, the literature on the fragility of RCTs in spine interventions such as vertebroplasty is sparse. As such, this study aimed to analyze the statistical reliability of RCTs assessing vertebroplasty efficacy, outcomes, and complications using statistical fragility metrics. We hypothesize that vertebroplasty outcomes will be statistically fragile, thereby assisting future assessments of the literature and subsequent applications of vertebroplasty in clinical practice.

METHODS

Systematic search strategy

This study conducted a systematic search of PubMed, Embase, and MEDLINE databases to identify randomized controlled trials published between January 1, 2010, and July 16, 2024. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[19] The search strategy employed various boolean combinations of keywords, synonyms, and term variations, including "vertebroplasty," "spine surgery," and "percutaneous." The comprehensive search strings are detailed in the Supplementary Material.

Eligible studies included RCTs that reported dichotomous outcomes and featured at least one treatment arm involving endoscopic lumbar decompression. Exclusion criteria encompassed studies published in non-English languages, cadaveric, biomechanical, animal, or *in vitro* studies, non-RCT designs, and studies without full-text availability. Titles and abstracts were screened by two independent reviewers, followed by a full-text review, with conflicts resolved by a third independent reviewer. Reasons for exclusion were documented, and the senior author and spine surgeon, S. K. C., confirmed the final study selection.

The revised Cochrane risk-of-bias tool was used to evaluate bias in the included RCTs.[20] This review focused on the statistical reporting and significance of outcomes rather than direct clinical outcomes, and thus, it did not meet the criteria for registration with the International Prospective Register of Systematic Reviews (PROSPERO). Only publicly accessible studies were analyzed, eliminating the need for institutional review board approval.

Study screening and data extraction

Key data extracted from the selected studies included the first author, year of publication, journal title, experimental and control group interventions, reported outcomes, results, number of patients lost to follow-up (LTF), and *P* values where available. Study characteristics are summarized in Table 1.

Outcome measures were categorized into subgroups where applicable, including complications, post-operative fracture, cement leakage, and pain. The vertebroplasty versus kyphoplasty subgroup included RCTs that directly compared the efficacy of the two procedures. Data extraction was performed independently by reviewers using standardized forms to ensure consistency.

Fragility analysis

Fragility analysis was conducted using a two-tailed Fisher's exact test to evaluate the statistical significance of reported outcomes at a threshold of $P < 0.05$. The FI was calculated for significant outcomes by determining the minimum number of event reversals required for the *P* value to rise above 0.05, rendering the results no longer statistically significant [Figure 1].

For nonsignificant outcomes, the rFI was calculated by manipulating event outcomes until the *P* value dropped below 0.05. The FQ was derived by dividing the FI or rFI by the study sample size, reflecting the proportion of patients needing an outcome reversal to alter statistical significance. Subgroup analyses were performed based on

outcome type and statistical significance. Fragility analysis results were summarized as medians with interquartile ranges (IQRs).

RESULTS

Search results

The initial database searches yielded 550 studies after removing duplicates. Following the title and abstract screening, 150 studies were excluded from the study. The remaining 159 full-text reports were assessed, with 40 randomized trials deemed suitable for inclusion in the final analysis. A PRISMA flow chart detailing the screening process and literature search outcomes is displayed in Figure 2.

Across all 40 RCTs, we identified 276 dichotomous outcomes [Table 2]. Thirty-six outcomes were classified as statistically significant ($P < 0.05$), and 240 outcomes were classified as statistically nonsignificant. For the 276 total outcomes, the median FI was 5 (IQR: 4–5), and the median FQ was 0.053 (IQR: 0.019–0.088), indicating that the reversal of only 5.3% of patients is required to alter the study significance of included RCTs. For the 36 significant outcomes, the median FI was 3 (IQR: 2–4), and the median FQ was 0.034 (IQR: 0.018–

Table 1: Characteristics of included studies

Author	Year	Journal	Sample size	Lost to follow-up
Klazen *et al*.	2010	*American Journal of Neuroradiology*	202	16
Rousing *et al*.	2010	*Spine*	50	1
Liu *et al*.	2010	*Osteoporosis International*	100	1
Farrokhi *et al*.	2011	*Journal of Neurosurgery: Spine*	82	7
Blasco *et al*.	2012	*Journal of Bone and Mineral Research*	125	30
Bae *et al*.	2012	*Spine*	256	0
Yang *et al*.	2012	*European Spine Journal*	76	1
Vogl *et al*.	2013	*Spine*	104	0
Dohm *et al*.	2014	*American Journal of Neuroradiology*	404	79
Orgera *et al*.	2014	*Cardiovascular and Interventional Radiology*	50	0
Chen *et al*.	2014	*Journal of Spinal Disorders and Techniques*	39	0
Chen *et al*.	2014	*Journal of Clinical Neuroscience*	96	7
Kroon *et al*.	2014	*Journal of Bone and Mineral Research*	74	7
Dohm *et al*.	2014	*American Journal of Neuroradiology*	408	27
Zhang *et al*.	2015	*Journal of Spinal Disorders and Techniques*	68	0
Zhang *et al*.	2015	*BMC Musculoskeletal Disorders*	50	0
Staples *et al*.	2015	*Archives of Osteoporosis*	78	8
Zhang *et al*.	2015	*Clinical Neurology and Neurosurgery*	39	7
Leali *et al*.	2016	*Clinical Cases in Mineral and Bone Metabolism*	400	0
Clark *et al*.	2016	*The Lancet*	120	7
Ruatti *et al*.	2016	*European Spine Journal*	143	18
Wang *et al*.	2016	*European Spine Journal*	206	0
Yang *et al*.	2016	*Spine*	135	28
Guo *et al*.	2017	*Medicine (United States)*	100	0
Lin *et al*.	2017	*World Neurosurgery*	68	0
Arabmotlagh *et al*.	2017	*Journal of Orthopaedic Research*	42	0
Wang *et al*.	2018	*International Journal of Clinical and Experimental Medicine*	68	0
Wang *et al*.	2018	*Oncology Letters*	86	0
Firanescu *et al*.	2019	*Cardiovascular and Interventional Radiology*	180	4
Xu *et al*.	2019	*Surgical Innovation*	42	0
Alhashash *et al*.	2019	*Global Spine Journal*	60	0
Sun *et al*.	2019	*World Neurosurgery*	60	3
Griffoni *et al*.	2020	*European Spine Journal*	113	0
Xie *et al*.	2022	*Computational and Mathematical Methods in Medicine*	309	33
Carli *et al*.	2023	*Radiology*	80	5
Zhou *et al*.	2023	*Orthopaedic Surgery*	79	5
Chabert *et al*.	2023	*Annals of Physical and Rehabilitation Medicine*	99	15
Lv *et al*.	2023	*Spine*	120	17
Alkhatatba *et al*.	2024	*Orthopedics*	44	3
Zhou *et al*.	2024	*Clinical Interventions in Aging*	94	0

	(+)	(-)
Treatment A	14	72
Treatment B	3	83
		0.009

	(+)	(-)
Treatment A	14	72
Treatment B	6	80
		0.094

Figure 1: Demonstration of statistical significance reversal using a 2 × 2 contingency table with a resulting fragility index = 3. *P* values were calculated using a two-tailed Fisher's exact test

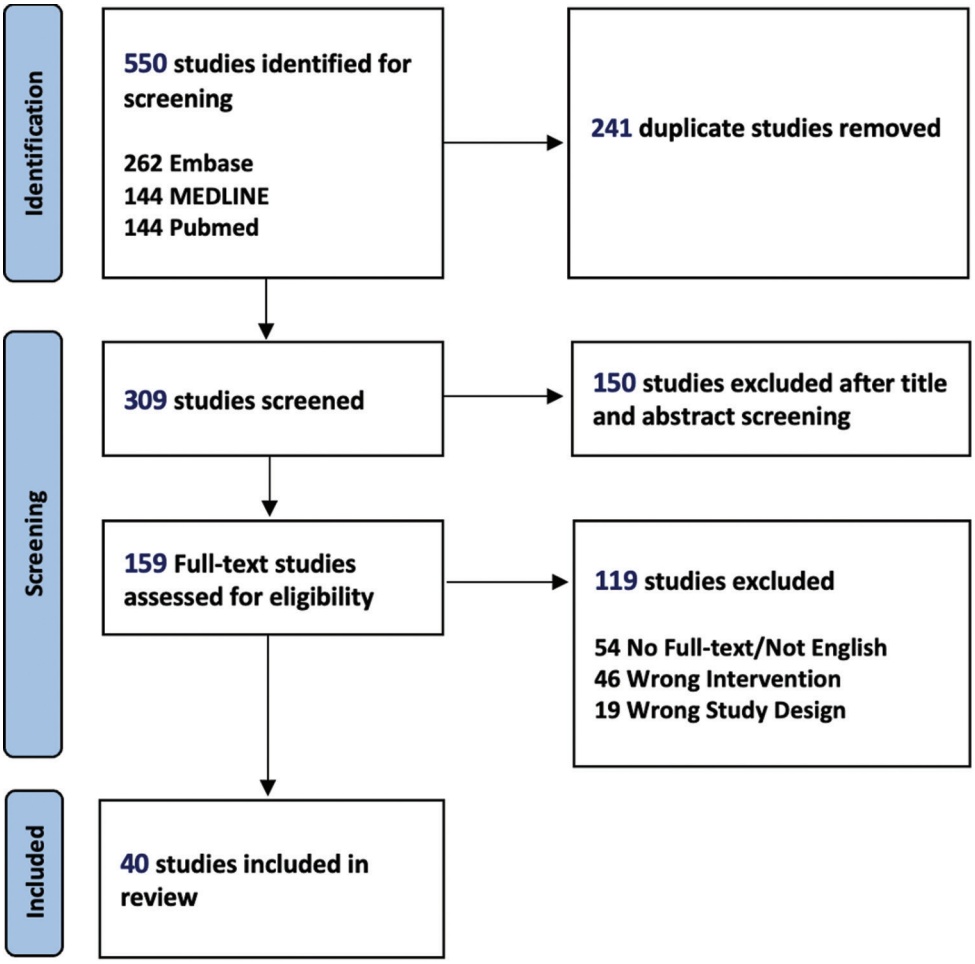

Figure 2: PRISMA flow chart of the study selection process

0.051). For the 240 nonsignificant outcomes, the median FI was 5 (IQR: 4–5), and the median FQ was 0.062 (IQR: 0.021–0.088).

We also conducted a subgroup analysis categorized by the type of reported outcomes [Table 3]. Both the complications subgroup and the vertebroplasty versus kyphoplasty subgroups were found to be the most fragile at a median FI of 4 (IQR: 4–5), 5 (IQR: 4–5) and an associated FQ of 0.013 (IQR: 0.010–0.036), 0.013 (IQR: 0.010–0.029), respectively, indicating that the reversal of just 1.3% of patients would alter the statistical significance of the findings. The cement leakage subgroup had a median FI of 3 (2–4) and an FQ of 0.041 (IQR: 0.026–0.063). The pain subgroup had an FI of 5 (4–7) and an FQ of 0.062 (IQR: 0.035–0.088). The postoperative fracture subgroup had the least fragile outcomes with an FI of 5 (IQR: 4–5) and an FQ of 0.088 (IQR: 0.047–0.088). Fracture-related outcomes were the most reported outcome ($n = 93$), whereas outcomes related to complications were the least reported ($n = 50$) [Table 3]. The number of patients with LTF was greater than the FI in 219 of the 276 outcomes (79.35%) [Table 2], this indicates that maintaining postoperative follow-up alone may be

Table 2: Statistical fragility of overall outcomes

	Number of outcomes	FI, median (IQR)	FQ, median (IQR)	Number of patients lost to follow-up> FI (%)
All RCT outcomes	276	5 (4–5)	0.053 (0.019–0.088)	79.35
Significant outcomes ($P<0.05$)	36	3 (2–4)	0.034 (0.018–0.051)	55.56
Nonsignificant outcomes ($P\geq0.05$)	240	5 (4–5)	0.062 (0.021–0.088)	80.0

RCT - Randomized clinical trial; IQR - Interquartile range; FQ - Fragility quotient; FI - Fragility index

Table 3: Statistical fragility of subgroup outcomes

	Number of outcomes	FI, median (IQR)	FQ, median (IQR)
Complications	50	4 (4–5)	0.013 (0.010–0.036)
Pain	76	5 (4–7)	0.062 (0.035–0.088)
Cement leakage	25	3 (2–4)	0.041 (0.026–0.063)
Fracture	93	5 (4–5)	0.088 (0.047–0.088)
Vertebroplasty versus kyphoplasty	65	5 (4–5)	0.013 (.010–.029)

IQR - Interquartile range; FQ - Fragility quotient; FI - Fragility index

sufficient to alter the significance of RCT findings for over three-quarters of the reported outcomes.

DISCUSSION

An increasing body of research on the robustness of orthopedic surgery studies has shown that statistically significant findings are often fragile, with similar patterns observed in spine surgery.[15-17,21-27] Among spine surgery procedure trends, there has been a marked decline in the utilization of vertebroplasty to treat VCFs,[3] motivated by comparative research over concerns about safety and inferior outcomes to alternative procedures.[4,5] Despite the high prevalence of VCFs in an aging population and the shift in the surgical management of VCFs, there is a paucity in the literature examining the robustness of vertebroplasty outcomes.[28,29] As such, the present study aimed to assess the fragility of RCTs on vertebroplasty outcomes. Among fragility metrics (FI, rFI, and FQ), FQ accounts for sample size. Thus, FQ overcomes limitations inherent to FI and rFI, which do not consider the proportion of patients affected,[30] and therefore was the focus of this study. With respect to FQ, we demonstrated major vertebroplasty outcomes have fragile statistical metrics, notably among outcomes related to nonfracture complications and comparisons to kyphoplasty.

The overall FQ for vertebroplasty RCT outcomes in the present study was 0.053 (IQR: 0.019–0.088), or a median of 5.3% of patients was necessary to reverse a given dichotomous vertebroplasty outcome. In comparison, Muthu *et al*. conducted a prior fragility analysis on 70 spine surgery RCTs and demonstrated a lower median FQ of 0.0148 (IQR: 0–0.033).[17] However, other orthopedic literature has also deemed notably higher FQs, such as 9.7% for RCTs on the management of distal radius fractures, as statistically fragile.[21] We also demonstrate for 79% of vertebroplasty outcomes, the number of patients with LTF in their respective studies is higher than the number of patients needed to reverse the significance of the outcomes. As such, while the FQ of dichotomous vertebroplasty RCT outcomes may be slightly higher than in prior fragility analysis of spine surgery RCTs, we nevertheless found dichotomous outcomes in vertebroplasty RCTs are highly fragile in the context of the broader orthopedic literature and by comparison to patient attrition rates.

We also examined any differences in FQ between significant versus nonsignificant findings, as significant findings reflect type I error, potentially leading to the false rejection of the null hypothesis and thus influencing the perceived indications, efficacy, or complications of the vertebroplasty procedure. We found significant vertebroplasty outcomes had a 45.2% lower median FQ of 0.034 (IQR 0.018–0.051) than the median FQ for nonsignificant vertebroplasty findings (0.062 [IQR 0.021–0.088]). For example, an included RCT known as the vertebroplasty for acute painful osteoporotic fractures trial was a major high-impact trial that concluded vertebroplasty was associated with improved postoperative pain relative to placebo.[31] However, the Numeric Rated Scale back pain scores at the latest (6-month) follow-up had an FQ of only 0.98%. In other words, a change in outcome for <1% of patients was needed to reverse this significant finding. In addition, 10 out of 61 (16.3%) originally eligible patients in the vertebroplasty cohort were LTF, and as such, their inclusion may have altered the study's conclusion that vertebroplasty is associated with significantly lower pain scores than placebo at 6-month follow-up. The low FQs associated with such significant findings highlight substantial concerns with the vertebroplasty RCT literature. Such overestimations of vertebroplasty outcomes relative to other surgical or nonoperative interventions may influence literature reviews and subsequent procedure recommendations in a manner that may not benefit, or ultimately even harm, patients.[32,33]

The fragility of individual outcome categories also differed, with postoperative fracture and pain outcomes having the highest median FQs. Despite fracture having the highest FQ, this outcome was still fragile, with a median FQ of

0.088 (IQR 0.047–0.088). For example, an included RCT by Blasco *et al*. demonstrated that vertebroplasty was associated with a significantly higher rate of new vertebral fracture development than conservative treatment.[34] However, we calculated an FQ of 0.008, signifying only 0.8% of patients were needed to reverse this outcome. In this study, 9 (9.5%) patients died before final follow-up. This highlights how patient mortality, especially in studies on cohorts with older patients, high-risk procedures, or limited sample size, is a necessary factor to consider it relates to the fragility of nonmortality outcomes. A prior meta-analysis by Ding *et al*. highlights that postoperative fracture recurrence or adjacent-level fracture is a major concern following vertebroplasty, with a pooled estimated incidence of 23.4%.[35] As vertebral fractures are associated with significantly increased mortality,[36-38] a majority priority of future research should be to ensure a more accurate assessment of postvertebroplasty fracture incidence. In addition, several comparisons in the literature between vertebroplasty and nonoperative management emphasize vertebroplasty are associated with superior postoperative pain scores.[39-42] However, our median FQ of 0.062 (IQR 0.035–0.088), although second-highest among outcome categories in this fragility analysis, suggests further robust RCTs are necessary to validate pain outcomes as well.

On the other hand, outcomes related to nonfracture complications and outcomes in studies comparing vertebroplasty to kyphoplasty had the lowest median FQs of 1.3% for both categories. While postoperative fracture and local cement leakage are the most common complications of vertebroplasty and thus are considered separately in this fragility analysis, other possible complications include pulmonary embolism,[43] fat embolism,[44] epidural hematoma,[45] and cardiac damage.[46,47] One possible reason for the high fragility of nonfracture complications may be due to the relative rarity and sporadic nature of nonfracture complications following vertebroplasty and its high dependence on patient comorbidities, which makes robust generalizations very difficult.

One of the most concerning findings in the present fragility analysis was the high fragility associated with outcomes among included studies comparing vertebroplasty to kyphoplasty.[48-52] The lack of robustness concerning these results is especially problematic because a large body of prior literature compares vertebroplasty to kyphoplasty and commonly utilizes postoperative metrics such as cement leakage, fracture, or other complications.[49,53,54] These studies suggest that vertebroplasty may be inferior to kyphoplasty concerning increased rate of cement extravasation, and otherwise have similar pain and complication-related outcomes. Such findings may have motivated the aforementioned declining rates in vertebroplasty utilization.[3] However, the high fragility among outcomes in comparative vertebroplasty studies highlights the necessity to corroborate or refute prior findings on vertebroplasty-kyphoplasty comparisons utilizing larger RCTs with greater patient retention rates before more definitive conclusions on the superiority of kyphoplasty, vertebroplasty, or nonoperative treatment can be made.[4]

As research progresses in the delineation of the appropriate indications and outcomes of vertebroplasty, other surgical options, or nonoperative management for the treatment of VCFs, our findings suggest more rigorous comparisons of treatment outcomes are necessary to inform clinicians on the best treatment strategy.[55] Simultaneously, the inclusion of fragility metrics such as FQ and comparisons to patient follow-up rates in conjunction with traditional *P* values may also be an effective way to mitigate overestimations of outcome reliability. Greater awareness of the fragility of outcomes in the vertebroplasty literature, along with the development of more robust RCTs comparing vertebroplasty and kyphoplasty, has the potential to significantly influence clinical decision-making.

Limitations

The present study has several limitations that warrant consideration. First, as fragility analyses are relatively novel in their application to the spine surgery literature, there are no standardized thresholds for fragility parameters such as FI or FQ to define a study as fragile. However, the authors propose emphasis on (1) the use of FQ, which corrects for study sample size, and (2) comparisons between the percentage of patients LTF and fragility to aid in the determination of a study's robustness. Furthermore, this vertebroplasty fragility analysis examined dichotomous outcomes, for which established methodologies and parameters are well-defined. However, there may be differences in the statistical fragility between dichotomous and continuous outcomes, which should be addressed in future research. Moreover, this analysis relies on metrics derived from *P* values in vertebroplasty studies to quantify outcome fragility. It does not account for other critical factors, such as variations in study design, inclusion and exclusion criteria, randomization and blinding protocols, or patient cohort characteristics, all of which influence the overall quality and generalizability of a study's outcomes. Despite these limitations, this study underscores the fragility of outcomes in vertebroplasty RCTs. The findings highlight the importance of incorporating fragility parameters, such as FQ, alongside traditional statistical measures like *P* values.

Looking forward, clinicians should interpret existing vertebroplasty RCT outcomes with caution and consider

fragility metrics. In addition, the lack of improvement in FQ over time in the present study suggests a fundamental shift in the design of RCTs is necessary. Future RCTs on vertebroplasty outcomes should prioritize patient retention efforts, expand on prior findings with larger sample sizes, and incorporate fragility metrics in their analyses alongside *P* value.

CONCLUSION

This study is the first to analyze the fragility of vertebroplasty RCT outcomes. It revealed significant vulnerabilities with a median FQ of 0.034, highlighting their susceptibility to small outcome changes. These findings, consistent with prior fragility analyses in spine surgery and orthopedics, emphasize the need for cautious interpretation of vertebroplasty outcomes in guiding clinical and policy decisions. Incorporating fragility metrics alongside traditional statistics and improving study design, sample size, and follow-up retention is critical to enhancing the reliability of future vertebroplasty research and optimizing patient care.

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Conflicts of interest
There are no conflicts of interest.

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SUPPLEMENTAL MATERIAL

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((“vertebroplasties”[All Fields] OR “vertebroplasty”[MeSH Terms] OR “vertebroplasty”[All Fields] OR “percutaneous vertebroplasty”[All Fields] OR “balloon kyphoplasty”[All Fields] OR “percutaneous kyphoplasty”[All Fields]) AND (“spine”[MeSH Terms] OR “spine”[All Fields] OR “spines”[All Fields] OR “spine s”[All Fields] OR (“spine”[MeSH Terms] OR “spine”[All Fields] OR “vertebral”[All Fields] OR “vertebrals”[All Fields]) OR (“spinal”[All Fields] OR “spinalization”[All Fields] OR “spinalized”[All Fields] OR “spinally”[All Fields] OR “spinals”[All Fields]) OR “spin*”[All Fields])) AND ((randomizedcontrolledtrial[Filter]) AND (2010:2024[pdat])).

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2. Limit 1 to (randomized controlled trial and yr=“2010 -Current”) 262