

# Vertebroplasty and balloon kyphoplasty versus conservative treatment for osteoporotic vertebral compression fractures

## A meta-analysis

Wei-Hsin Yuan, MD<sup>a,b,c,\*</sup>, Hui-Chen Hsu, MD<sup>d</sup>, Kaun-Lin Lai, MD<sup>b,e</sup>

### Abstract

**Objective:** Although the majority of available evidence suggests that vertebroplasty and kyphoplasty can relieve pain associated with vertebral compression fractures (VCFs) and improve function, some studies have suggested results are similar to those of placebo. The purpose of this meta-analysis was to compare the outcomes of vertebroplasty and kyphoplasty with conservative treatment in patients with osteoporotic VCFs.

**Methods:** Medline, Cochrane, and Embase databases were searched until January 31, 2015 using the keywords: vertebroplasty, kyphoplasty, compression fracture, osteoporotic, and osteoporosis. Inclusion criteria were randomized controlled trials (RCTs) in which patients with osteoporosis, and VCFs were treated with vertebroplasty/kyphoplasty or conservative management. Outcome measures were pain, function, and quality of life. Standardized differences in means were calculated as a measure of effect size.

**Main results:** Ten RCTs were included. The total number of patients in the treatment and control groups was 626 and 628, respectively, the mean patient age ranged from 64 to 80 years, and the majority was female. Vertebroplasty/kyphoplasty was associated with greater pain relief (pooled standardized difference in means = 0.82, 95% confidence interval [CI]: 0.374–1.266,  $P < 0.001$ ) and a significant improvement in daily function (pooled standardized difference in means = 1.273, 95% CI: 1.028–1.518,  $P < 0.001$ ) as compared with conservative treatment. The pooled estimate indicated vertebroplasty/kyphoplasty was associated with higher quality of life (pooled standardized difference in means = 1.545, 95% CI: 1.293–1.798,  $P < 0.001$ ). Subgroup analysis of 8 vertebroplasty studies and 2 kyphoplasty studies that reported pain data, however, indicated that vertebroplasty provided greater pain relief than conservative treatment but kyphoplasty did not.

**Conclusion:** Vertebroplasty may provide better pain relief than balloon kyphoplasty in patients with osteoporotic VCFs, both may improve function, and their effect on quality of life is less clear.

**Abbreviations:** CI = confidence interval, PMMA = polymethylmethacrylate, RCT = randomized controlled trial, VAS = visual analog scale, VCF = vertebral compression fracture.

**Keywords:** compression fracture, kyphoplasty, meta-analysis, osteoporosis, vertebroplasty

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<sup>a</sup> Division of Radiology, Taipei Municipal Gan-Dau Hospital (Managed by Taipei Veterans General Hospital), <sup>b</sup> School of Medicine, National Yang Ming University,

<sup>c</sup> Department of Radiology, Taipei Veterans General Hospital, <sup>d</sup> Medical Imaging Department, Taipei Beitou Health Management Hospital, <sup>e</sup> Department of Neurology, Taipei Municipal Gan-Dau Hospital (Managed by Taipei Veterans General Hospital), Taipei, Taiwan, ROC.

\* Correspondence: Wei-Hsin Yuan, Division of Radiology, Taipei Municipal Gan-Dau Hospital (Managed by Taipei Veterans General Hospital), No.12, 225 Lane, Zhi-Sing Road, Taipei 11260 Taiwan ROC (e-mail: williamyuan.tw@gmail.com)

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## 1. Introduction

Osteoporosis is a common condition of the elderly, particularly females, and vertebral compression fractures (VCFs) are one of the most common manifestations of osteoporosis.<sup>[1,2]</sup> VCFs occur in approximately 20% of individuals over 70 years of age.<sup>[3]</sup> The fractures can result in persistent pain, an inability to perform the activities of daily life, and a marked decrease in quality of life.<sup>[4,5]</sup> Reduction of pain and stabilization of the vertebrae are the goals of treatment of VCFs.<sup>[4,5]</sup> Many patients respond to conservative treatment consisting of rest or activity modification, analgesics, and bracing. However, in a large portion of patients conservative treatment is ineffective, and good surgical outcomes are hampered because of low bone mineral density, and thus surgery is typically reserved for patients with significant vertebral instability or neurological compromise.<sup>[6]</sup>

Percutaneous vertebroplasty and balloon kyphoplasty are minimally invasive methods of treating VCFs.<sup>[7]</sup> In percutaneous vertebroplasty, polymethylmethacrylate (PMMA) is injected into the vertebral body to stabilize the fracture.<sup>[7]</sup> In balloon kyphoplasty, a balloon is used to raise the vertebral body height, followed by injection of PMMA.<sup>[7]</sup> Studies have shown that both procedures reduce pain associated with VCFs and improve

function as compared with nonoperative therapy.<sup>[6,8–15]</sup> However, recent studies have reopened debate as to their effectiveness. An uncontrolled study suggested that short-term pain relief and improved function after vertebroplasty was unclear,<sup>[16]</sup> and 2 multicenter randomized trials showed that the improvement of pain and function was similar between patients who received vertebroplasty and those that received a sham injection.<sup>[17,18]</sup> Some authors, however, have questioned the methodology of these trials.<sup>[19]</sup> A pooled analysis of 5 randomized trials by Liu et al<sup>[20]</sup> has also suggested that while there appears to be some value of vertebroplasty for relieving pain, the possibility of a placebo effect should be considered. Studies have also suggested that there is an increased risk of fractures in vertebra adjacent to the treated level,<sup>[18,21,22]</sup> though other studies have indicated the risk is low or nonexistent.<sup>[23]</sup>

The aim of the present study was to perform a meta-analysis to compare the efficacy vertebroplasty and kyphoplasty versus conservative management for the treatment of osteoporotic VCFs.

## 2. Materials and methods

### 2.1. Literature search strategy and study selection

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>[24]</sup> Medline, Cochrane, and Embase databases were searched from inception until January 31, 2015 using combinations of the keywords: vertebroplasty, kyphoplasty, compression fracture, osteoporotic, and osteoporosis. Reference lists of relevant studies were hand-searched. Studies were identified by 2 independent reviewers, and when there was uncertainty regarding eligibility a third reviewer was consulted and disagreements resolved by consensus. The approval by an institutional review board is not required for this study because human subjects were not studied.

Inclusion criteria for the analysis were randomized controlled trial (RCT), patients with osteoporosis and VCFs, intervention group received balloon kyphoplasty or vertebroplasty, and control patients conservative treatment. Nonrandomized trials, letters, comments, editorials, case reports, proceedings, and personal communications were excluded. Studies in which patients had cancer, pathological fractures, corticosteroid-induced osteoporosis, or received surgical treatment were also excluded. In addition, nonEnglish and nonChinese language articles were also not considered for inclusion.

### 2.2. Data extraction and statistical analysis

Two reviewers independently extracted data from the included studies. When there was uncertainty regarding any points, a third reviewer was consulted. Data extracted from studies that met the inclusion criteria included the name of the first author, year of publication, study design, demographic data of subjects, patient diagnoses, type of intervention, length of follow-up, and numerical data of the outcomes of interest.

The outcomes measures considered were pain, function, and quality of life. Standardized differences in means and 95% confidence intervals (CIs) were calculated, and used as the measure of effect size.<sup>[25]</sup> A standardized difference in means greater than 0 indicates a greater reduction of pain, greater improvement in function, and better quality of life in the treatment group as compared to the control group. A 2-sided

$P < 0.05$  was considered statistically significant. A  $\chi^2$ -based test of homogeneity was performed using Cochran  $Q$  statistic and  $I^2$ . For the  $Q$  statistic, a value of  $P < 0.10$  was considered to indicate statistically significant heterogeneity.  $I^2$  illustrates the percentage of the total variability in effect estimates among trials that is due to heterogeneity rather than to chance, and a value  $> 50\%$  was considered to indicate significant heterogeneity. A random-effects model of analysis (DerSimonian–Laird method) was used if significant heterogeneity was detected ( $I^2 > 50\%$  or Cochran  $Q$   $P < 0.1$ ). Otherwise, a fixed-effect model of analysis was used. Sensitivity analysis was performed on the basis of the leave-one-out approach. Subgroup analysis was performed according to treatment modality (i.e., vertebroplasty and kyphoplasty). Funnel plots and 1-sided Egger test were performed to evaluate publication bias. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

### 2.3. Risk of bias assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).<sup>[25]</sup>

The quality assessment was performed by the independent reviewers, and a third reviewer was consulted for any uncertainties.

## 3. Results

### 3.1. Literature search and study characteristics

A flow diagram of the study selection is shown in Fig. 1. After the initial identification of 172 articles, 97 were excluded, and the full texts of 75 were reviewed. Subsequently, 65 articles were excluded, the reasons for which are shown in Fig. 1. Thus, 10 studies were included in the meta-analysis.<sup>[8–11,17,18,26–29]</sup>

All of the included studies were RCTs, and the total number of patients in the treatment and control groups was 626 and 628, respectively. The mean age of patients in the 10 studies ranged from 64 to 80 years, and the majority of the patients were female. Eight of the studies examined vertebroplasty, and 2 studies compared the effect of kyphoplasty with nonsurgical treatment. Three studies had a follow-up duration of less than 6 months, among which the follow-up duration of 1 study was only 2 weeks (Table 1).

### 3.2. Pain

There was evidence of heterogeneity across the 10 studies that reported pain data (Cochran  $Q = 142.3$ ,  $P < 0.001$ ,  $I^2 = 93.7\%$ ); therefore, a random effects model of analysis was performed to calculate the pooled estimates. Five of the 10 studies demonstrated a significant reduction in pain. Pooled results indicated that patients in treatment group had greater pain relief than those in the control group (pooled standardized difference in means = 0.820, 95% CI: 0.374–1.266,  $P < 0.001$ ; Fig. 2A).

In both treatment type subgroups, there was large heterogeneity across studies (kyphoplasty:  $Q = 73.0$ ,  $P < 0.001$ ,  $I^2 = 98.6\%$ ; vertebroplasty:  $Q = 63.4$ ,  $P < 0.001$ ,  $I^2 = 89.0\%$ ), and thus random-effects models were used to pool estimates of individual studies. As compared with patients treated conservatively, the change of visual analog scale (VAS) pain score was higher in patients treated with balloon kyphoplasty; however, the results

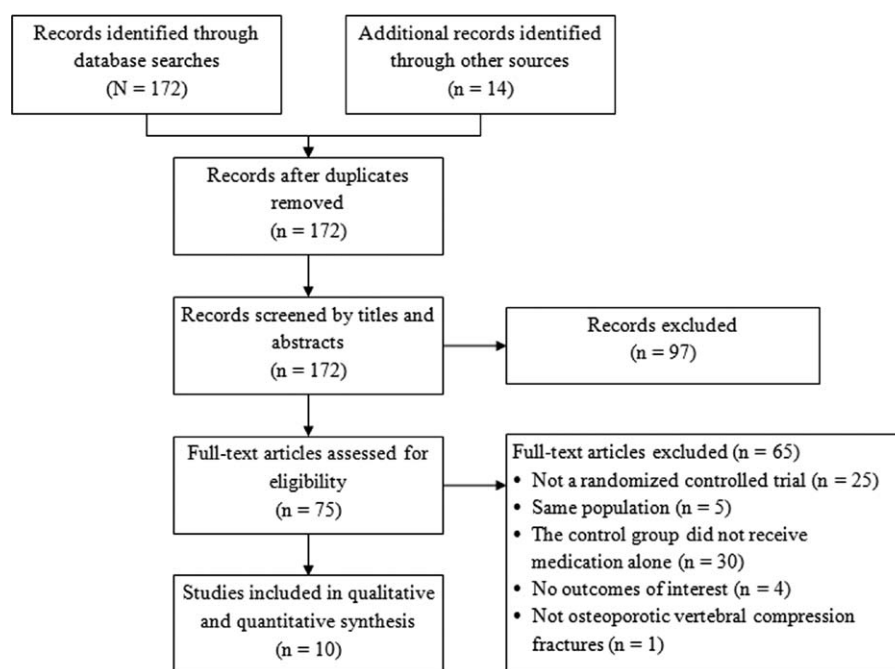


Figure 1. Flow diagram of study selection.

**Table 1**  
Summary of basic characteristics of selected studies for meta-analysis.

References	Study design	Diagnosis of patient	No. of patients	Intervention	Age, y	Male, %	Duration of follow up	Scale of pain	Scale of function	Scale of quality of life
Chen et al <sup>[26]</sup>	RCT	Chronic painful osteoporotic spinal fractures	46	Percutaneous vertebroplasty	64.63 (9.10)	30	12 mo	VAS	RMDQ	
Blasco et al <sup>[27]</sup>	RCT	Painful osteoporotic vertebral fractures	64	Conservative treatment Vertebroplasty	66.49 (9.11) 71.33 (9.95)	30 27	12 mo	VAS		QUALEFFO
Boonen et al <sup>[28]</sup>	RCT	Acute painful vertebral fractures	149	Conservative Kyphoplasty	75.27 (8.53) 72.2 (8.45)	18 23	24 mo	VAS	RMDQ	EQ-5D
Farrokhi et al <sup>[11]</sup>	RCT	Osteoporotic VCFs	40	Nonsurgical treatment Percutaneous vertebroplasty	74.1 (6.05) 72 (7.75)	23 25	36 mo	VAS	Oswestry LBP scale	
Xie et al <sup>[29]</sup>	RCT	Acute/subacute osteoporotic VCFs	77	Optimal medical therapy Percutaneous kyphoplasty	74 (8.0) 67 (10)	29 61	9 mo	VAS	Barthel Index	SF-36 (PCS/MCS)
Klazen et al <sup>[10]</sup>	RCT	Osteoporotic VCFs	101	Conservative treatment Percutaneous vertebroplasty	67 (7) 75.2 (9.8)	49 31	11.4 mo	VAS	RMDQ	EQ-5D
Rousing et al <sup>[9]</sup>	RCT	Acute/semiacute osteoporotic vertebral	101	Conservative treatment Percutaneous vertebroplasty	75.4 (8.4) 80 (7.75)	31 24	12 mo	VAS	Barthel Index	EQ-5D
Kallmes et al <sup>[17]</sup>	RCT	Painful osteoporotic VCFs	24 68	Conservative treatment Vertebroplasty	80 (5.5) 73.4 (9.4)	12.50 22	1 mo	VAS	RMDQ	EQ-5D
Buchbinder et al <sup>[18]</sup>	RCT	Painful osteoporotic vertebral fractures	63 38	Control Percutaneous vertebroplasty	74.3 (9.6) 74.2 (14.0)	27 18	6 mo	VAS	RMDQ	EQ-5D
Voormolen et al <sup>[6]</sup>	RCT	Chronic painful osteoporotic VCFs	40 18 16	Sham procedure Percutaneous vertebroplasty Optimal pain medication	78.9 (9.5) 72 (6.25) 74 (8.25)	22 22 12	2 wk	VAS	RMDQ	QUALEFFO

EQ-5D = EuroQol-5 dimensions, PCS/MCS = physical composite scale/mental health composite scale, QUALEFFO = Quality of Life Questionnaire of the European Foundation for Osteoporosis, RCT = randomized controlled trial, RMDQ = Roland Morris Disability Questionnaire, SF-36 = Short-Form 36, VAS = visual analogue scale, VCF = vertebral compression fracture.

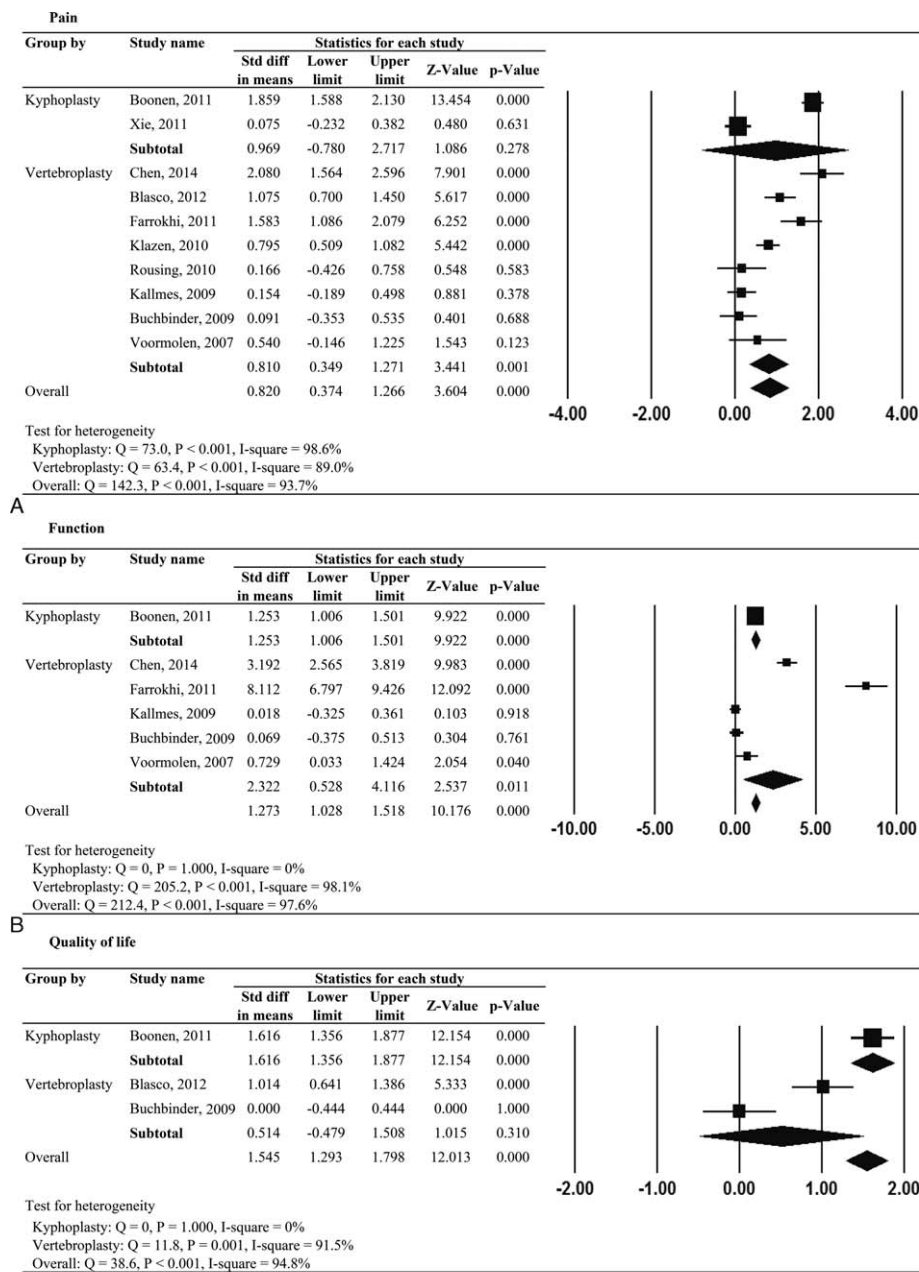


Figure 2. Forest plots of treatment effect for (A) pain, (B) functional outcome, and (C) quality of life.

did not reach statistical significance (pooled standardized difference in means=0.969, 95% CI: -0.780–2.717,  $P = 0.278$ ). Patients treated with vertebroplasty had a significantly greater decrease in pain as compared to those treated conservatively (pooled standardized difference in means=0.810, 95% CI: 0.349–1.271,  $P = 0.001$ ; Fig. 2A).

### 3.3. Functional outcome

There was evidence of heterogeneity across the 6 studies that reported functional outcome data (Cochrane  $Q = 212.4, P < 0.001, I^2 = 97.6\%$ ). In addition, 5 studies in the vertebroplasty subgroup had large heterogeneity (Cochrane  $Q = 205.4, P < 0.001, I^2 = 98.1\%$ ). Therefore, random effects models of analysis

were performed to calculate the pooled estimates. Patients who received vertebroplasty or balloon kyphoplasty had a significantly better improvement in daily function as compared with patients who were treated conservatively (pooled standardized difference in means=1.273, 95% CI: 1.028–1.518,  $P < 0.001$ ; Fig. 2B). The results were consistent in the subgroup analysis. There was improvement in functional outcomes for both kyphoplasty and vertebroplasty as compared to the control group (kyphoplasty: pooled standardized difference in means=1.253, 95% CI: 1.006–1.501,  $P < 0.001$ ; vertebroplasty: pooled standardized difference in means=2.322, 95% CI: 0.528–4.116,  $P = 0.011$ ; Fig. 2B). However, there was only 1 study in the kyphoplasty subgroup: the Xie study only provided posttreatment outcomes regarding function and quality of life. This was not sufficient to be

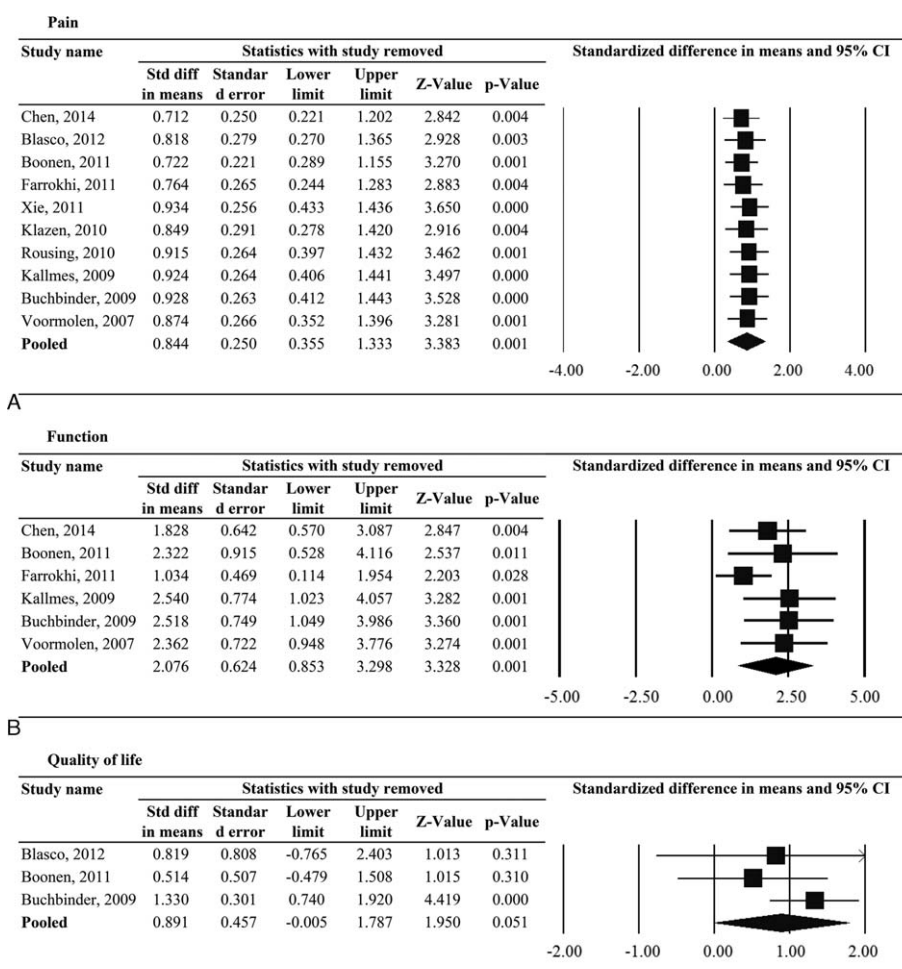


Figure 3. Sensitivity-analysis of treatment effect for (A) pain, (B) functional outcome, and (C) quality of life.

included in the subgroup analyses regarding function and quality of life because the study only provided posttreatment data, and we only analyzed changes from the baseline that could be calculated.

**3.4. Quality of life**

There was evidence of heterogeneity across 3 studies that provided quality of life data with a follow-up period longer than 6 months (Cochrane  $Q=38.6$ ,  $P<0.001$ ,  $I^2=94.8\%$ ); therefore, random effects models of analysis were performed to calculate the pooled estimates. The pooled estimate was significantly higher in the treatment group than in control group (pooled standardized difference in means=1.545, 95% CI: 1.293–1.798,  $P<0.001$ ; Fig. 2C). Results of subgroup analysis revealed that there was a beneficial effect on quality of life for kyphoplasty (pooled standardized difference in means=1.616, 95% CI: 1.356–1.877,  $P<0.001$ ), but not for vertebroplasty (pooled standardized difference in means=0.514, 95% CI: -0.479–1.508,  $P=0.310$ ; Fig. 2C). However, there was only 1 study in the kyphoplasty subgroup: the Xie study only provided posttreatment outcomes regarding function and quality of life. This was not sufficient to be included in the subgroup analyses regarding function and quality of life because the study only provided posttreatment data, and we only analyzed changes from the baseline that could be calculated.

**3.5. Sensitivity analysis**

Sensitivity analysis using the leave-one-out approach showed that the magnitude and direction of the associations between vertebroplasty/kyphoplasty and pain relief and functional outcome did not vary considerably (Fig. 3A and B), indicating that no single study had a significant impact on these outcome measures. For quality of life, 1 study had a substantial influence on the pooled estimates when removed (Fig. 3C).

**3.6. Publication bias**

Funnel plots for the evaluation of publication bias for pain and functional outcome are presented in Fig. 4A and B. No significant asymmetry was observed, indicating no evidence of publication bias (Egger test: 1-tailed  $P=0.402$  and  $0.125$  for pain and function, respectively). Publication bias analysis for quality of life was not performed as there were not enough studies to detect funnel plot asymmetry.

**3.7. Risk of bias assessment**

Results of the risk of bias assessment are presented in Fig. 5. While overall the risk of bias was low, an unclear or high risk of bias was present as a result of blinding of participants and

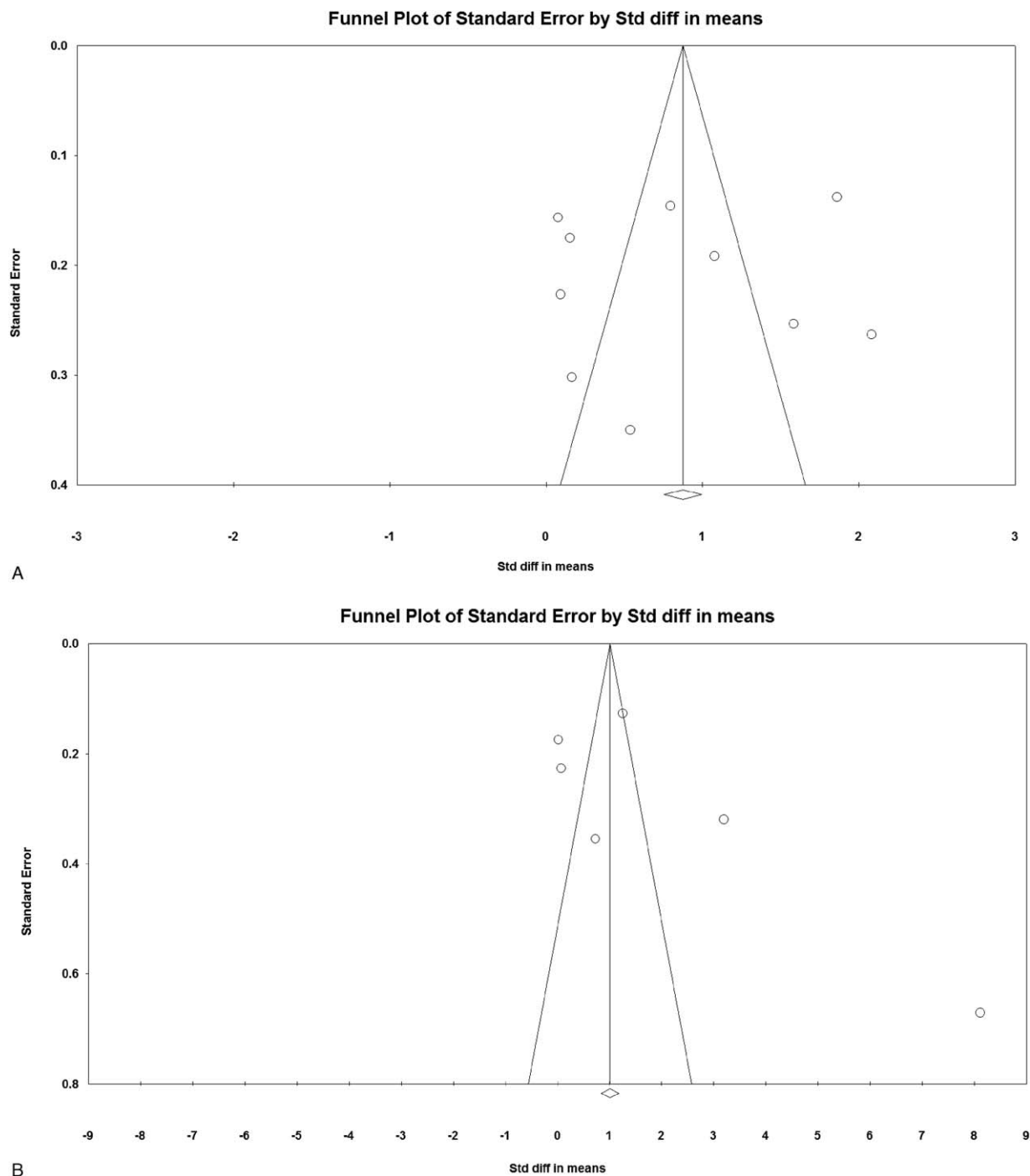


Figure 4. Funnel plots for evaluation of publication bias for (A) pain and (B) functional outcome.

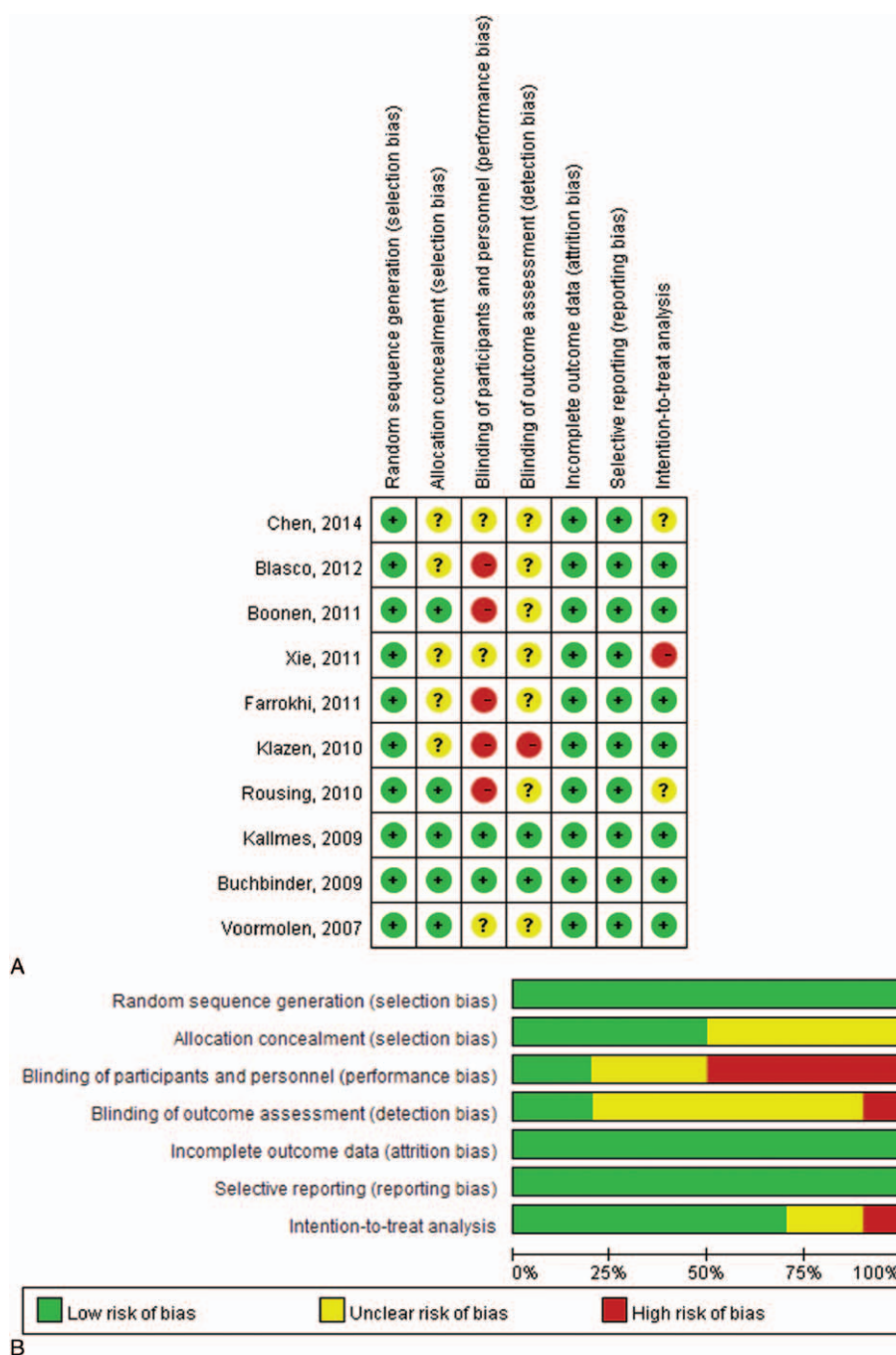
personnel (performance bias), and blinding of outcome assessment (detection bias).

**4. Discussion**

This meta-analysis examining vertebroplasty or balloon kyphoplasty for osteoporotic compression fractures indicates that overall the procedures reduce pain and improve function and quality of life as compared with conservative treatment. Analysis by surgerytype, however, indicated that pain relief of kyphoplasty was similar to that of conservative management, but pain

relief of vertebroplasty was greater than that of conservative management, both procedures improved functional outcomes to a greater degree than conservative treatment, and that while kyphoplasty improved quality of life to a greater degree than conservative treatment, there was no difference in quality of life improvement between vertebroplasty and conservative treatment. However, there was only 1 kyphoplasty study that examined quality of life and function.

While vertebroplasty and kyphoplasty are minimally invasive procedures, they are not without risk, and complications including pulmonary embolism, infection, and paraplegia have



**Figure 5.** Summary of quality assessment. (A) Risk of potential bias of individual studies and (B) risk of bias of all included studies.

been reported.<sup>[30–32]</sup> Thus it is important to determine the value and efficacy of the procedures, and if certain subgroups of patients are more likely to receive benefit than others. To this end, a number of prior meta-analyses have attempted to address this issue. In addition, most prior analyses have focused on pain relief and have not considered functional outcomes or quality of life as examined in the present analysis.

An early meta-analysis published in 2007 by Gill et al<sup>[12]</sup> included 14 vertebroplasty and 7 kyphoplasty studies reporting that both kyphoplasty and vertebroplasty resulted in a more than 5-point drop in VAS pain scores in the immediate postoperative period ( $P < 0.00001$ ), and both procedures reduced pain to the

same degree. Pain scores at a final follow-up, though, were similar to those of the initial postoperative scores for both procedures. This analysis, however, included both randomized and nonRCTs. A 2012 performed meta-analysis by Shi et al<sup>[33]</sup> including 9 studies used to calculate the weighted mean differences to evaluate pain reduction at different times after vertebroplasty, as well as quality of life (as assessed by pain-related disability) and recurrence of vertebral fractures. Pain scores were similar between patients who received vertebroplasty and sham injections at 1 to 29 days and 90 days; however, as compared with nonoperative therapy, vertebroplasty reduced pain at all times studied. Quality of life was improved in patients

who received vertebroplasty as compared to control patients, and the risk of new fractures was similar between vertebroplasty and control groups.

Liu et al<sup>[20]</sup> performed a meta-analysis of 5 RCTs that was published in 2013 that examined pain relief at different time points after vertebroplasty as compared with conservative management. The results indicated no difference in pain relief between patients that received vertebroplasty and conservative management at 2 weeks and 1 month. However, pain relief in the vertebroplasty groups was greater than that of the conservative management group at 3, 6, and 12 months. Importantly, on subgroup analysis pain scores were similar between patients that received vertebroplasty and sham injection from 2 weeks to 6 months. The authors, however, did not examine functional outcomes or quality of life. A 2014 meta-analysis by Tian et al<sup>[34]</sup> included 5 RCTs demonstrated that that VAS pain scores of patients who received vertebroplasty were significantly lower than those of patients treated conservatively at up to 48 weeks after treatment, and there was no difference in the incidence of adjacent vertebral fractures between patients treated with vertebroplasty or conservative management (odds ratio=2.06, 95% CI: 0.26–16.29,  $P=0.50$ ). A recent (2014) comprehensive review of the literature by Lamy et al<sup>[4]</sup> concluded that the efficacy of vertebroplasty/kyphoplasty for controlling pain associated with a VCF remains a matter of controversy and that the procedures should be reserved for patients in whom analgesic and conservative management have failed. The authors also reported that based on recent studies the procedures increase the risk of new fractures, particularly in vertebrae adjacent to those treated. However, while the review of the literature was comprehensive, no meta-analysis of the available data was performed.

The present review was limited to RCTs, and the literature search only identified 2 RCTs examining kyphoplasty. Boonen et al<sup>[28]</sup> randomized 300 patients with 1 to 3 vertebral fractures and pain to receive kyphoplasty or nonsurgical therapy and assessed pain, quality of life, function, and disability over a 24-month period. The kyphoplasty group exhibited a greater improvement in back pain that was statistically significant at 24 months. Kyphoplasty was also associated with statistically significant greater improvements in Short-Form 36 physical component summary scores at 6 months, but not at 12 or 24 months. During the follow-up period, no difference in the number of patients with new radiographic vertebral fractures was noted (47.5% kyphoplasty, 44.1% nonsurgical). Xie et al<sup>[29]</sup> randomly assigned 164 patients to percutaneous kyphoplasty or conservative treatment. Although pain was improved 24 hours postoperatively, with an average follow-up of 9 months VAS pain scores, and measures of function and quality of life were similar between the 2 groups.

The present analysis was unable to adequately compare the 2 procedures, as only 2 of the included studies examined kyphoplasty. Though limited, analysis by surgery type, however, indicated that pain relief of kyphoplasty was similar to that of conservative management, but pain relief of vertebroplasty was greater than that of conservative management. Prior studies have indicated that both procedures are effective for treating osteoporotic VCF, though vertebroplasty appears to be associated with higher cement leakage and new fracture rates than kyphoplasty.<sup>[35–38]</sup> Cement leakage and new fractures may certainly affect overall pain and quality of life and should be considered when deciding to perform one procedure or the other.

There are a number of limitations to this analysis that should be considered. Although all of the studies were RCTs, there was significant heterogeneity among the studies and potential bias from inadequate blinding of patients and personnel. In addition, the numbers of patients in the studies were small, and the surgical techniques and outcome measures varied. The methods used to examine outcomes, especially those regarding quality of life, varied markedly between studies, although all are accepted and validated instruments.<sup>[39–41]</sup> Although the outcome measures were different among the included studies, we only analyzed changes from the baseline that could be calculated, and standardized difference in mean was also used to elucidate the heterogeneity between studies as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>[42]</sup> No better method for addressing heterogeneity exists. Because of the small sample size in the studies, there is concern of inadequate balance after randomization. However, there was no significant publication bias or small-study effect in funnel plots (i.e., when small studies are consistently more positive, or negative, than larger studies), and by using a random-effect model the small studies will get larger weights; therefore, the direction of pooled results would not tend toward large studies.<sup>[42]</sup> In addition, inadequate balance after randomization can also be assessed from attrition bias and intention-to-treat. In the quality assessment, these 2 factors did not have big bias or impact on the included studies. Vertebroplasty and kyphoplasty were considered together as there were only 2 studies that examined kyphoplasty; however, the subgroup analysis, though limited, indicated that vertebroplasty was associated with greater pain relief than conservative management whereas kyphoplasty was not. Complications of the procedures and the possibility of fractures in adjacent vertebrae were not examined, and the follow-up duration varied markedly between the studies.

In conclusion, the results of this meta-analysis examining vertebroplasty and balloon kyphoplasty for osteoporotic compression fractures indicate that overall the procedures reduce pain and improve function and quality of life as compared with conservative treatment. Analysis by surgery type, however, indicated that pain relief of kyphoplasty was similar to that of conservative management, but pain relief of vertebroplasty was greater than that of conservative management, both procedures improved functional outcomes to a greater degree than conservative treatment, and that while kyphoplasty improved quality of life to a greater degree than conservative treatment, there was no difference in quality of life improvement between vertebroplasty and conservative treatment. These results need to be interpreted with caution, however, as only 2 studies examined kyphoplasty and only 1 of these studies examined function and quality of life.

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