

New vertebral fractures after osteoporotic vertebral compression fracture between balloon kyphoplasty and nonsurgical treatment PRISMA

Hui-Min Li, MD^a, Ren-Jie Zhang, MD^a, Hai Gao, MD^b, Chong-Yu Jia, MD^a, Jian-Xiang Zhang, PhD^a, Fu-Long Dong, PhD^a, Cai-Liang Shen, PhD^{a,*}

Abstract

Background: Because of aging of population, osteoporotic vertebral compression fracture (OVCF) appears an increasing incidence rate. Conservative therapy (CT) and balloon kyphoplasty (BKP) have been used to treat OVCFs. However, an increase in new vertebral compression fractures at nontreated levels following BKP is of concern. It is still not clear whether new fractures were a result of BKP and the purpose of this meta-analysis was to evaluate the new fractures risk after BKP compared with CT.

Methods: An exhaustive literature search of PubMed, EMBASE, and the Cochrane Library was conducted to identify randomized controlled trials and prospective nonrandomized controlled study that compared BKP with CT for patients suffering OVCF. A random-effect model was used. Results were reported as standardized mean difference or risk ratio with 95% confidence interval.

Results: Twelve studies were included and there was no significant difference in total new fractures ($P = .33$) and adjacent fractures ($P = .83$) between 2 treatments. Subgroup analyses did not demonstrate significant differences in follow-up period, mean age, anti-osteoporosis therapy, and the proportion of women.

Conclusion: Our systematic review revealed that an increased risk of fracture of vertebral bodies was not associated with BKP compared with CT.

Abbreviations: BKP = balloon kyphoplasty, CT = conservative therapy, ODI = Oswestry Disability Index, OVCF = osteoporotic vertebral compression fracture, RCT = randomized controlled trial, VAS = visual analogue scale.

Keywords: balloon kyphoplasty, conservative treatment, kyphoplasty, meta-analysis, new osteoporotic compression vertebral fracture

1. Introduction

Osteoporosis is the most common orthopedic disease and osteoporotic vertebral compression fracture (OVCF) is the most

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^a Department of Orthopedics, the First Affiliated Hospital of Anhui Medical University, Anhui, ^b Department of Orthopedics, the First Affiliated Hospital of USTC (Anhui Provincial Hospital), China.

* Correspondence: Cai-Liang Shen, Department of Orthopedics, the First Affiliated Hospital of Anhui Medical University, 210 Jixi Road, Hefei, Anhui 230022, China (e-mail: shencaliang1616@163.com).

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serious outcome of osteoporosis. Current therapies for vertebral fractures include nonsurgical and surgical treatment. Nonsurgical treatment, including bed rest, opioid analgesia, muscle relaxants, bracing, external fixation, sometimes resolves pain slowly^[1] and exacerbate bone demineralization, which ineluctably increase the risk of fracture.

During the last few decades, balloon kyphoplasty (BKP) has become widely used all over the world.^[2–6] BKP, where a balloon is filled in the vertebra to achieve partial reduction before cement injection,^[7] not only alleviates intolerable pain but also stabilizes the fractured vertebral body.^[8–15] Despite the demonstrated benefit, some authors have stated that BKP increases the risk for subsequent vertebral fractures,^[16] while other studies have found a similar incidence of recompression between BKP and conservative therapy (CT).^[17,18] Furthermore, some researchers have suggested that the procedure carries a low risk of adjacent fractures.^[19] Controversy still exists as to whether BKP increases fracture morbidity by either inducing or facilitating subsequent vertebral fractures and there are no data comparing BKP with CT to evaluate any increased risk of new fractures following treatment. Thus, the purpose of this meta-analysis was to determine whether this technique increased new level vertebral fractures and adjacent vertebral fractures.

2. Methods

2.1. Search strategy

We conducted an exhaustive literature search of PubMed, EMBASE, and the Cochrane Library to identify randomized

controlled trials and prospective nonrandomized controlled study that compared BKP with CT for patients suffering OVCF. The search terms included “kyphoplasty” or “vertebral augmentation” and “new fracture” or “refracture” or “secondary fracture” or “subsequent fracture” and “conservative treatment” or “conservative therapy” and “osteoporotic vertebral compression fractures.” The example of detailed search strategy of PubMed is reported in eTable 1, <http://links.lww.com/MD/C531>. We did not limit the languages or publication date. The literature search was last updated on March 31, 2017. Two reviewers independently searched all the titles; abstracts and references of the relevant studies were also reviewed for additional worthy literatures. When there was uncertainty, full-text articles were obtained. Any divergence was resolved by agreement between the reviewers.

2.2. Selection of studies

- (1) Participants: The study population consisted of patients who are aged 50 years or older, had back pain of no more than 12 months' duration, had a new fracture that was certified by magnetic resonance imaging (MRI), and must be a painful OVCF between the T4-L5 level before treatment.
- (2) Interventions: The intervention in the experimental group was BKP as a minimally invasive technique to treat OVCF. Other types of minimally invasive technique were excluded.
- (3) Comparisons: The intervention in the control group was CT.
- (4) Outcomes: Studies were qualified when at least one of the following outcomes were given: improvement on the Visual Analogue Scale (VAS) and the Oswestry Disability Index (ODI), numbers of new vertebral fractures (total and adjacent to the treated vertebra).
- (5) Study design: Randomized controlled trials and prospective clinical trials were regarded as eligible in the present study. Case-control study, case report, retrospective study, systematic review, and meta-analysis were excluded.

2.3. Data extraction

Two reviewers independently performed the data extraction from the qualified studies. Any disagreement was resolved by discussion or by consulting a third reviewer. The indispensable study characteristics involving details of methodology, sample size, age, sex distribution, experimental and control interventions, and outcomes were extracted.

The outcome measures of interest consisted of clinical indexes (VAS scores and ODI scores) and numbers of new vertebral fractures (total and adjacent to the treated vertebra).

2.4. Risk of bias assessment

Two reviewers applied the risk of bias tool to appraise all the included literatures according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0),^[20] respectively.

The parameters of appraisal covered random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias (baseline balance). All the domains were defined as low risk of bias, high risk of bias, or unclear risk of bias.

2.5. Statistical analysis

In this meta-analysis, we calculated the risk ratio (RR) and its 95% confidence interval (95% CI) for the dichotomous data and

the standardized mean difference (SMD) and its 95% CI for the continuous data. Statistical heterogeneity^[21] was assessed using I^2 and Chi-squared tests at a significance level of $P < .05$. A fixed effects model was performed if there was no evidence of heterogeneity ($I^2 < 50\%$) among these studies, and if the evidence of heterogeneity was tested, a random effects model was replaced. On the basis of duration of follow-up [short-term (≤ 3 months), mid-term (≥ 12 months)], subgroup analyses were performed for VAS scores. We performed the sensitivity analyses using a fixed-effect model, and excluding the largest and most weighted trials. Furthermore, we conducted meta-regression analyses to appraise the potential effect of mean age, the proportion of women, follow-up period, the number of prevalent fractures, and anti-osteoporosis therapy on the numbers of new vertebral fractures. Besides, funnel plots were used to examine the possibility of publication bias about numbers of new vertebral fractures. The statistical analysis was performed by Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) and Stata version 14.0 (Stata Corp, College Station, TX).

3. Results

3.1. Study search

A summary of the study selection process is shown in Fig. 1. There were altogether 753 relevant literatures inspected from the electronic search. Two hundred ten studies were excluded because they were duplicates. After assessing the titles and abstracts, 510 studies were eliminated because they did not meet the eligibility criteria. After verifying the full-text of the remaining 33 studies, 8 prospective randomized controlled trials^[17,18,22-27] and 4 prospective clinical trials^[19,28-30] with 1951 patients finally were included in this meta-analysis. Furthermore, we also classified the duration of follow-up as short-term (≤ 3 months) or mid-term (≥ 12 months).

3.2. Study characteristics

Table 1 summarizes the main characteristics of studies included. The baseline information of 2 groups were balanced and comparable. Of the 8 identified randomized controlled trials and 4 prospective clinical trials, 3 studies^[22,26,27] were a multicenter trial and the remaining trials were all from single trial site. Among the remaining studies, 3 studies^[17,23,25] were conducted in China, 1 study^[18] was conducted in Greece, 1 study^[28] was from Korea, 1 study^[19] was from Slovenia, and 3 studies^[24,29,30] were conducted in Germany. Furthermore, the duration of follow-up was less than 12 months in 1 study^[30] and the remaining studies reported the outcomes at the end of 12 months or more.

3.3. Risk of bias in the included studies

The risk of bias for the included studies is presented in Fig. 2. Only 1 study^[18] was regarded as having a low risk of bias, 5 studies^[18,22,24,26,27] showed an appropriate randomization, and 2 studies^[17,18] described allocation concealment in detail. Two studies^[17,18] reported an adequate blinding for both participants and outcomes assessors.

3.4. New vertebral fractures

Eight studies^[17,18,22,24,26,27,29,30] provided data for new vertebral fractures. We observed similar rates of new vertebral fractures

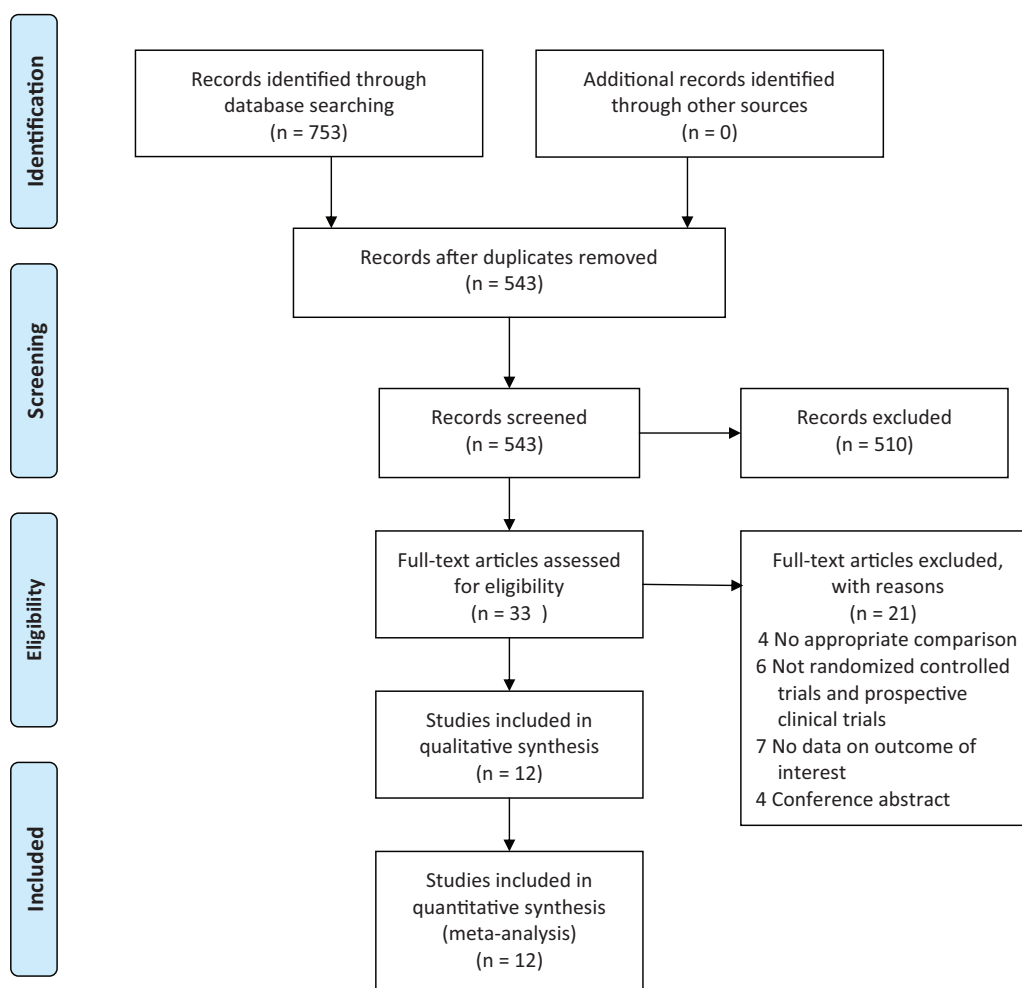


Figure 1. Flow diagram of study selection.

when comparing the BKP group with the CT group [RR=0.86, 95% confidence interval (95% CI) 0.63~1.17, $P=.33$; $I^2=32\%$; Fig. 3]. We also analyzed the incidence of new vertebral fractures adjacent to the treated one. We found that there was no statistically significant difference for new vertebral fractures

adjacent to the treated one (RR=1.04, 95% CI 0.71~1.53, $P=.83$; $I^2=0\%$; Fig. 4). The score on the ODI was evaluated between 2 groups and there was no statistically significant difference (SMD=-0.22, 95% CI -0.57 to 0.13, $P=.22$, $I^2=69\%$; Fig. 5).

Table 1
Demographic characteristics of the included studies.

Study	Year	Study design	Sample size		Gender (F/M)		Age, y		Follow-up, mo	Lost to follow-up
			BKP	CT	BKP	CT	BKP	CT		
Kasperk et al ^[29]	2005	Pro	40	20	6/34	5/15	68.7 (42–83)	70.1 (34–85)	6	0
Kasperk et al ^[30]	2010	Pro	40	20	6/34	5/15	68.7±8.5	70.1±12.3	36	4
Boonen et al ^[26]	2011	RCT	149	151	34/115	34/117	72.2 (44.5–95.2)	74.1 (52.8–89.1)	24	68
Berenson et al ^[27]	2011	RCT	77	64	28/40	26/35	64.8 (37.6–88.0)	63.0 (39.5–83.4)	12	60
Huang and Zhang ^[25]	2012	RCT	35	35	11/24	12/23	72±18	72	12	UC
Movrin ^[19]	2012	Pro	46	61	10/36	12/49	67.8±5.4	73.8±7.5	12	0
Lee et al ^[28]	2012	Pro	82	149	29/53	61/88	76.8±11.5	66.2±6.3	12	28
En and Hao ^[23]	2013	RCT	77	87	47/30	43/44	67±10	67±7	12	9
Korovessis et al ^[18]	2013	RCT	86	82	23/63	26/56	72.3 (69.9–74.7)	69.6 (66.6–72.5)	14	12
Van Meirhaeghe ^[22]	2013	RCT	149	151	34/115	34/117	72.2 (44.5–95.2)	74.1 (52.8–89.1)	24	UC
Bastian et al ^[24]	2013	RCT	57	55	10/47	14/41	73.6±8.4	76.0±9.4	12	5
Yi et al ^[17]	2014	RCT	79	121	25/54	63/58	70.9±10.04	63.9±15.51	49.4	0

BKP = balloon kyphoplasty, CT = conservative therapy, Pro = prospective clinical trial, RCT = randomized controlled trial, UC = unclear.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bastian 2013	+	-	-	+	+	+	+
Berenson 2011	+	?	?	?	+	+	?
Boonen 2011	+	?	-	-	+	+	?
En 2013	?	?	+	+	+	+	?
Huang 2012	?	?	?	?	+	+	?
Kasperk 2005b	-	-	-	+	-	+	+
Kasperk 2010a	-	-	-	+	+	+	+
Korovessis 2013	+	+	+	+	+	+	+
Lee 2012	-	-	-	-	+	+	+
Movrin 2012	-	-	-	-	+	+	+
Van Meirhaeghe 2013	+	-	-	+	+	+	+
Yi 2014	?	+	+	+	+	+	?

Figure 2. Risk of bias assessment of each included study.

3.5. Subgroup analyses, sensitivity analyses, meta-regression analyses, and publication bias

Subgroup analyses based on duration of follow-up (short-term (≤ 3 months), mid-term (≥ 12 months)) did not show significant differences (Fig. 6).

Sensitivity analyses did not alter the results except to exclude the largest and most weighted trials for the score on the ODI (Table 2).

Meta-regression analyses demonstrated no effect of follow-up period, mean age, anti-osteoporosis therapy, the proportion of women in decreasing new vertebral fractures (Fig. 7). However, the number of prevalent fractures notably influenced the number of new vertebral fractures and a higher risk of occurring more new vertebral fractures when the number of prevalent fractures were more than 2 (Fig. 8).

Publication bias is shown in Fig. 9 and there was no publication bias about new vertebral fractures.

4. Discussion

OVCF has afflicted most aged people. Except for CT, BKP has become more popular for treating OVCF, as this technique was described by Galibert et al.^[31] As a minimal invasive spinal surgery technique, BKP has been proven the advantage of pain relief.^[11,32] However, any new medical technology has some complications and risks, and these techniques are not exceptions. For example, cement leakage and new vertebral fractures after BKP have been reported.^[33,34] Especially for complications of new vertebral fractures, there is a great deal of debate about whether it is induced by the technique. Some studies have reported that an increased fracture incidence after kyphoplasty in patients with osteoporosis,^[35,36] and the percentage of subsequent fractures varies from 1 to 26.^[36,37] It remains unclear whether new vertebral body fractures are due to the augmentation with bone cement or related to the natural progression of osteoporosis. Many biomechanical and clinical studies have been published to explore this issue so as to determine the risk factors of new vertebral body fractures.^[38-40]

The exact mechanism for recompression is still unclear, but many studies indicated that BKP increased stiffness and strength. In addition, due to the injection of bone cement, the augmented vertebra was likely stiffer than the adjacent vertebra,^[16] leading to fractures at the adjacent levels.^[41] However, according to a 3-dimensional, nonlinear finite element model study,^[42] they found that vertebral body fractures in the adjacent vertebrae after

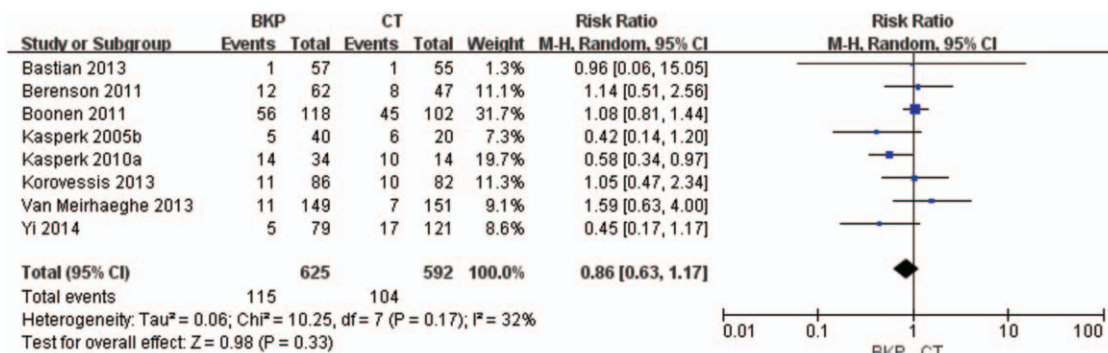


Figure 3. Forest plots of the included studies comparing new vertebral fractures in patients who underwent BKP and those who underwent CT. BKP=balloon kyphoplasty, CT=conservative therapy.

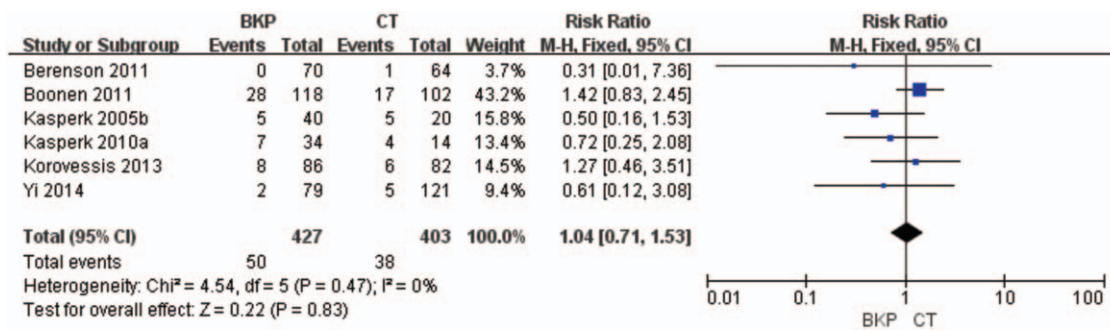


Figure 4. Forest plots of the included studies comparing adjacent vertebral fractures in patients who underwent BKP and those who underwent CT. BKP = balloon kyphoplasty, CT = conservative therapy.

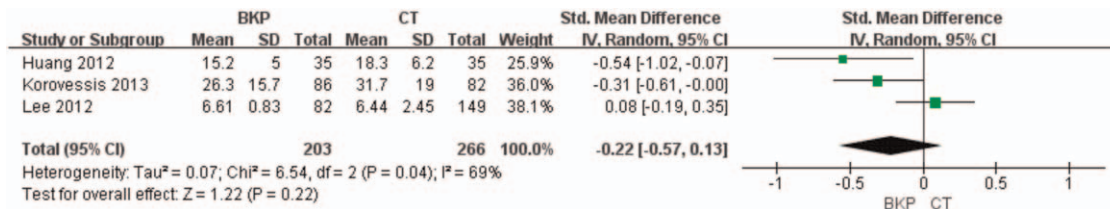


Figure 5. Forest plots of the included studies comparing the score on the Oswestry Disability Index (ODI) in patients who underwent BKP and those who underwent CT. BKP = balloon kyphoplasty, CT = conservative therapy.

kyphoplasty were not induced by the elevated stiffness of the treated vertebra, but instead, the anterior shift of the upper body was the dominating factor. Besides, Klotzbuecher et al^[43] summarized the literature and performed a statistical synthesis of the risk of future fracture, given a history of prior fracture, and then they found patients with a vertebral fracture were more likely to have a new vertebral fracture than patients without. Furthermore, some authors indicated that the number of prevalent fractures were associated with the risk of subsequent fractures.^[44,45] Another risk factor of new fractures of adjacent vertebral bodies is cement leakage into the disk and some

previous studies suggested that the contextual environment was changed by the stiffening and the loss of vertical elasticity of the 2 proximate vertebrae.^[17,46] As many other authors, it is still uncertain that what the precise role of each factor might be.

However, there are few randomized clinical studies that have reported on this topic. In this meta-analysis, we directly compared BKP and CT and included 625 patients in BKP group and 592 patients in CT group, to evaluate whether new vertebral fractures after BKP are simply the result of the natural progression of osteoporosis or if they should be regarded as a consequence of this minimally invasive surgery. The results

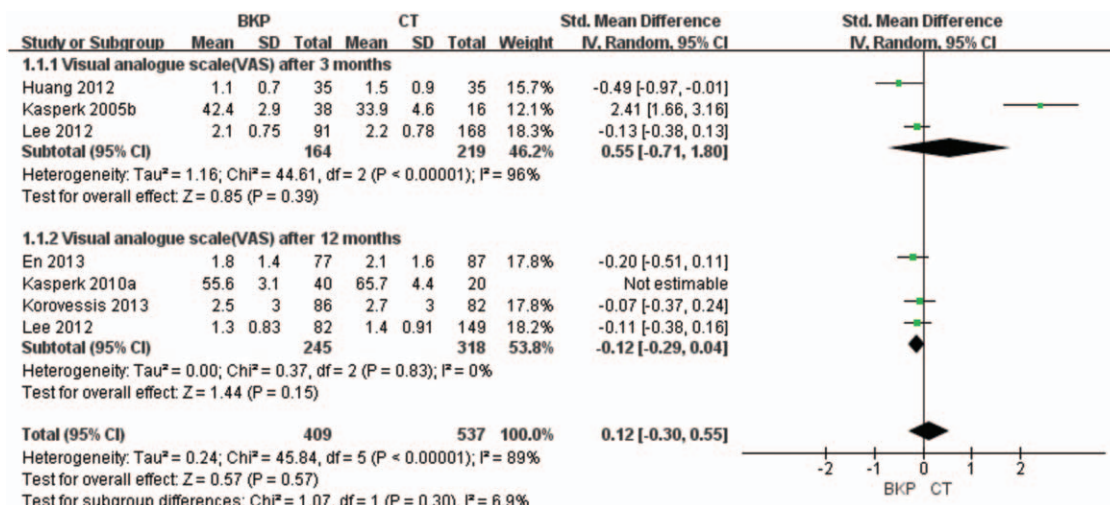


Figure 6. Forest plots of the included studies comparing the score on the visual analogue scale (VAS) after 3 and 12 months in patients who underwent BKP and those who underwent CT. BKP = balloon kyphoplasty, CT = conservative therapy.

Table 2

Sensitivity analyses.

Sensitivity analysis	Measures of effects size and precision			Heterogeneity <i>I</i> ²
	Point estimate	95% CI	<i>P</i>	
New vertebral fractures				
All studies (random-effect model with RR)	0.86	0.63–1.17	.33	32%
All studies (fixed-effect model with RR)	0.92	0.74–1.15	.47	32%
Excluding the largest trial	0.77	0.53–1.12	.17	22%
Excluding the most weighted trial	0.77	0.53–1.12	.17	22%
Adjacent vertebral fractures				
All studies (random-effect model with RR)	1.04	0.71–1.54	.83	0%
All studies (fixed-effect model with RR)	1.04	0.71–1.53	.83	0%
Excluding the largest trial	0.76	0.43–1.32	.32	0%
Excluding the most weighted trial	0.76	0.43–1.32	.32	0%
ODI scores				
All studies (random-effect model with SMD)	−0.22	−0.57 to 0.13	.22	69%
All studies (fixed-effect model with SMD)	−0.16	−0.34 to 0.03	.1	69%
Excluding the largest trial	−0.38	−0.63 to −0.12	.004	0%
Excluding the most weighted trial	−0.38	−0.63 to −0.12	.004	0%

CI=confidence interval, ODI=the Oswestry Disability Index, RR=relative risk, SMD=standardized mean difference.

indicate that there was no significant difference in the recompression after kyphoplasty when compared with conservative treatment. And the following factors may not be potential confounding factors that contributed to heterogeneity: follow-up period, mean age, anti-osteoporosis therapy, the proportion of

women, and only 1 prevalent fracture. However, 2 or more prevalent fractures may be potential confounding factors that had a significant effect on the target. Besides, we find that there was no significant difference in pain relief after 3 months and after 12 months, most likely as a result of fracture healing, and

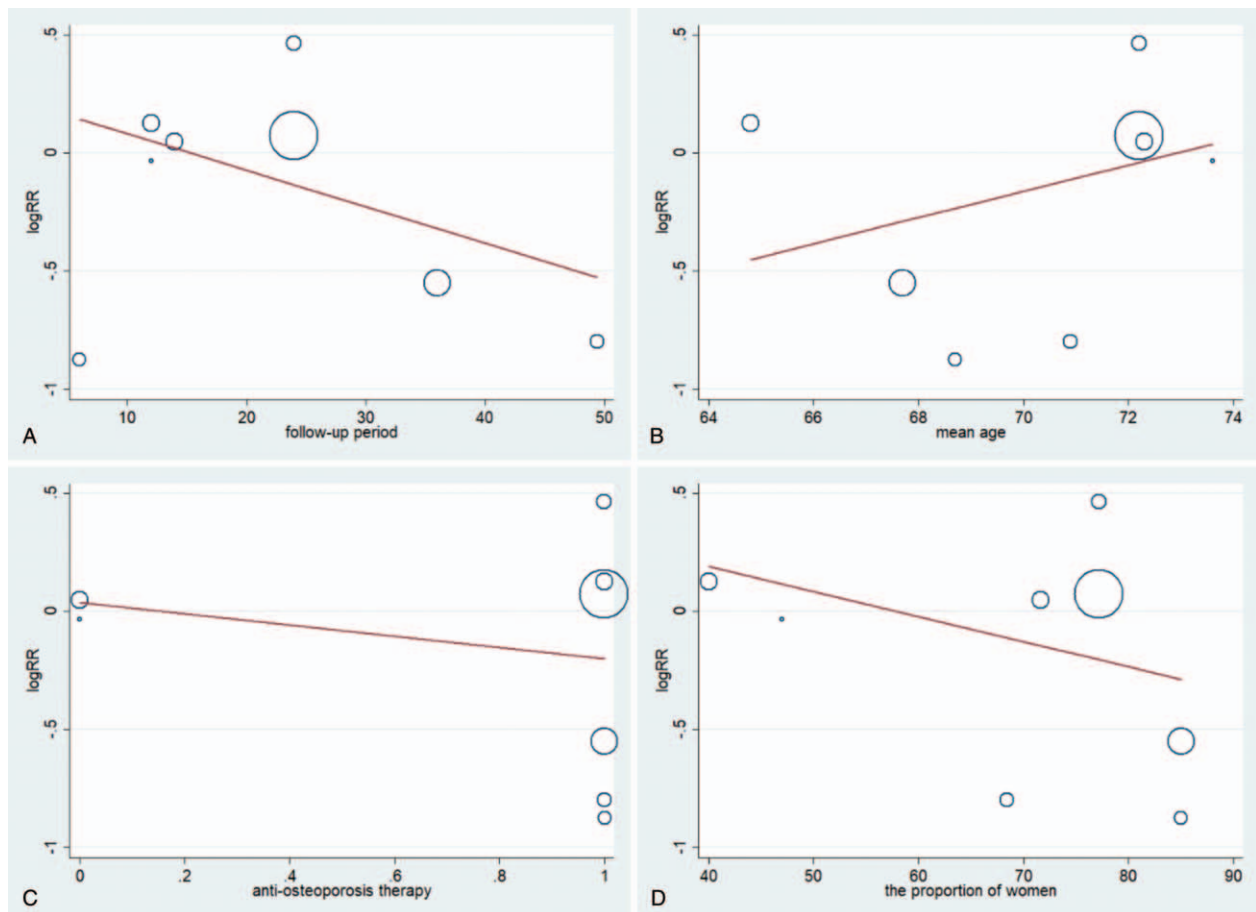


Figure 7. Meta-regression analyses about the effect of (A) follow-up period; (B) mean age; (C) anti-osteoporosis therapy; (D) the proportion of women in decreasing new vertebral fractures.

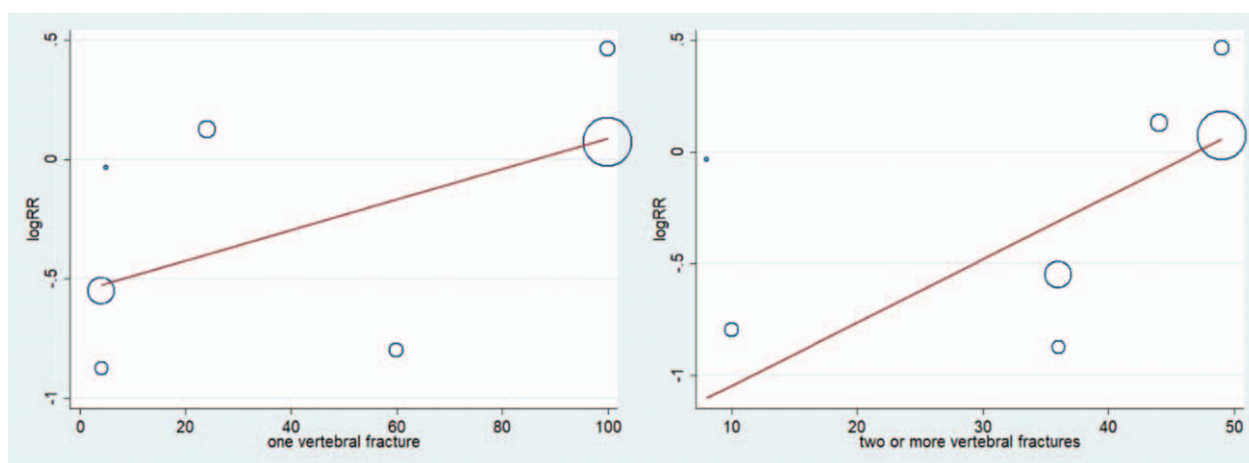


Figure 8. Meta-regression analyses about the effect of the number of prevalent fractures: (left) 1 vertebral fracture; (right) 2 or more vertebral fractures.

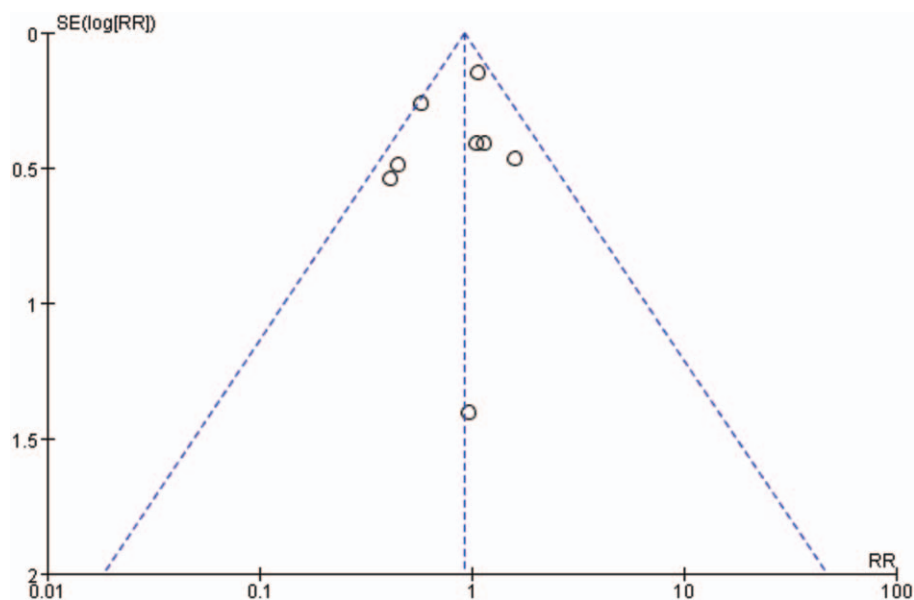


Figure 9. Funnel plot for total number of new vertebral fracture between the 2 treatments.

these findings were similar to the results of other studies.^[47,48] Therefore, we believe that the natural progression of osteoporosis is associated with the presence of new vertebral fractures.

5. Limitations

One limitation in this review is reporting bias. Another limitation is that all the included studies are searched through online database but not included unpublished studies, which might have led to a publication bias in our meta-analyses. However, any meta-analyses have the risk of publication, and we believe that our final result is convincing. Therefore, our results should be interpreted and applied prudently.

6. Conclusion

According to our systematic review, the BKP technique could be optimal choice compared with CT but must evaluate the number

of prevalent fracture in these patients. Furthermore, the BKP does not increase the risk of new vertebral fractures and adjacent level fractures.

Author contributions

Cai-Liang Shen designed the study. Hui-Min Li and Ren-Jie Zhang screened studies and extracted data. Disagreements were resolved by discussion with Hai Gao. Chong-Yu Jia did the statistical analyses and prepared figures. Hui-Min Li, Ren-Jie Zhang, Jian-Xiang Zhang, and Fu-Long Dong reviewed the results, interpreted data, and wrote the manuscript. All authors saw and approved the final version of the paper.

- Conceptualization:** Cailiang Shen.
- Data curation:** Hui-Min Li, Ren-Jie Zhang.
- Methodology:** Chong-Yu Jia.
- Software:** Chong-Yu Jia.
- Supervision:** Hai Gao.

Writing – original draft: Hui-Min Li, Ren-Jie Zhang.

Writing – review & editing: Jian-Xiang Zhang, Fu-Long Dong.

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