Systematic Review

Timing of Percutaneous Balloon Kyphoplasty for Osteoporotic Vertebral Compression Fractures

Donghua Liu, Master, Jiao Xu, Master, Qiang Wang, Master, Longyu Zhang, Master, Shi Yin, Master, Bo Qian, Master, Xingxuan Li, Master, Tianlin Wen, MD, PhD, and Zhiwei Jia, MD, PhD

From: Department of Orthopedics, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China

Address Correspondence: Zhiwei Jia, MD, PhD Department of Orthopedics, Dongzhimen Hospital Beijing University of Chinese Medicine, Beijing, China E-mail: jiazhiweivip@163.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-11-2022
Revised manuscript received: 11-23-2022
Accepted for publication: 12-20-2022

Free full manuscript: www.painphysicianjournal.com

Background: Percutaneous balloon kyphoplasty (PKP) is widely used to treat osteoporotic vertebral compression fractures (OVCFs). In addition to rapid and effective pain relief, the ability to recover the lost height of fractured vertebral bodies and reduce the risk for complications are believed to be the main advantages of this procedure. However, there is no consensus on the appropriate surgical timing for PKP.

Objectives: This study systematically evaluated the relationship between the surgical timing of PKP and clinical outcomes to provide more evidence for clinicians to choose the intervention timing.

Study Design: Systematic review and meta-analysis.

Methods: The PubMed, Embase, Cochrane Library, and Web of Science databases were systematically searched for relevant randomized controlled trials and prospective, and retrospective cohort trials published up to November 13, 2022. All included studies explored the influence of PKP intervention timing for OVCFs. Data regarding clinical and radiographic outcomes and complications were extracted and analyzed.

Results: Thirteen studies involving 930 patients with symptomatic OVCFs were included. Most patients with symptomatic OVCFs achieved rapid and effective pain relief after PKP. In comparison to delayed PKP intervention, early PKP intervention was associated with similar or better outcomes in terms of pain relief, improvement of function, restoration of vertebral height, and correction of kyphosis deformity. The meta-analysis results showed there was no significant difference in cement leakage rate between early PKP and late PKP (odds ratio [OR] = 1.60, 95% CI, 0.97–2.64, $P = 0.07$), whereas delayed PKP had a higher risk for adjacent vertebral fractures (AVFs) than early PKP (OR = 0.31, 95% CI: 0.13–0.76, $P = 0.01$).

Limitations: The number of included studies was small, and the overall quality of the evidence was very low.

Conclusions: PKP is an effective treatment for symptomatic OVCFs. Early PKP may achieve similar or better clinical and radiographic outcomes for treating OVCFs than delayed PKP. Furthermore, early PKP intervention had a lower incidence of AVFs and a similar rate of cement leakage compared with delayed PKP. Based on current evidence, early PKP intervention might be more beneficial to patients.

Key words: Percutaneous balloon kyphoplasty, osteoporotic vertebral compression fractures, osteoporosis, surgery, operative timing

Pain Physician 2023: 26:231-243

Osteoporosis is a progressive, age-related illness that is increasing dramatically with the aging of the global population (1,2). This sharp increase has raised broader concerns regarding osteoporosis and osteoporosis-related fractures (3,4). Osteoporosis-related fractures play a vital role in the morbidity and mortality of elderly patients (5-7). Osteoporotic vertebral compression fractures (OVCFs), the most common osteoporosis-related fractures, are often accompanied by physiological lesions and psychological sequelae, including severe back pain, loss of vertebral height, kyphotic deformity, negative mood, and even depression, particularly among the elderly (8-12). These symptoms will periodically continue in some cases and may result in a marked negative impact on the activities of daily living and quality of life (9,13).

PKP is widely accepted by physicians and patients as a surgical procedure for symptomatic OVCFs (3,14). In addition to yielding immediate and effective pain relief, this procedure also enables restoration of vertebral height and improvement of kyphotic deformity by using a balloon to inflate the vertebral body and subsequently stabilize it with the injection of acrylic cement (14,15). Moreover, the reduced incidence of bone cement leakage is another important feature of PKP (16). Current guidelines primarily recommend that patients undergo initial therapy attempts with conservative measures to avoid over-treatment due to surgery and then indicate surgical treatment if conservative measures are not clinically effective or if there is radiographic progression of the fracture (17-19). The course of conservative management demands more non-steroidal anti-inflammatory drugs and longer bed rest. In addition, prolonged bed rest may result in pressure ulcers, venous thrombosis of the lower extremity, hypostatic pneumonia, and further progression of osteoporosis (19-21). The characteristics of OVCFs change over time, and persistent vertebral compression may lead to chronic pain, neural compromise, dysfunction, and vertebral cleft (9,14). Therefore, the appropriate duration of conservative therapy is a vital factor for symptomatic OVCFs to achieve clinical benefit.

The appropriate timing for a shift from conservative treatment to PKP is still unclear. Moreover, current guidelines do not provide consensus recommendations (9,22-30). Therefore, in the current study, we systematically investigated clinical, radiographic outcomes and complications according to the surgical timing of PKP to provide current evidence for clinicians.

Methods

The present study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the guidelines for assessing the methodological quality of systematic reviews (31).

Search Strategy

Using the PubMed, Embase, Web of Science, and Cochrane library databases, a comprehensive literature search was performed to identify relevant PKP studies on November 13, 2022. No language restrictions were set when searching for the articles. Two researchers performed the study independently and 2 different retrieval methods were used. The first search was performed using MeSH terms, including "compression fracture*," "osteoporotic fracture,*" "spinal fracture," "kyphoplasty," "balloon vertebroplasty," and "time factors." Subsequently, the second search was performed using multiple keywords, including "compression fracture," "osteoporotic fracture," "kyphoplasty," "PKP," "balloon vertebroplasty," "timing," "times," "early," "late," "acute," "sub-acute," "delay," "chronic." Finally, all articles retrieved using both search methods were integrated to include as many potentially relevant studies as possible. Additionally, articles in reference lists of the retrieved studies that met the eligibility criteria and reviews were also manually searched for any pertinent supplementary articles.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) patients experienced symptomatic OVCFs; 2) received PKP treatment at different times depending on the interval between fracture and procedure; 3) randomized controlled trials, prospective cohort trials, or retrospective cohort trials; 4) at least one of the following main outcomes reported, visual analog scale (VAS) scores, Oswestry Disability Index (ODI), local kyphosis angle (LKA), height of fractured vertebra, incidence of bone cement leakage, and adjacent vertebral fractures (AVFs); 5) and publication without language restriction.

Studies reporting vertebral burst fracture, vertebral pathological fractures caused by multiple myeloma, metastatic bone disease, or hemangioma, reviews, letters, case reports, or meeting proceedings, and those with incomplete information and no outcomes of interest reported were excluded.

Data Extraction

Two researchers extracted the information by carefully reading the full text of all selected studies according to a unified standard. Disagreement was resolved by consensus discussion between the reviewers; if necessary, a third researcher made the final decision in cases of dispute. The information extracted included article characteristics such as publication time, country, surgical time of different groups, sample size, population demographics, and follow-up duration. Radiographic outcomes included preoperative and postoperative vertebral height and kyphotic angle, while clinical outcomes included preoperative and postoperative VAS and ODI scores. Finally, complications included the incidence of bone cement leakage and AVFs. If the study included 3 or more groups according to the time of receiving PKP, only the data of the earliest and latest group were extracted.

Risk of Bias Assessment

Two researchers independently evaluated the risk of bias in the included studies using the Methodological Index for Non-Randomized Studies (MINORS) tool (32). Risk assessment included selection bias, adequacy of outcome measurements, comparability of groups, publication bias, and other potential sources of bias. Disagreements were resolved by unified consensus discussion, and a third researcher arbitrated in cases where disputes persisted.

Quality Assessment

The quality of evidence was formally assessed for each study according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework (33-35). The quality of evidence was defined as follows: high, the effect estimation is very close to the true effect value; moderate, the estimated value is very likely to be close to the true value; low, the true value may be very different from the estimated value; and very low, the estimate is very likely to be very different from the true value, and the estimate is uncertain.

Data Synthesis

Meta-analysis was performed if ≥ 2 of the included studies had homogeneous clinical and statistical results. If it was not possible to perform a pooled analysis, a qualitative descriptive analysis was performed.

Results

Literature Search and Screen

A total of 776 articles were retrieved in the preliminary search of the PubMed, Embase, Cochrane Library, and Web of Science databases, of which 659 remained after duplicates were removed. Next, a review of the titles and abstracts of these articles excluded 644 studies. The remaining 15 articles qualified for full-text assessment, and 2 were excluded based on the inclusion and exclusion criteria. Finally, 13 articles were included in the study. A flow diagram illustrating the systematic literature search is presented in Fig. 1.

Basic Characteristics of the Included Studies

This systematic review included 3 prospective cohort trials (14,19,26) and 10 retrospective cohort trials (3,8,9,16,23,25,27-30), including 930 patients with symptomatic OVCFs. These studies were from the United States, Germany, China, Turkey, Japan, and South Korea, and were published between 2004 and 2022. A summary of these studies is presented in Table 1.

Risk of Bias Assessment

The risk of bias in the included studies is summarized in Table 2. All included studies were prospective or retrospective cohort trials; therefore, the risk of bias was assessed using the MINORS tool (28). Regarding these comparative trials, the mean MINORS score was 17.6 (range, 13 to 21), which accounted for 77.3% (17.6/24) of the gross scores. The results indicated that the included studies had a moderate risk of bias.

Quality of Evidence

According to the GRADE guidelines, the quality of the observational studies was not upgraded and was designated as very low. The quality of evidence is summarized in Table 3. The overall quality of included studies was very low.

Vertebral Body Height

Ten studies (8,14,16,19,23,25-28,30) reported restoration of anterior vertebral body height, and all reported excellent restoration after early PKP. Vertebral body height restoration rates are summarized in Table 4. Among these, 7 studies (8,16,19,23,25-27) reported significantly better restoration of vertebral height in early PKP than in delayed PKP ($P < 0.05$). Takahashi et al (14) reported that the percentage of anterior vertebral height remained higher in early PKP (68.0%) than in delayed PKP (53.6%) at the final follow-up ($P = 0.002$); however, there was no significant difference in the height of vertebral recovery (20.1% versus 23.0%; $P = 0.425$). Liu et al (28) and Ding et al (30) found that there was no significant difference between the early and the delayed PKP with respect to the postoperative vertebral body height restoration ($P > 0.05$), while delayed PKP had a more severe loss of vertebral height at the follow-up ($P < 0.05$).

Local Kyphotic Angle

Ten studies (8,9,14,19,23,25-29) assessed the local kyphotic angle, with the outcomes summarized in Table 5. Minamide et al (9) and Takahashi et al (14) reported

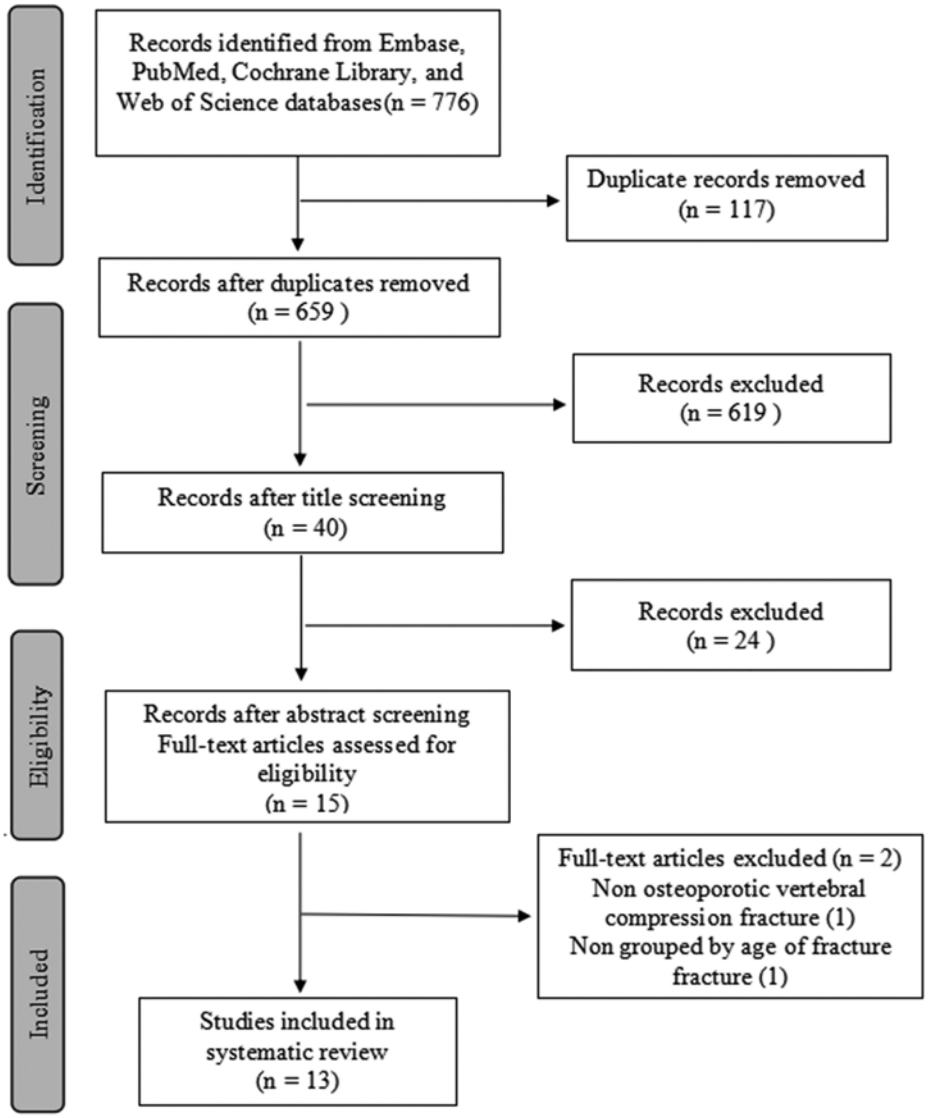

Fig. 1. *The flow chart of study selection.*

that the local kyphotic angle was lower in the early PKP than in the delayed PKP ($P < 0.05$); however, there was no significant difference in the local kyphotic angle recovery ($P > 0.05$). Additionally, Liu et al (19) and Liu et al (29) reported that the postoperative local kyphotic angle was not significantly different between early PKP and delayed PKP ($P > 0.05$), the difference was significant only at the 6 months and 24 months follow-up, respectively ($P < 0.05$). Crandall et al (26) reported that postoperative improvement in the local kyphotic angle was not significantly different between early and delayed PKP ($P > 0.05$). However, the other 5 studies (8,19,23,25,29) reported that the improvement of local kyphotic angle was significantly greater in the early PKP group than in the delayed PKP group ($P < 0.05$).

Pain Relief

All included studies (3,8,9,14,16,19,23,25-30) reported patient preoperative and postoperative pain. Minamide et al (9) used a numerical pain rating scale to assess back pain among patients, while other studies evaluated back pain using a VAS. A summary of pain outcomes evaluated using the VAS is presented in Table 6. In all studies, the patients experienced excellent fracture-related pain relief, and VAS scores significantly decreased after PKP ($P < 0.05$). Four studies (14,19,27,29)

Table 1. *Study characteristics of the included studies.*

Study	Year	Country	Study design	Time of surgery		Sample size		Mean age (y)		Gender (M/F)		Follow-up
				Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	
Liu et al 2022 [27]	2022	China	RCS	< 24h	≥ 1m	52	47	70.5	67.9	10/42	11/36	6m
Palmowski et al [8]	2020	Germany	RCS	< 2w	> 6w	100	39	72.2	70.4	27/73	12/27	NA
Liu et al 2020 [28]	2020	China	RCS	< 1w	2w-4w	55	24	67.4	67.9	19/36	7/17	24m
Zhou et al [23]	2019	China	RCS	≤ 4w	> 4w	36	26	70.2	73.6	2/34	2/24	≥ 6m
Minamide et al [9]	2018	Japan	RCS	≤ 4w	> 4w	32	19	74.6	77.1	6/26	4/15	1.2y
Takahashi et al [14]	2018	Japan	PCS	≤ 2m	> 2m	27	45	79.39	77.9	8/19	14/31	> 6m
Yao et al [29]	2015	China	RCS	< 1w	> 2w	36	28	64.3	64.1	14/22	10/18	12m
Ding et al [30]	2015	China	RCS	< 2w	2w-4w	39	43	67.9	69.2	11/28	12/31	6m
Guan et al [3]	2012	China	RCS	< 2w	2w-4w	46	71	68.6	69.2	15/31	25/46	3d
Oh et al [16]	2010	South Korea	RCS	≤ 3w	> 2m	21	29	62.3	66.9	8/13	7/22	8-15m
Park et al [25]	2010	South Korea	RCS	≤ 2w	> 2w	20	20	84.5	81.9	0/20	0/20	6-24m
Erkan et al [19]	2009	Turkey	PCS	< 10w	> 16w	15	13	70.0	74.0	4/11	4/9	18m
Crandall et al [26]	2004	United States	PCS	< 10w	> 16w	23	24	76.0	72.0	7/16	5/19	6-24m

PCS, Prospective cohort study; RCS, Retrospective Study; NA, Not available.

found that the improvement of VAS was significantly greater in early PKP than in delayed PKP ($P < 0.05$). The other 9 studies (3,8,9,16,23,25,26,28,30) demonstrated no statistically significant differences in postoperative improvement in back pain between early and delayed PKP ($P > 0.05$).

Oswestry Disability Index Scores

Seven studies (3,19,23,27-30) assessed function according to the ODI. The postoperative average ODI score significantly decreased after PKP in these studies ($P < 0.05$). Only Liu et al (27) and Yao et al (29) reported that the improvement of ODI score was significantly greater in early PKP than in delayed PKP ($P < 0.05$). The other studies (3,19,23,28,30) reported the differences were not significant between early and delayed PKP ($P > 0.05$). Table 6 summarizes the functional outcomes evaluated according to the ODI.

Bone Cement Leakage

Eight of the included studies evaluated bone cement leakage (3,14,16,19,23,28-30), with outcomes summarized in Table 7. Guan et al (3) reported that the incidence of bone cement leakage in delayed PKP was significantly lower than that in early PKP ($P < 0.05$). However, Yao et al (29) got the opposite result. They found the incidence of bone cement leakage in delayed PKP was significantly higher than in early PKP ($P < 0.05$). In addition, the other studies (14,16,19,23,28,30) reported that there was no significant difference in the incidence of bone cement leakage between early and delayed PKP ($P > 0.05$). The results of the pooled analysis are shown in Fig. 2. No significant difference was observed in the incidence of cement leakage between early and delayed PKP (odds ratio [OR] = 1.60, 95% CI: 0.97–2.64, $P = 0.07$).

Adjacent Vertebral Fracture

Four studies (9,16,19,23) assessed AVFs (Table 7). Three (9,19,23) reported a significantly higher occurrence rate of AVFs in delayed PKP compared with early PKP ($P < 0.05$). Only Oh et al (16) reported similar results

Table 2. *The MINORS scores for non-RCTs.*

Items[A]	Liu et al 2022 [27]	Palmowki et al [8]	Liu et al 2020 [28]	Zhou et al [23]	Minamide et al [9]	Takahashi et al [14]	Yao et al [29]	Ding et al [30]	Guan et al [3]	Oh et al [16]	Park et al [25]	Erkan et al [19]	Crandall et al [26]
1. A clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	0	0	0	2	2
3. Prospective collection of data	0	0	0	0	0	2	0	0	0	0	0	2	2
4. Endpoints appropriate to the aim of the study	2	1	2	2	1	2	2	2	1	1	1	1	1
5. Unbiased assessment of the study endpoint	2	2	2	2	1	1	2	2	0	0	1	1	1
6. Follow-up period appropriate to the aim of the study	2	0	2	1	2	1	2	2	0	1	1	2	1
7. Loss to follow up less than 5%	2	2	2	2	2	2	2	2	2	2	2	2	2
8. Prospective calculation of the study size	0	0	0	0	0	2	0	0	0	0	0	0	0
Additional criteria for comparative studies													
9. An adequate control group	2	1	2	1	1	1	2	2	1	2	1	1	1
10. Contemporary groups	2	2	2	2	2	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	1	2	2	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	2	2	2	2	2	2	2	2	2	2	2
Total scores[B]	20	16	20	18	16	21	20	20	13	14	14	19	18

MINORS Methodological Index for Non-Randomized Studies.
A The items are scored as follows: 0 (not reported); 1 (reported but inadequate); or 2 (reported and adequate).
B Maximum MINORS score is 24 for comparative studies.

between early and delayed PKP in terms of AVFs incidence (*P* > 0.05). The pooled analysis was conducted in these studies (Fig. 3) and demonstrated that the incidence of adjacent vertebral fracture in delayed PKP was significantly higher than in early PKP (OR = 0.31, 95% CI: 0.13–0.76, *P* = 0.01).

Discussion

OVCFs are significantly increasing among the elderly due to the aging of the population, which not only represents a formidable challenge to medical systems but also a substantial socioeconomic burden on society (9,11). PKP has been widely used as a mainstay treatment for OVCFs because of its excellent clinical efficacy and low risk for complications (15,36,37). The timing of surgery is an important factor impacting clinical outcomes. For example, early intervention may result in unnecessary procedures, whereas delayed intervention may be a compromise plan for treatment (38,39). However, little is known about the optimal timing for PKP (40). To the best of our knowledge, this is the first systematic review that aimed to investigate whether the timing of PKP intervention affects the overall efficacy.

The main findings of the current study indicated that patients with symptomatic OVCFs achieved rapid and effective pain relief after PKP, and patients with OVCFs who underwent early surgery showed comparable or better pain relief than those who underwent delayed surgery. Early PKP intervention was associated with similar or better outcomes in terms of improvement of function, restoration of vertebral height, and improvement of kyphotic deformity com-

Table 3. *Grading of clinical studies following GRADE guidelines.*

Study	Study design	Risk of bias	Indirectness	Imprecision	Publication bias	Large effect	Plausible residual confounding	Total	Quality of evidence
Liu et al 2022 [27]	RCS	-1	0	NA	0	0	0	-1	Very low
Palmowski et al[8]	RCS	-1	0	NA	-1	0	0	-2	Very low
Liu et al 2020 [28]	RCS	-1	0	NA	0	0	0	-1	Very low
Zhou et al [23]	RCS	-2	0	NA	-1	0	0	-3	Very low
Minamide et al [9]	RCS	−1	0	NA	−1	0	0	−2	Very low
Takahashi et al [14]	PCS	−1	0	NA	−1	0	0	−2	Very low
Yao et al [29]	RCS	-1	0	NA	0	0	0	-1	Very low
Ding et al [30]	RCS	-1	0	NA	0	0	0	-1	Very low
Guan et al [3]	RCS	−2	0	NA	−1	0	0	−3	Very low
Oh et al [16]	RCS	−2	0	NA	−1	0	0	−3	Very low
Park et al [25]	RCS	−2	0	NA	−1	0	0	−3	Very low
Erkan et al [19]	PCS	−1	0	NA	−1	0	0	−2	Very low
Crandall et al [26]	PCS	−1	0	NA	−1	0	0	−2	Very low

PCS, Prospective cohort study; RCS, Retrospective cohort study; NA, Not available.

Table 4. *Radiological outcomes of vertebral body height restoration rate.*

Study	Group	Anterior vertebral HRR		Middle vertebral HRR		Posterior vertebral HRR	
		postoperative	Final follow-up	postoperative	Final follow-up	postoperative	Final follow-up
Liu et al 2022 [27]	early (< 24h)	30.4	30.5 (6m)	NA	NA	NA	NA
	delayed (≥ 1m)	10.0	12.1 (6m)	NA	NA	NA	NA
Takahashi et al [14]	early (≤ 2m)	NA	38.6% (> 6m)	NA	NA	NA	39.6% (> 6m)
	delayed (> 2m)	NA	32.9% (> 6m)	NA	NA	NA	16.5% (> 6m)
Ding et al [30]	early (< 2w)	25.0	NA	22.6	NA	NA	NA
	delayed (2w-4w)	23.5	NA	21.9	NA	NA	NA
Oh et al [16]	early (≤ 3w)	NA	53.3% (13m)	NA	NA	NA	NA
	delayed (> 2m)	NA	8.6% (13m)	NA	NA	NA	NA
Park et al [25]	early (≤ 2w)	NA	46.2% (3m)	NA	52.6% (3m)	NA	NA
	delayed (> 2w)	NA	28.2% (3m)	NA	36.6% (3m)	NA	NA
Erkan et al [19]	early (< 10w)	NA	36% (18m)	NA	NA	NA	NA
	delayed (> 16w)	NA	22% (18m)	NA	NA	NA	NA
Crandall et al [26]	early (≤ 10w)	66.7%	N/A	NA	NA	NA	NA
	delayed (≥ 16w)	52.3%	N/A	NA	NA	NA	NA
Zhou et al [23]	early (≤ 4w)	17.50%	10.5% (6m)	NA	NA	NA	NA
	delayed (> 4w)	7.20%	3.6% (6m)	NA	NA	NA	NA

HRR, height restoration rate; NA, not available

HHR (%)

Change in angle (°) = Preoperative local kyphotic angle - Postoperative local kyphotic angle =

$$\frac{\text{(postoperative fractured vertebral height - preoperative fractured vertebral height)}}{\text{(mean adjacent vertebral height - preoperative fractured vertebral height)}} \times 100$$

pared with delayed PKP intervention. Futhermore, the meta-analysis results showed that the cement leakage rate was not significantly different between early PKP and delayed PKP, whereas delayed PKP was associated with a higher risk for AVFs than early PKP.

Back pain associated with OVCFs may be unavoid-

Table 5. *Radiological outcomes of local kyphotic angle.*

Study	Group	Local kyphotic angle (°)			Change in angle (°)
		Preoperative	Postoperative	Final follow-up	
Liu et al 2022 [27]	early (< 24h)	23.75 ± 2.11	15.87 ± 2.30	16.62 ± 2.58 (6m)	NA
	delayed (≥ 1m)	24.09 ± 2.83	16.87 ± 2.20	17.75 ± 2.75 (6m)	NA
Minamide et al [9]	early (< 4w)	10.1 ± 8.1	6.4 ± 6.9	9.5 ± 6. 9 (1.2y)	NA
	delayed (> 4w)	27.6 ± 7.0	19.8 ± 7.2	28.4 ± 10.0 (1.2y)	NA
Liu et al 2020 [28]	early (< 1w)	21.23 ± 2.12	7.23 ± 0.76	8.21 ± 0.34 (24m)	NA
	delayed (2-4w)	21.86 ± 2.10	7.21 ± 0.72	9.98 ± 0.39 (24m)	NA
Takahashi et al [14]	early (≤ 2m)	19.4 ± 7.2	NA	12.4 ± 5.4 (> 6m)	NA
	delayed (> 2m)	24.9 ± 8.1	NA	16.3 ± 8.3 (> 6m)	NA
Yao et al [29]	early (< 1w)	13.8 ± 6.6	7.3 ± 5.0	7.2 ± 4.5 (12m)	NA
	delayed (> 2w)	13.8 ± 6.4	10.8 ± 5.8	10.1 ± 4.9 (12m)	NA
Park et al [25]	early (≤ 2w)	NA	NA	NA	8.8
	delayed (> 2w)	NA	NA	NA	4.2
Erkan et al [19]	early (< 10w)	22.2 ± 4.7	N/A	9.7 ± 3.2 (18m)	6.2 ± 3.7
	delayed (> 16w)	24.6 ± 5.3	N/A	17.4 ± 3.7 (18m)	4.6 ± 2.8
Crandall et al [26]	early (≤ 10w)	15.0	8.0	NA	NA
	delayed (≥ 16w)	15.0	10.0	NA	NA
Palmowski et al [8]	early (< 2w)	NA	NA	NA	3.8
	delayed (> 6w)	NA	NA	NA	1.7
Zhou et al [23]	early (≤ 4w)	12.7 ± 4.5	7.3 ± 2.9	11.4 ± 7.3(6m)	NA
	delayed (> 4w)	17.6 ± 5.8	14.4 ± 4.5	16.1 ± 8.1(6m)	NA

Change in angle (°) = Preoperative local kyphotic angle − Postoperative local kyphotic angle
NA: Not available

able, and in most cases, it may subside over a period of weeks or months; however, it is not uncommon for back pain to progress to chronic pain (41). In this study, we found that most patients with OVCFs benefited from effective pain relief after PKP. Moreover, patients with OVCFs who underwent early surgery showed comparable or better pain relief than those who underwent delayed surgery. Several factors probably contributed to the similar results. First, bone cement restores the mechanical stability of microfractures, increases the strength of the fractured vertebra, and decreases stimulation of free nerve endings at the fracture site, which may be the primary factor in pain relief (42-44). Second, the hardening process of polymethylmethacrylate releases a large amount of heat. This quantity of heat inactivates terminal nerve endings at the fracture site, which is another important contribution to pain relief (44,45). In addition, PKP can restore the normal spinal sequence of patients, reduce the compensatory activity of the paravertebral muscles, and promote fracture rehabilitation. These may explain the long-lasting effects of PKP on pain relief (46). Finally, Yokoyama et al reported that vertebroplasty relieved the pain by releasing pressure in the fractured vertebral body (47). In the early stages of OVCFs, the pressure is relatively greater owing to bleeding and exudation at the fracture site. Therefore, pressure release was greater after early PKP, resulting in a greater pain relief outcome. This may explain the difference in pain relief between early and delayed PKP.

The ability to restore vertebral body loss height and improve kyphotic deformity is believed to be the main advantage of PKP (25). Increasing attention has been devoted to the negative impact of local kyphotic deformities and loss of vertebral height. A fractured vertebral body may collapse due to repeated stress before cement augmentation is performed. Constant loss of vertebral height can cause severe local kyphotic deformities and even result in neurological deficits (48). Additionally, Sliverman et al (41) revealed that the severity of spinal deformity is a major factor that adversely affects the quality of life, mental health, and life span, which are effects that are, in part, independent of pain. In the current study, we found that the improvements of vertebral height and local kyphotic deformity in delayed PKP are not as great as the improvements in early PKP. This may be because the fracture healing process has progressed to the bone remodeling stage in delayed PKP. It is difficult to restore vertebral body height even with balloon tamp inflation due to hard callus formation (16). Generally, hard callus formation at the fracture site of cortical fractures in adults takes 3 to 6 weeks (49). Yang et al (50) reported that cancellous fractures heal faster than cortical fractures, and kyphotic deformity and vertebral height may be repaired because of hard callus formation within one month after OVCF. These findings are consistent with those obtained in this study. Therefore,

Table 6. *Clinical outcomes of VAS and ODI.*

Study	Group	VAS score			ODI score		
		Preoperative	Postoperative	Final follow-up	Preoperative	Postoperative	Final follow-up
Liu et al 2020 [28]	early (< 1w)	7.21	2.71	1.60 (24m)	78.55	36.22	20.12 (24m)
	delayed (2w-4w)	7.21	3.58	1.67 (24m)	79.43	37.90	20.87 (24m)
Takahashi et al [14]	early (≤ 2m)	7.72	NA	1.99 (> 6m)	NA	NA	NA
	delayed (> 2m)	7.30	NA	3.04 (> 6m)	NA	NA	NA
Yao et al [29]	early (≤ 1w)	7.60	2.41	1.91 (12m)	72.79	21.22	20.06 (24m)
	delayed (> 2w)	7.50	2.90	2.47 (12m)	72.91	26.04	23.67 (24m)
Ding et al [30]	early (< 2w)	7.17	3.48	3.51 (6m)	48.67	24.12	24.34 (6m)
	delayed (2w-4w)	6.95	2.65	3.21 (6m)	51.15	21.58	21.86 (6m)
Guan et al [3]	early (< 2w)	7.48	2.30	NA	52.14	19.33	NA
	delayed (2-4w)	7.59	2.52	NA	50.28	19.77	NA
Oh et al [16]	early (≤ 3w)	7.80	2.50	2.30 (8-15m)	NA	NA	NA
	delayed (> 2m)	7.10	3.00	3.00 (8-15m)	NA	NA	NA
Park et al [25]	early (≤2 w)	7.62	NA	2.75 (3m)	NA	NA	NA
	delayed (> 2w)	7.24	NA	2.85 (3m)	NA	NA	NA
Crandall et al [26]	early (≤ 10w)	7.30	4.30	NA	NA	NA	NA
	delayed (≥ 16w)	7.30	4.30	NA	NA	NA	NA
Zhou et al [23]	early (≤ 4w)	7.30	2.40	2.30 (6m)	52.60	17.30	15.60 (6m)
	delayed (> 4w)	6.90	2.30	2.20 (6m)	50.50	18.80	17.60 (6m)
Liu et al 2020 [28]	early (< 1w)	7.21	2.71	1.60 (24m)	78.55	36.22	20.12 (24m)
	delayed (2w-4w)	7.21	3.58	1.67 (24m)	79.43	37.90	20.87 (24m)

VAS, visual analog scale; ODI, The Oswestry Disability Index; NA, Not available.

early PKP can not only prevent a collapse of the vertebra but also restore vertebral height and improve local kyphotic deformity.

As a minimally invasive percutaneous procedure, PKP has a lower risk for cement leakage due to inflatable bone tamps; nevertheless, cement leakage remains the most common complication of bone cement augmentation technology (51,52). Although most cement leakage in PKP does not cause clinical symptoms, symptomatic leakage could have disastrous consequences for patients, such as pulmonary embolism and cardiovascular distress. Furthermore, Harrington et al (53) reported that bone cement that leaks into the intervertebral foramen or spinal canal may compress nerve tissue and lead to severe nerve damage. Lin et al (54) reported an association between persistent chronic back pain and cement leakage into the intervertebral disc. Thus, reducing cement leakage is an important measure for ensuring the surgical safety of PKP. Our results of the pooled analysis showed there was no significant difference in cement leakage between early PKP and delayed PKP. In addition, some studies have reported that cement leakage seems to depend more on the surgeon's technique and operation procedure (54-56). Zhu et al reported that the volume of cement injected, viscosity of bone cement, and cortical bone of the fractured vertebral body are most closely related to the occurrence of cement leakage (57). Therefore, detailed CT examination before surgery, perfect image monitoring during the operation, skilled operation, and precise control of the amount of bone cement might be effective measures to reduce the incidence of bone cement leakage.

The mechanism underlying the occurrence of AVFs remains controversial. Berlemann et al (58) believed that the cement augmentation procedure increased the rate of AVFs because the bone cement may lead to more stress on adjacent vertebrae. However, Farrokhi et al (59) observed a higher incidence of AVFs in the conservatively treated group than in the percutaneous vertebroplasty group. In the present study, we found that the incidence of AVFs was higher in delayed PKP. Several factors may have contributed to this finding. First, the severe kyphotic deformity of delayed PKP increases the load on adjacent vertebrae. Abnormal sagittal alignment of vertebral bodies has been reported to contribute to AVFs (48,58,60,61). Second, repeated compressive loading over the fracture site can lead to bone loss near the endplate and subsequent endplate injury in delayed PKP. This increases the risk for cement extension to the disc level and the incidence of new AVFs (62). Third, repeated trauma during normal activity may create a void effect over the fracture site in delayed PKP. This void effect can reduce the inter-gradient effect between the bone and cement and increase the incidence of AVFs (45,63). Finally, several studies have demonstrated that long periods of bed rest have a negative impact on the back muscles in delayed PKP. The loss of muscle mass weakens the protection of the vertebral bodies and increases the risk for new compression fractures (64-66).

Cancellous fracture healing is a complex process but has long been ignored by the academic community. Han et al (67) proposed a hypothesis for cancellous healing. They divided the process into 5 overlapping stages in chronological order, including bleeding, cell proliferation, woven bone formation, lamellar bone formation, and bone remodeling stages. This hypothesis supported the outcomes of this study. It is becoming increasingly difficult for PKP to restore vertebral height because of the onset of bone remodeling in delayed PKP.

Nevertheless, this study had some limitations. First, we included studies published only in PubMed, Embase, Web of Science, and Cochrane library databases, limiting the source of data and possibly leading to selection bias. Second, there was a lack of high-quality studies in the included articles. All included studies were observational trials, and the overall quality of the evidence was very low. Finally, meta-analysis of clinical and radiographic outcomes could not be performed due to the lack of homogeneity among in these studies, so a descriptive analysis is performed at last.

Table 7. *Complications outcomes of cement leakage and adjacent vertebral fracture.*

Study	Group	Bone cement leakage (%)	Adjacent vertebral fracture (%)
Liu et al 2020 [28]	early (< 1w)	14.6	N/A
	delayed (2w-4w)	12.5	N/A
Minamide et al [9]	early (< 4w)	NA	9.4
	delayed (> 4w)	NA	31.6
Takahashi et al [14]	early (< 4w)	3.7	NA
	delayed (> 2m)	2.2	NA
Yao et al [29]	early (< 1w)	7. 9	NA
	delayed (> 2w)	16. 7	NA
Ding et al [30]	early (< 2w)	15.4	NA
	delayed (2-4w)	7.0	NA
Guan et al [3]	early (< 2w)	26.0	NA
	delayed (2-4w)	11.3	NA
Oh et al [16]	early (≤ 3w)	38.1	9.5
	delayed (> 2m)	20.7	6.9
Erkan et al [19]	early (< 10w)	10.0	13.0
	delayed (> 16w)	4.0	30.0
Zhou et al [23]	early (≤ 4w)	10.7	5.6
	delayed (> 4w)	12.5	26.9

NA, not available

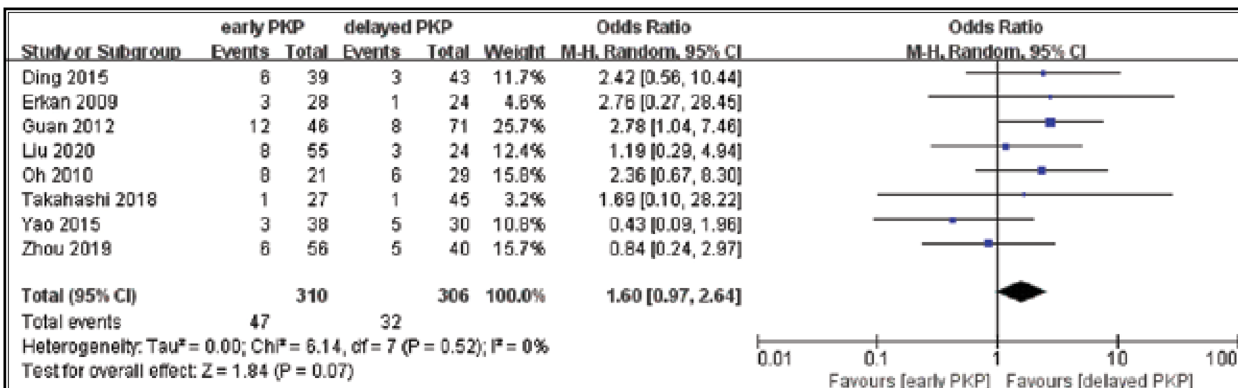

Fig. 2. *Odds ratio in bone cement leakage rate between early PKP and delayed PKP groups.*

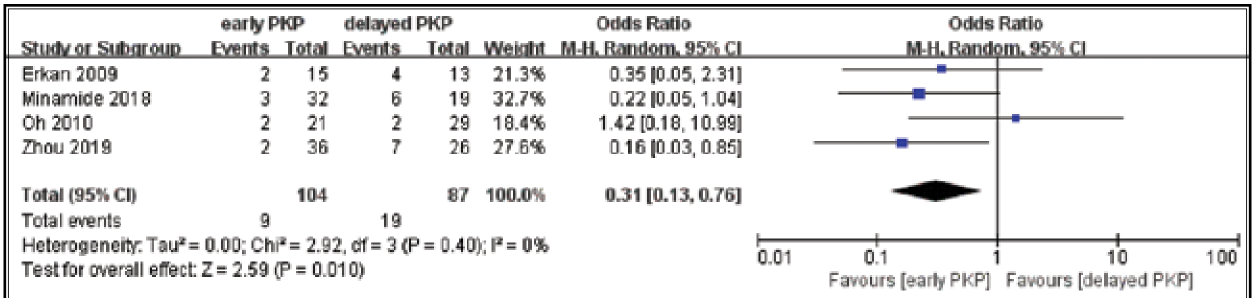

Fig. 3. *Odds ratio in incidence of AVFs between early PKP and delayed PKP groups.*

Conclusions

Based on current evidence, PKP yields excellent pain relief in those with symptomatic OVCFs. Early PKP may achieve similar or better clinical and radiographic outcomes for treating OVCFs than delayed PKP. Furthermore, early PKP intervention had a lower incidence of AVFs and was not associated with higher risks of cement leakage than was delayed PKP. Therefore, early PKP intervention might be more beneficial to patients. Nevertheless, larger and higher-quality studies are needed to prove this conclusion.

PROSPERO Registration Information

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022332850

References

1. Pisani P, Renna MD, Conversano F, et al. Major osteoporotic fragility fractures: Risk factor updates and societal impact. *World J Orth*op 2016; 7:171-181.
2. Reginster JY, Burlet N. Osteoporosis: A still increasing prevalence. *Bone* 2006; 38:S4-S9.
3. Guan H, Yang H, Mei X, Liu T, Guo J. Early or delayed operation, which is more optimal for kyphoplasty? A retrospective study on cement leakage during kyphoplasty. *Injury* 2012; 43:1698-1703.
4. Ploeg WT, Veldhuizen AG, The B, Sietsma MS. Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: A systematic review. *Eur Spine J* 2006; 15:1749-1758.
5. Iqbal MM, Sobhan T. Osteoporosis: A review. *Mo Med* 2002; 99:19-24.
6. Johnell O. Advances in osteoporosis: Better identification of risk factors can reduce morbidity and mortality. *J Intern Med* 1996; 239:299-304.
7. Verbrugge LM, Lepkowski JM, Imanaka Y. Comorbidity and its impact on disability. *Milbank Q* 1989; 67:450-484.
8. Palmowski Y, Balmer S, Bürger J, Schömig F, Hu Z, Pumberger M. Influence of operative timing on the early post-operative radiological and clinical outcome after kyphoplasty. *Eur Spine J* 2020; 29:2560-2567.
9. Minamide A, Maeda T, Yamada H, et al. Early versus delayed kyphoplasty for thoracolumbar osteoporotic vertebral fractures: The effect of timing on clinical and radiographic outcomes and subsequent compression fractures. *Clin Neurol Neurosurg* 2018; 173:176-181.
10. Chen AT, Cohen DB, Skolasky RL. Impact of nonoperative treatment, vertebroplasty, and kyphoplasty on survival and morbidity after vertebral compression fracture in the medicare population. *J Bone Joint Surg Am* 2013; 95:1729-1736.
11. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; 359:1761-1767.
12. Ross PD, Fujiwara S, Huang C, et al. Vertebral fracture prevalence in women in Hiroshima compared to Caucasians or Japanese in the US. *Int J Epidemiol* 1995; 24:1171-1177.
13. Ito Y, Hasegawa Y, Toda K, Nakahara S. Pathogenesis and diagnosis of delayed vertebral collapse resulting from osteoporotic spinal fracture. *Spine J* 2002; 2:101-106.
14. Takahashi S, Hoshino M, Terai H, et al. Differences in short-term clinical and radiological outcomes depending on timing of balloon kyphoplasty for painful osteoporotic vertebral fracture. *J Orthop Sci* 2018; 23:51-56.
15. Garfin SR, Yuan HA, Reiley MA. New technologies in spine: Kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. *Spine (Phila Pa 1976)* 2001; 26:1511-1515.
16. Oh GS, Kim HS, Ju CI, Kim SW, Lee SM, Shin H. Comparison of the results of balloon kyphoplasty performed at different times after injury. *J Korean Neurosurg Soc* 2010; 47:199-202.
17. Pfeil A, Lehmann G, Lange U. [Update DVO guidelines 2017 on "Prophylaxis, diagnostics and treatment of osteoporosis in postmenopausal women and men" : What is new, what remains for rheumatologists?]. *Z Rheumatol* 2018; 77:759-763.
18. Klazen CA, Lohle PN, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): An open-label randomised trial. *Lancet* 2010; 376:1085-1092.
19. Erkan S, Ozalp TR, Yercan HS, Okcu

G. Does timing matter in performing kyphoplasty? Acute versus chronic compression fractures. *Acta Orthop Belg* 2009; 75:396-404.

20. Edidin AA, Ong KL, Lau E, Kurtz SM. Morbidity and mortality after vertebral fractures: Comparison of vertebral augmentation and nonoperative management in the Medicare population. *Spine (Phila Pa 1976)* 2015; 40:1228-1241.
21. Allen C, Glasziou P, Del Mar C. Bed rest: A potentially harmful treatment needing more careful evaluation. *Lancet* 1999; 354:1229-1233.
22. Kanis JA, Harvey NC, McCloskey E, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int* 2020; 31:1-12.
23. Zhou X, Meng X, Zhu H, Zhu Y, Yuan W. Early versus late percutaneous kyphoplasty for treating osteoporotic vertebral compression fracture: A retrospective study. *Clin Neurol Neurosurg* 2019; 180:101-105.
24. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 2014; 25:2359-2381.
25. Park HT, Lee CB, Ha JH, Choi SJ. Results of kyphoplasty according to the operative timing. *Current Orthopaedic Practice* 2010; 21:489-493.
26. Crandall D, Slaughter D, Hankins PJ, Moore C, Jerman J. Acute versus chronic vertebral compression fractures treated with kyphoplasty: Early results. *Spine J* 2004; 4:418-424.
27. Liu H, Wang W, Huang Y, Hu X, Li X, Yang H. Influence of different surgical timing after percutaneous kyphoplasty for osteoporotic vertebral compression fractures: A retrospective study. *Int J Clin Pract* 2022; 2022:7500716.
28. Liu D, Niu H. Surgical timing of percutaneous kyphoplasty for osteoporotic vertebral compression fracture in elderly. *Orthopedic Journal of China* 2020; 28:887-891.
29. Yao S, Xie H, Chen M. Clinical observation of percutaneous kyphoplasty at different times in treatment of osteoporotic vertebral compression fracture. *Orthopedic Journal of China* 2015; 23:1662-1666.
30. Ding KH, Ji B, Zhou QJ, Sun YB, Zuo SQ, Wang QG. Treatment timing for kyphoplasty with bone cement injection in patients with thoracolumbar vertebral compression fractures. *Chinese Journal of Tissue Engineering Research* 2015; 19:6962-6965.
31. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *International Journal of Surgery* 2021; 88:105906.
32. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): Development and validation of a new instrument. *ANZ J Surg* 2003; 73:712-716.
33. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64:383-394.
34. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64:401-406.
35. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924-926.
36. Zhu RS, Kan SL, Ning GZ, et al. Which is the best treatment of osteoporotic vertebral compression fractures: Balloon kyphoplasty, percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network meta-analysis. *Osteoporos Int* 2019; 30:287-298.
37. Lieberman IH, Dudeney S, Reinhardt MK, Bell G. Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures. *Spine (Phila Pa 1976)* 2001; 26:1631-1638.
38. Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: Three-months follow-up in a clinical randomized study. *Spine (Phila Pa 1976)* 2009; 34:1349-1354.
39. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361:557-568.
40. Kim WS, Kim KH. Percutaneous osteoplasty for painful bony lesions: A technical survey. *Korean J Pain* 2021; 34:375-393.
41. Silverman SL. The clinical consequences of vertebral compression fracture. *Bone* 1992; 13 Suppl 2:S27-S31.
42. Zhao G, Liu X, Li F. Balloon kyphoplasty versus percutaneous vertebroplasty for treatment of osteoporotic vertebral compression fractures (OVCFs). *Osteoporos Int* 2016; 27:2823-2834.
43. Baroud G, Bohner M. Biomechanical impact of vertebroplasty. Postoperative biomechanics of vertebroplasty. *Joint Bone Spine* 2006; 73:144-150.
44. Belkoff SM, Mathis JM, Jasper LE, Deramond H. The biomechanics of vertebroplasty. The effect of cement volume on mechanical behavior. *Spine (Phila Pa 1976)* 2001; 26:1537-1541.
45. Tanigawa N, Komemushi A, Kariya S, et al. Relationship between cement distribution pattern and new compression fracture after percutaneous vertebroplasty. *AJR Am J Roentgenol* 2007; 189:W348-W352.
46. Lee JH, Kwon JT, Kim YB, Suk JS. Segmental deformity correction after balloon kyphoplasty in the osteoporotic vertebral compression fracture. *J Korean Neurosurg Soc* 2007; 42:371-376.
47. Yokoyama K, Kawanishi M, Yamada M, et al. Comparative study of percutaneous vertebral body perforation and vertebroplasty for the treatment of painful vertebral compression fractures. *AJNR Am J Neuroradiol* 2012; 33:685-689.
48. Okamoto Y, Murakami H, Demura S, et al. The effect of kyphotic deformity because of vertebral fracture: A finite element analysis of a 10 degrees and 20 degrees wedge-shaped vertebral fracture model. *Spine J* 2015; 15:713-720.
49. Frost HM. The biology of fracture healing. An overview for clinicians. Part II. *Clin Orthop Relat Res* 1989; 294-309.
50. Yang CC, Chien JT, Tsai TY, Yeh KT, Lee RP, Wu WT. Earlier vertebroplasty for osteoporotic thoracolumbar compression fracture may minimize the subsequent development of adjacent fractures: A retrospective study. *Pain Physician* 2018; 21:E483-E491.
51. Wang HS, Kim HS, Ju CI, Kim SW. Delayed bone cement displacement following balloon kyphoplasty. *J Korean Neurosurg Soc* 2008; 43:212-214.
52. Voggenreiter G. Balloon kyphoplasty is effective in deformity correction of osteoporotic vertebral compression fractures. *Spine (Phila Pa 1976)* 2005; 30:2806-2812.
53. Harrington KD. Major neurological complications following percutaneous vertebroplasty with polymethylmethacrylate: A case report. *J Bone Joint Surg Am* 2001; 83:1070-1073.

54. Lin EP, Ekholm S, Hiwatashi A, Westesson PL. Vertebroplasty: cement leakage into the disc increases the risk of new fracture of adjacent vertebral body. *AJNR Am J Neuroradiol* 2004; 25:175-180.
55. Kim DH, Vaccaro AR. Osteoporotic compression fractures of the spine; current options and considerations for treatment. *Spine J* 2006; 6:479-487.
56. Barr JD, Barr MS, Lemley TJ, McCann RM. Percutaneous vertebroplasty for pain relief and spinal stabilization. *Spine (Phila Pa 1976)* 2000; 25:923-928.
57. Zhu SY, Zhong ZM, Wu Q, Chen JT. Risk factors for bone cement leakage in percutaneous vertebroplasty: A retrospective study of four hundred and eighty five patients. *Int Orthop* 2016; 40:1205-1210.
58. Berlemann U, Ferguson SJ, Nolte LP, Heini PF. Adjacent vertebral failure after vertebroplasty. A biomechanical investigation. *J Bone Joint Surg Br* 2002; 84:748-752.
59. Farrokhi MR, Alibai E, Maghami Z. Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures. *J Neurosurg Spine* 2011; 14:561-569.
60. Fribourg D, Tang C, Sra P, Delamarter R, Bae H. Incidence of subsequent vertebral fracture after kyphoplasty. *Spine (Phila Pa 1976)* 2004; 29:2270-2277.
61. Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; 285:320-323.
62. Sun YC, Teng MM, Yuan WS, et al. Risk of post-vertebroplasty fracture in adjacent vertebral bodies appears correlated with the morphologic extent of bone cement. *J Chin Med Assoc* 2011; 74:357-362.
63. Kruger A, Oberkircher L, Kratz M, Baroud G, Becker S, Ruchholtz S. Cement interdigitation and bone-cement interface after augmenting fractured vertebrae: A cadaveric study. *Int J Spine Surg* 2012; 6:115-123.
64. Yang EZ, Xu JG, Huang GZ, et al. Percutaneous vertebroplasty versus conservative treatment in aged patients with acute osteoporotic vertebral compression fractures: A prospective randomized controlled clinical study. *Spine (Phila Pa 1976)* 2016; 41:653-660.
65. Paddon-Jones D, Sheffield-Moore M, Urban RJ, et al. Essential amino acid and carbohydrate supplementation ameliorates muscle protein loss in humans during 28 days bedrest. *J Clin Endocrinol Metab* 2004; 89:4351-4358.
66. Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. *Am J Physiol* 1996; 270:E627-E633.
67. Han D, Han N, Xue F, Zhang P. A novel specialized staging system for cancellous fracture healing, distinct from traditional healing pattern of diaphysis corticalfracture? *Int J Clin Exp Med* 2015; 8:1301-1304.