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Systematic Reviews /Meta-analyses

The effect of time to balloon kyphoplasty on osteoporotic vertebral compression fractures: a systematic review with meta-analysis

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ABSTRACT

Background: Vertebral compression fractures (VCFs) cause significant morbidity in the elderly population. This study aimed to determine the difference in pain-related outcomes in the elderly population who suffered vertebral body fractures, treated with balloon kyphoplasty at "early" (<4 weeks) and "late" (>4 weeks) stages. To the best of our knowledge, this has not been previously evaluated in a meta-analysis.

Methods: We conducted a systematic literature review as per PRISMA guidelines using databases that included PubMed, EMBASE, Cochrane and Scopus.

The search included adults (age 19+) who sustained osteoporotic vertebral compression fractures that were treated with BKP, grouped by time to intervention as compared to conservative treatment to determine impact on radiographic and clinical outcomes.

Results: A total of 9 studies were included from a total of 139 screened records eligible for title and abstract screening after deduplication (39 PubMed, 85 EMBASE, 6 Cochrane, 50 Scopus). The total study sample size was 595. Of these, 6 studies defined their "Early" group as < 4 weeks and were included in our sub-analyses. In regard to pain scores we found a significant improvement in pain score in the early vs. late group. However, we did not find a significant correction in kyphotic correction.

Conclusions: Our study suggests that early treatment of vertebral compression fractures with Balloon Kyphoplasty (BKP), defined as < 4 weeks, provides a statistically significant improvement in pain scores and kyphotic angle correction compared to late treatment (>4 weeks). However, no statistically significant differences were observed in terms of height restoration or the risk of adjacent level fractures. These findings support the benefits of early intervention for pain relief and alignment, though further research is needed to standardize methodologies and assess long-term outcomes.

FDA device/drug status: Not applicable.

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Background

Vertebral compression fractures (VCFs) in the elderly are common and have the potential to cause significant morbidity in this typically frail population. A 2006 analysis by Johnell et al. estimated that in the year 2000, 9 million osteoporotic fractures occurred globally, of which 1.4 million were vertebral fractures. While many VCFs will go on to heal without intervention, certain fractures will result in either delayed union, or painful nonunion, and may contribute to progressive kyphosis with worsening sagittal imbalance, a known driver of pain and disability [1].

Vertebral augmentation procedures, including balloon kyphoplasty (BKP) have demonstrated efficacy in improving pain and functional outcomes in patients presenting with osteoporotic VCFs. [2]. In acute and some subacute fractures, kyphoplasty may be able to restore vertebral height and segmental alignment [3]. By restoring vertebral body height, sagittal plane deformity and its resultant disability may be reduced in this frail patient population [4].

When comparing BKP with conservative management for painful vertebral compression fractures, Meirhaeghe et al. noted significant improvement in quality of life, pain scores, and segmental angulation compared to the nonsurgical group when treated within 3 months of pain onset [5]. Likewise, in a randomised controlled trial conducted by Boonen et al., it was demonstrated that BKP had a significant improvement compared to nonsurgical intervention with respect to improved back pain, quality of life, disability, and reduction in back pain scores, but demonstrated no difference in re-fracture risk [6]. The efficacy of BKP for VCFs has, however, been disputed by some groups. Lee et al. demonstrated in their prospective cohort study that painful VCFs treated conservatively have similar ODI and VAS scores to kyphoplasty at 1 year; however, in this study few of the BKPs were treated in the acute phase, defined in their study as less than 3 weeks of injury [7].

In the current body of literature, there is equipoise with regards to whether the length of time elapsed between the initial injury and the time of cement augmentation of the injured vertebrae impacts patient outcomes. This systematic review is aimed at addressing the question of whether timing of BKP affects pain-related outcomes, as well as secondary outcomes that include height restoration, local kyphotic angle and/or risk of subsequent adjacent fractures. To the best of our knowledge, this has not been previously evaluated in a systematic review and meta-analysis. Our hypothesis at the outset of this study was that early kyphoplasty, defined as < 4 weeks from suspected onset of vertebral compression fracture, would lead to better pain scores as compared to delayed kyphoplasty, defined as > 4 weeks.

Methods

Search strategy

We conducted a systematic literature review as per PRISMA guidelines. Our search strategy included terms relating the intervention of balloon kyphoplasty with treatment outcomes. These terms included: “Balloon Kyphoplasty”, “Vertebral Fracture”, “Early versus late”, and “Timing”. The language restriction was English, including studies from 2003-2022. The following electronic bibliographic databases were searched: PubMed, Embase, Scopus, and Cochrane. For a more detailed search strategy please see Table 1. Our analysis took place on 1/8/2022.

Inclusion criteria included adults >18 years old, who sustained an osteoporotic vertebral compression fracture that was treated with BKP, grouped by time to intervention as compared to conservative treatment to determine the impact on radiographic and clinical outcomes. The intervention group included patients who failed conservative treatment.

Studies that were excluded were non-English language studies without translation, cadaveric, and animal studies. Additionally, we excluded systematic reviews, meta-analyses, and duplicate studies. Lastly, we did not include studies with patients that had pathologic fractures secondary to neoplasm or infection, and those that did not report clinical or radiographic outcomes.

Table 1
Search strategy

Pubmed	(kyphoplasty) AND (treatment outcome [MeSH Terms]) AND (spinal fracture [MeSH Terms]) AND (time factors [MeSH Terms])
Embase	’kyphoplasty’/mj AND (’time’/exp OR ’time to treatment’/exp) AND ’treatment outcome’/exp
Scopus	(TITLE-ABS-KEY (kyphoplasty) AND TITLE-ABS-KEY ("treatment outcomes") AND TITLE-ABS-KEY ("time factor") OR TITLE-ABS-KEY ("time to treatment)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND LIMIT-TO (SUBJAREA , "MEDI"))
Cochrane	(kyphoplasty): ti, ab, kw AND (treatment outcomes):ti, ab,kw AND ("time factor"): ti, ab,kw"

Table 2
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Studies including adult patients with radiographic evidence of at least one vertebral compression fracture 2. Compression fracture treated with percutaneous balloon Kyphoplasty 3. Studies that reported on time from injury to intervention	1. Non-English language studies without a translated version 2. Animal studies 3. Duplicates 4. Systematic reviews 5. Meta-analysis 6. Cadaveric studies 7. Lack of reporting clinical outcomes 8. Paediatric patients (under 18 years of age) 9. Patients with pathologic fractures secondary to neoplasm/infection

The following search strategy was used for each database: Pubmed: (kyphoplasty) AND (treatment outcome [MeSH Terms]) AND (spinal fracture [MeSH Terms]) AND (time factors[MeSH Terms]). Embase: ’kyphoplasty’/mj AND (’time’/exp OR ’time to treatment’/exp) AND ’treatment outcome’/exp. Scopus: (TITLE-ABS-KEY (kyphoplasty) AND TITLE-ABS-KEY ("treatment outcomes") AND TITLE-ABS-KEY ("time factor") OR TITLE-ABS-KEY ("time to treatment")) AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "re")) AND (LIMIT-TO (SUBJAREA, "MEDI") (see Table 1).

Study selection

Two review authors (BW and CC) reviewed and screened abstracts of studies retrieved by the search strategy above independently and those deemed likely to meet the inclusion criteria were selected for full text review (see Table 2). The same 2 independent reviewers (BW and CC) performed a full text review and assessed for inclusion in the systematic review. Any disagreement between reviewers was resolved through discussion between both independent reviewers and the senior author (RR). Finally, all studies selected for inclusion in the systematic review had their references manually screened for additional articles that met inclusion criteria which were not captured in the formal search strategy.

Data extraction and data items

For all selected articles, data was extracted utilizing a standardized form for the assessment of study quality and defined metrics. This included: a standardized, prepiloted form for assessment of study quality and evidence synthesis. Other data extracted included: study design/methodology, patient demographics, recruitment, follow up rates, timing of measurement, radiographic parameters, follow up pain scores/survey data, information for assessment of the risk of bias, kyphoplasty angle, vertebral height restoration, and subsequent adjacent fractures. Two review authors who were not blinded (BW and CC) extracted data independently, discrepancies were identified and resolved through

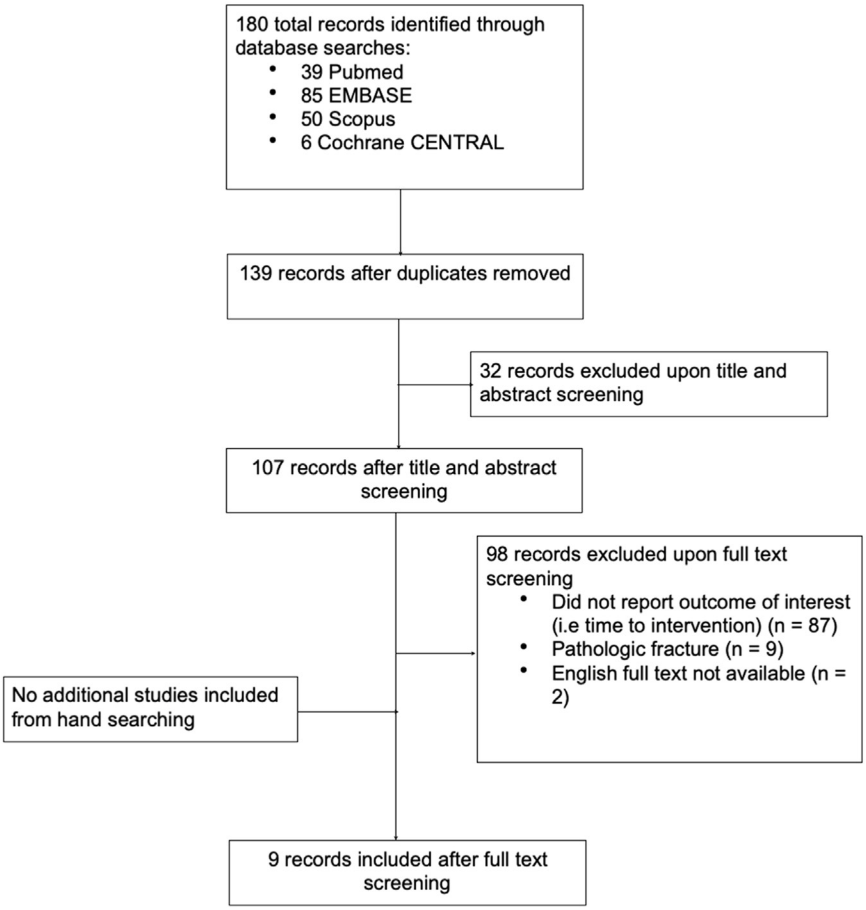

Fig. 1. PRISMA flow chart.

discussion with (RR), missing data was requested from study authors through email or mail communication.

Risk of bias in individual studies, summary measures and synthesis of results

Two authors (BW and CC) independently assessed the risk of bias, taking into consideration study design, methodology, randomization, blinding, completeness of outcome data, and sources of bias. For non-randomized studies the NOS (Newcastle-Ottawa scale) for quality assessment was used. The level of evidence for each study is summarized in Table 4.

Risk of bias across studies

Quantitative synthesis was used when the indicated studies were sufficiently homogenous. Furthermore, heterogeneity was analyzed with a Meta-regression and followed up with a funnel plot for verification.

We could not perform a funnel plot for risk of publication bias as the sensitivity of the test would be too low for a dataset of fewer than 10 studies.

Data analysis

The principal characteristics of included studies were summarized in tabular form. A detailed narrative synthesis summary of clinical, radiographic outcomes, and complications is presented in Table 5.

A meta-analysis of eligible studies was performed to check the effects of kyphoplasty timing on pain scores, kyphoplasty angle, vertebral height restoration, and subsequent adjacent fractures. The risk ratio was used to pool the effect sizes of dichotomous data and standardized mean differences and mean differences were used for continuous data. CI was set at 95%. Random effects model was used when the outcomes were measured using multiple scales for example pain scores. Otherwise, a fixed effect model was used.

Heterogeneity/subgroup analysis

A substantial level of heterogeneity was observed across studies for pain scores (I^2= 77%, p=.0003), height restoration (I^2=93%, p=<.00001), and local kyphosis correction (I^2=86%. p<.0001). This statistical heterogeneity may reflect the variation in patient populations, study methodologies, differences in follow-up periods, and differences in outcome measures (ODI, VAS, etc.).

Low Heterogeneity was observed for the risk of subsequent adjacent fractures (I^2 = 32%, p=.23). This is likely due to the uniformity in the outcome measured across these 3 studies.

Results

A total of 9 studies looking at clinical outcomes based on time to kyphoplasty in adults were included from 180 studies from 4 databases (39 PubMed, 85 EMBASE, 6 Cochrane, 50 Scopus) eligible for title and abstract screening after deduplication (Fig. 1). The total sample size of included studies was 588.

Six of the 9 studies were retrospective cohorts; the remaining 3 were prospective cohorts. A majority of these studies were undertaken in a single center setting in the US, as opposed to being conducted as multi-center trials.

The average of the BKP patients in the Early group (< 4 weeks) was 73 years old, and 74 years old in the Late group (>4 weeks). There

Table 3
Demographics of the early and late groups

	Early group (<4 weeks)	Late group (>4 weeks)
Total (n)	316	279
Average age	73 y/o	74 y/o
Male	77/316 (24%)	73/279 (26%)
Female	239/316 (76%)	206/279 (74%)

Table 4
Level of evidence analysis

Article	Selection	Comparability	Outcome	Total
Guan 2012	4	2	1	7
Park 2010	3	2	1	6
Palmowski 2020	4	0	1	5
Oh 2010	4	2	3	9
Minamide 2018	4	2	3	9
Zhou 2019	4	2	3	9
Takahashi 2018	4	2	3	9
Crandall 2004	4	2	3	9
Erkan 2009	4	1	3	8

were predominantly females in both groups with 76% in the Early group and 74% in the Late group. The mean T score was -2.86 in the early (<4 weeks) group and -2.98 in the late (>4 weeks) group. The standard mean difference of T-scores between both groups was not statistically significant (p=.61). The duration of follow-up ranged from 2 days [8] to 420 days [9,10] (see Table 3).

Of the 9 studies that met inclusion criteria, all studies reported clinical pain scores. Only 4 reported changes in local kyphotic angle, another 4 reported changes in vertebral height after BKP, 5 reported new fractures after BKP and another 5 reported adjacent subsequent vertebral deformity. Another 4 studies discussed cement leakage as a complication.

Meta-analysis

As pain scores were measured on different scales, a random effects model was applied to the data for meta-analysis. The pooled effect size based on the *standardised* mean difference of each scaled score was 0.77 with a 95% CI of 0.36 to 1.17 (p=.0002) (Fig 2A). The highest effect size of 1.32 was reported by Park et al., (2010). Likewise, the standardised mean differences for VAS and ODI were statistically significant with an improvement of 0.53 with a 95% CI of 0.01 to 1.05 (p=.04) for VAS scores and 1.18 with a 95% CI of 0.66 to 1.71 (p<.0001) for standardised mean difference of ODI scores (Fig. 2B, Fig. 2C).

The total mean difference of VAS showed an improvement of 1.01 points with a 95% CI of 0.02 to 2.00. However, this was not statistically significant (p=.05). The heterogeneity was high (I^2=85%)

The overall mean difference of ODI showed an improvement of 3.21 points with a 95% CI of 1.61 to 4.81, which was statistically significant (p<.0001).

The overall mean difference of height restoration was 2.09% with a 95% CI of -2.35% to 6.52%, favoring early BKP. However, these results were not statistically significant p=.36 (Fig. 3). This means height restoration did not depend on the time to kyphoplasty. The heterogeneity was also very high for this data at (I^2=97%).

The kyphotic angle showed an average improvement of 2.11 with 95% CI of 1.29 and 2.92 (p<.0001) (Fig. 4) The heterogeneity was high I^2=86% due to differences in methods and follow-up times of the studies.

The odds of a subsequent adjacent fracture did not change significantly based on time to kyphoplasty with an average effect size of 0.38 [0.14, 1.01, 95% CI] (p=.05) (Fig. 5). The heterogeneity was low for this data at (I^2=32%) likely due to the uniformity of the measured outcome.

Discussion

This study aimed to determine whether early (<4 weeks from injury) kyphoplasty had any clinical or radiographic benefits after a vertebral compression fracture in comparison to late intervention (>4 weeks from injury). Although there was limited literature available on the timing of intervention and the varying definitions for "early" versus "late" balloon kyphoplasty across the included studies made meta-analysis challenging [8,10–12]. We chose to define "Early" as less than 4 weeks, as this corresponds to the approximate time point when mineralization of cartilaginous material in the fracture site begins with radiographic evidence of hard callus formation [13]. (Fig. 6) As a result, study timeframes that overlapped this cut-off, (i.e. the "subacute" populations from Palmowski and Oh et al) were grouped into the "Late" cohort [14]. The rationale was to minimise the probability of making a Type 1 statistical error.

Pain scores

Despite varying definitions, the findings from the included studies were fairly consistent. Regarding pain-related outcomes, all studies favored improvement when kyphoplasty was performed before 4 weeks. The average effect size of 0.77 suggested improved pain-related outcomes with earlier intervention. Takahashi et al. reported significantly better VAS scores in their early group (< 2 months) compared to their late group. Our meta-analysis shows pain scores in the Early group, defined as < 4 weeks from injury to procedure, had significantly better pain relief as measured using the VAS, ODI, and NPRS scale.

There are a few possible explanations for inferior pain score improvements in the delayed kyphoplasty group as compared to the early group, the most obvious one being that early intervention allows for improved fracture reduction, which in turn may improve sagittal alignment and reduce pain related to compensatory mechanisms. These compensatory mechanisms include mechanical facet overload in the lumbar spine, pelvic retroversion, and thoracic hypokyphosis with paraspinal muscle spasms [15].

It is of interest, however, that although there seem to be improved pain scores with early versus late BKP, even patients undergoing late intervention were observed to have significant improvement in pain scores following the procedure. This is likely in part due to the stabilizing and load sharing effect of the cement in the setting of an unhealed vertebral body fracture with persistent micromotion. Another possible mechanism for pain reduction, even in the setting of late intervention with uncorrected focal kyphosis relates to endplate nociceptor activation after a fracture. The basivertebral nerve, originating from the sinuvertebral nerves, innervates the vertebral endplates [16]. Furthermore, in many cases, vertebral augmentation stabilizes endplate fractures as the cement tracks through the fracture site [17–19]. and this stabilising effect confers pain relief even in the setting of suboptimal reduction and segmental malalignment.

Significant early reduction in pain is likely to assist in early mobilisation of patients with osteoporotic vertebral body fractures. Palmowski et al. reported that 96% of patients were fully mobilised within 1 day after BKP [8]. We theorise that facilitation of early mobility may lower mortality rate, although there was not any data on mortality rate captured in the studies included in this analysis. The hypothesis that early mobilisation occurring as a result of early cement augmentation would be consistent with what has been observed in the hip fracture literature, which has demonstrated that early surgery translates to improved survival at follow up [20,21]. The ability for early balloon kyphoplasty to affect mobility (and thus mortality) may be reason enough to consider offering early intervention after injury, particularly in this elderly, frail population. Further study of the effect of kyphoplasty timing on mortality is necessary, however, in order to draw any conclusions.

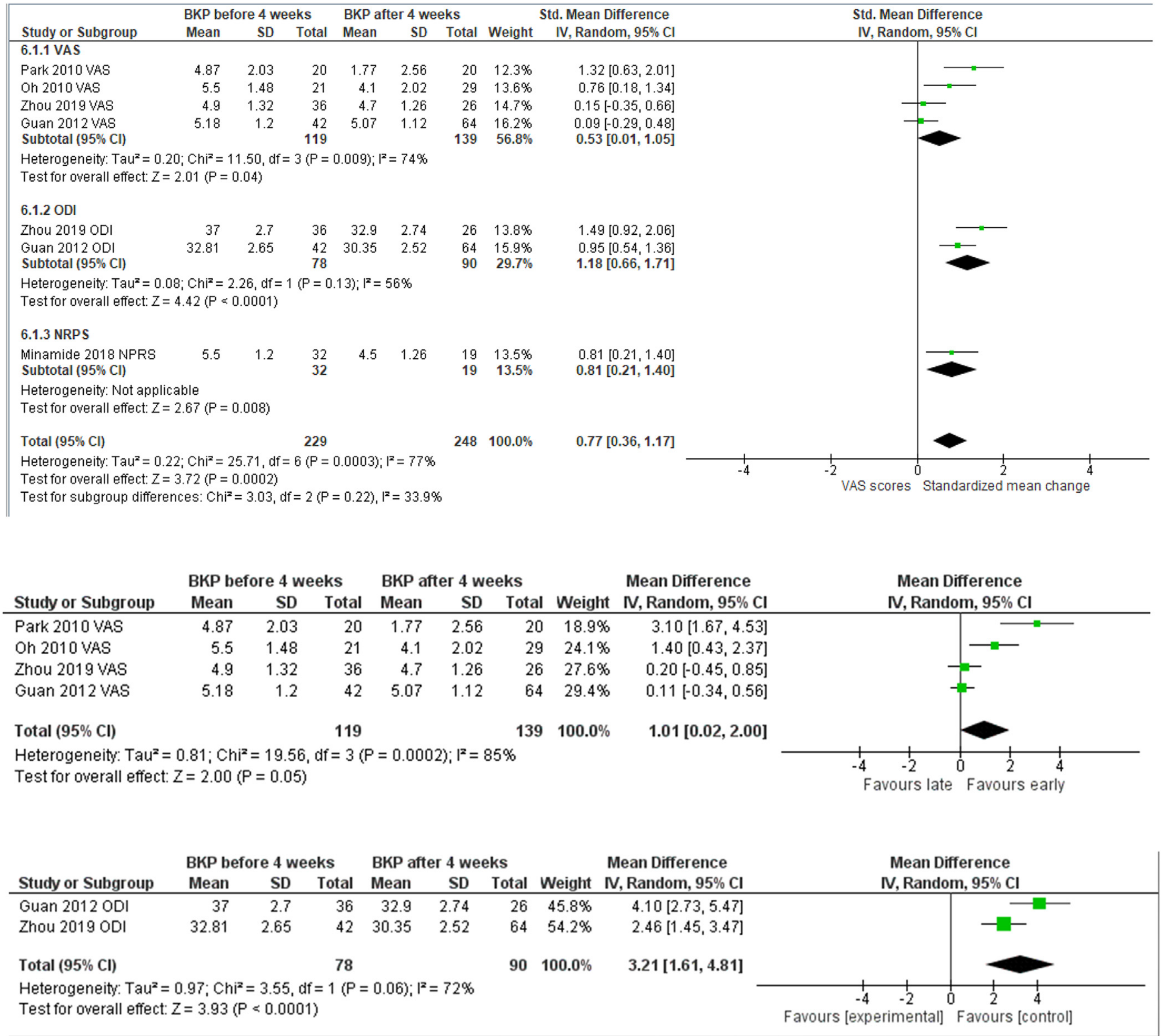

Fig. 2. (A) Standardized mean difference in pain related outcomes (PROs), early (<4 weeks) vs. late (>4 weeks). (B) Mean difference in VAS pain scores, early (<4 weeks) vs. late (>4 weeks). c Mean difference in ODI scores, early (<4 weeks) vs. late (>4 weeks).

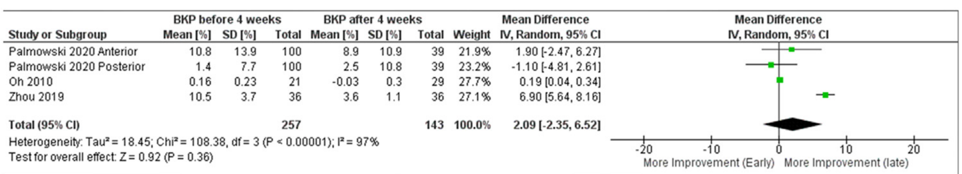

Fig. 3. Mean difference in height restoration (%), early (<4 weeks) vs. late (>4 weeks).

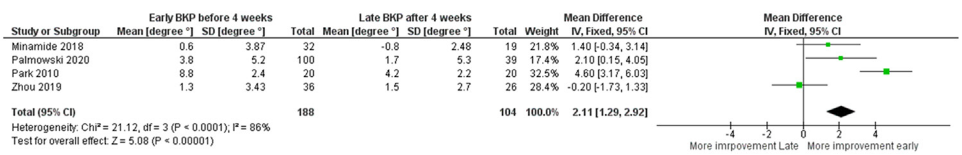

Fig. 4. Mean difference (degrees) in local kyphosis correction early (<4 weeks) vs. late (>4 weeks).

Complications

Six of the 9 included studies reported cement leakage. Of these studies, only Guan et al. reported a significant difference (p=.032) in the prevalence of a Type C cement leakage (cement extravasation across cortical bone), with reduced rates of cement leakage with delayed intervention. The authors hypothesised that in the instance of delayed intervention, organised hematoma and fibrous tissue that forms secondary to the fracture form and prevent cement extravasation across cortical bone. Additionally, all 6 of these studies reported asymptomatic cement leak-

Table 5
Narrative synthesis summary table

Author/Year	Study Design	Demographics	Definition of Early vs. Late Intervention	Clinical Outcomes	Radiographic Outcomes	Complications Reported	Follow-up (days)
Guan 2012	Retrospective cohort	N=106 (Early: 42, M:F=15:27, Age: 68.82±8.99; Late: 64, M:F=25:39, Age: 69.23±9.68)	Early: <2 weeks, Late: >4 weeks	VAS, ODI: Significant improvement in both groups; no significant difference between groups	Significant restoration of vertebral height in both groups; significant difference in RR between groups (p=.045)	Cement leakage: Significant difference in type C leakage location (p=.032); decreased risk of leakage with delayed operation	3
Park 2010	Retrospective cohort	N=40 (Early: 20, all female, Age: 84.55; Late: 20, all female, Age: 81.9)	Early: <2 weeks, Late: >2 weeks	VAS: Significant pain reduction in both groups; no significant difference between groups	Significant difference in restoration height and Cobb angles between groups	None	120 (VAS) >180
Palmowski 2020	Retrospective cohort	N=139 (Early: 100, M:F=27:73, Age: 72.2±11.5; Late: 39, M:F=12:27, Age: 70.4±9.6)	Early: <2 weeks, Late: >6 weeks	VAS: Significant pain reduction in all groups on the second postoperative day	Significant improvement in AVBH, MVBH, and LKA in all groups; ≥10% height restoration in acute/early, subacute, and chronic groups	Cement leakage: 15.2% of patients had cement leakage on postoperative radiographs	2
Oh 2010	Retrospective cohort	N=50 (Early: 21, M:F=8:13, Age: 62.3; Late: 29, M:F=7:22, Age: 66.9)	Early: <3 weeks, Late: >8 weeks	VAS: Significant pain relief in all groups; positive outcomes according to Macnab's criterion	Significant increase in vertebral height in acute and subacute groups; no significant increase in chronic group	Cement extravasation: Symptomatic cement extravasation in one acute case; severe pyogenic spondylitis in one chronic case	>240
Minamide 2018	Retrospective cohort	N=51 (Early: 32, M:F=6:26, Age: 74.6; Late: 19, M:F=4:15, Age: 77.1)	Early: <4 weeks, Late: >4 weeks	NPRS: Significant improvement in both groups; better LBP levels in early group (p<.05)	Local kyphosis significantly higher in late group at last follow-up (p<.001); no significant difference in correction pre/post-op	Reduced rate of subsequent fracture in early group; greater incidence of neighboring vertebral deformity in late group (p<.05)	>420
Zhou 2019	Retrospective cohort	N=62 (Early: 36, M:F=2:34, Age: 70.2±7.6; Late: 26, M:F=2:24, Age: 73.6±8.4)	Early: <4 weeks, Late: >4 weeks	VAS, ODI: Significant reduction in both groups; no significant difference between groups	LKA significantly less in early group at all time points; restored height greater in early group post-op and at 6 months	Reduced rate of subsequent fracture in early group; no significant difference in cement leakage rate between groups	180
Takahashi 2018	Prospective cohort	N=72 (Early: 27, M:F=8:21, Age: 79.9±5.1; Late: 45, M:F=14:31, Age: 77.9±5.9)	Early: <8 weeks, Late: >8 weeks	VAS: Lower preoperative VAS for LBP in early group; no significant difference in VAS with/without ASD or new fracture	Better preservation of final relative anterior vertebral height and kyphotic angle in early group; higher fracture lines and angular motion in late group	Cement leakage, dislodgement, ASD, new fracture, reoperation: similar complications in both groups; asymptomatic cement leakage in 2 patients	>180

(*continued on next page*)

Table 5 (*continued*)

Author/Year	Study Design	Demographics	Definition of Early vs. Late Intervention	Clinical Outcomes	Radiographic Outcomes	Complications Reported	Follow-up (days)
Crandall 2003	Prospective cohort	N=47 (Early: 23, M:F=7:16, Age: 76; Late: 24, M:F=5:19, Age: 72)	Early: <10 weeks, Late: >8 weeks	VAS, ODI: Significant pain alleviation during kyphoplasty in both groups; no significant difference in ODI scores	More acute fractures reducible (p=.01); significant improvement in local kyphosis in both groups; no significant difference in kyphosis correction between groups	No complications with cement or catheter/balloon reported	>180
Erkan 2009	Prospective cohort	N=28 (Early: 15, M:F=4:11, Age: 70; Late: 13, M:F=4:9, Age: 74)	Early: <10 weeks, Late: >16 weeks	% change in VAS, % change in ODI: Significant improvement in both groups; no significant difference between groups	Significant improvement in height restoration and local kyphosis angle in both groups; greater improvement in acute group (p<.05)	Subsequent vertebral fracture: 13% in acute group, 30% in chronic group; cement leakage: 10% in acute group, 4% in chronic group	>420

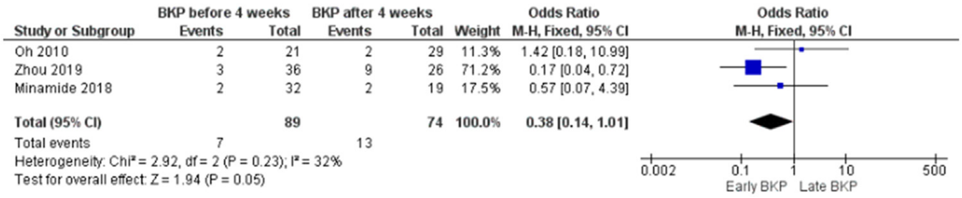

Fig. 5. Difference in risk of subsequent adjacent fracture early (<4 weeks) vs. late (>4 weeks).

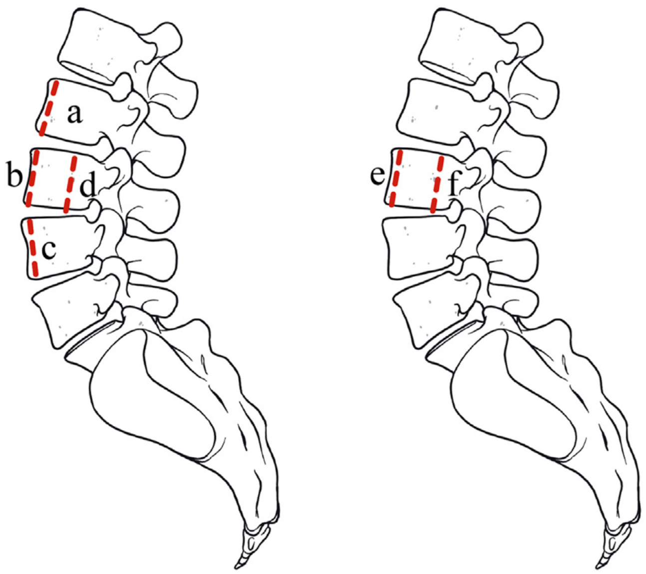

Fig. 6. Method used for determining vertebral body height restoration rate as demonstrated by Kim et al. (2011). Vertebral body height before compression fracture (Y): Y = (a + c)/2. Anterior height restoration (A): A = [(e - b)/Y] × 100 (%). Middle height restoration (M): M = [(f - d)/Y] × 100 (%).

age except for Oh et al. Oh et al. describe one case of a female patient in the acute group that experienced symptomatic cement extravasation into the posterior spinal canal which necessitated treatment by posterior decompression and cement removal [14].

With respect to adjacent segment fracture, Minamide et al. noted fewer subsequent adjacent level fractures in the acute group, defined as < 4 weeks (3/32) compared to the chronic group, defined as >4 weeks (6/19). This was statistically significant with a p-value <.040. Similarly, Erkan et al. noted fewer subsequent adjacent level fractures in the acute group, defined as <10 weeks (13%) compared to the chronic group, defined as >16 weeks (30%), although this was not statistically different, and a p-value was not reported. It is unclear whether a statistically significant difference in rates of adjacent segment fracture would have been observed had their definition of early surgery been 4 weeks or less [9,15].

Although the exact mechanism by which subsequent adjacent vertebral fractures remains unclear it is speculated adjacent segment fracture relates to mismatched densities between the cement augmented level and the adjacent level which is cyclically loaded above the much denser cemented level, resulting in a vertebral fracture [22].

Radiographic outcomes: vertebral height restoration

One of the concerns pertaining to vertebral compression fractures is the development of increased thoracic kyphosis or loss of lumbar lordosis. Downstream sequelae resulting from a shift in the patient's sagittal vertical axis (SVA), may worsen back pain as a consequence of worsening sagittal imbalance, and may further increase the risk of additional fractures [8]. Severe cases may develop decompensated sagittal imbalance and profoundly impaired HRQOL and functional status. As such, it is important to attempt to restore vertebral body height and segmental alignment when managing VCFs with cement augmentation.

The data collected by Park et al. and Guan et al. suggest that to maximize vertebral height restoration and correction of kyphosis, balloon kyphoplasty within 2 weeks of a vertebral fracture is optimal [23,24]. Both these studies reported vertebral height correction as a restoration rate. This percentage was calculated by dividing the height regained postoperatively by the height lost x 100. The prefractured vertebral height was estimated from the mean of the measurements of the closest uninjured vertebrae cephalad and caudal to the treated level [23]. Please see Fig. 6 with caption for further explanation of the method of calculation below [25].

Park et al reported height restoration of the anterior and middle portion of the vertebrae was 22.6% and 25.3% respectively in their Early (< 2 weeks) group. Beyond 2 weeks, height restoration of 12.9% and 17.9% were seen respectively.

Although both groups in this study saw statistically significant increases in vertebral height post-BKP compared to preintervention (p<.05), the Early group saw an even greater increase in vertebral height in both the anterior and middle portions of the vertebral body compared to the Late group with a p-value of <.012, and <.015 respectively [23].

Similarly, Guan et al. found a statistically significant improvement in the mean restoration rate in the Early group was 31.21 +/- 3.57% vs. 28.43 +/- 4.97% in the Late group (p<.045), This suggests that vertebral body height was better restored with earlier intervention [24].

Furthermore, Palmowski et al. noted similar findings, even in the > 6-week group, statistically significant improvements were seen in the anterior and middle portions of the vertebral body with regard to height, (mean diff of 8.9% and 10.75%, respectively). However, the observed improvement in fracture reduction was of smaller magnitude when compared with the early group, where the mean difference percentage in the restoration of the anterior and posterior vertebral body height was 11.3% and 11.9% respectively (all p-values <.05) [8].

This suggests that there may be an optimal time window for achieving a more anatomical reduction of the fracture. That said, improvements in radiographic parameters may still be seen as late as 6 weeks postfracture; however, these radiographic improvements are likely to be inferior when compared to earlier intervention.

Park et al., Guan et al., and Palmowski et al. all reported greater preservation/restoration of vertebral height with improved segmental kyphosis correction occurred with earlier intervention as compared to later. As speculated by Zhou et al., "spontaneous height correction at the fresh fracture stage is easy, while fibrous tissue and bone healing at the late fracture stage could hinder the positioning correction" [26]. This may provide a physiological explanation for the statistical differences seen in the observed extent of vertebral body height restoration and restoration rate favoring the early over late intervention.

The challenge in assessing these studies was in the variation of how groups were defined and how outcomes were measured and reported. For example, an acute vertebral fracture was defined as anywhere from <2 weeks to as far out as 10 weeks. Moreover, some of these studies allocated patients into these groups as determined by the age of the fracture based on the patient's reported onset of symptoms.

It is important to note that the radiographic methods used to measure vertebral height varied between the different included studies. The various methods included using fracture-to-non-fracture ratio, restoration rate, or fractions of referenced height [11,14,15]. The lack of consistent methodologies and variables made it challenging to perform a synthesis of this data. As mentioned in our analysis, the high degree of heterogeneity in the data may have impacted the statistical analysis, making it more difficult to identify meaningful associations or differences between early and late groups. Thus, drawing definitive conclusions regarding vertebral body height restoration and timing of BKP is difficult, and more methodologically rigorous study is necessary.

Unlike measurements for vertebral height, most studies used validated outcome measures when reporting pain scores. All studies were prospective or retrospective cohort studies and selection bias was relatively low. Across all quality dimensions, only 2 were judged to have low quality. Despite differences in how groups were defined all studies showed fairly consistent qualitative and quantitative findings.

Limitations

The study search strategy was constructed to be as comprehensive as possible and so any study involving adult patients (age >18 years old) was screened and reviewed. As seen in the Narrative Synthesis Summary Table, each included study had an average age that was indeed greater than 65 years of age. Therefore, we believe the findings of our meta-analysis reflect the typical age of patients that experience osteoporotic vertebral compression fractures and that receive balloon kyphoplasties, maintaining adequate external validity.

Some limitations of our study are that we conducted a meta-analysis of prospective cohort studies. As a result, there may be selection bias. One way to potentially minimize this selection bias would involve the use of a large, prospective registry.

Considering a majority of these studies were undertaken in a single center setting in the US, the sample studied may not necessarily be generalizable to a broader population of patients that have sustained VCFs. This limitation could potentially be overcome by conducting multicenter studies on the timing of intervention in BKP.

Another limitation in conducting this meta-analysis was determining how to group studies given their varying definitions and categorization of their study population. There were varying definitions of the timeframe for what constitutes an acute, versus subacute, versus chronic vertebral compression fracture. Future studies investigating this topic should consider categorizing patients by their stage of bone healing as determined by radiographic imaging rather than by patient-reported time of injury. This would help reduce recall bias and improve reliability and the power of the study.

Lastly, this systematic review focused exclusively on BKP and the impact of timing of intervention on clinical and radiographic outcomes. While BKP remains the most performed procedure for vertebral body cement augmentation, there are newer devices for cement augmentation that are gaining popularity that do not rely on a balloon for fracture reduction. Notably, there exists some data showing that titanium implantable vertebral augmentation devices may be able to achieve comparable, or even superior clinic outcomes compared to BKP [27]. However, it is unclear if the findings of this study pertaining to time to intervention in BKP can be generalized to these newer devices.

Conclusions

This systematic review and meta-analysis demonstrate that earlier kyphoplasty (<4 weeks) is associated with statistically significant improvements in pain scores and kyphotic angle correction compared to delayed intervention (>4 weeks). However, no significant differences were observed in height restoration or the risk of subsequent adjacent segment fractures between the early and late groups.

Several factors influence the timing of vertebral augmentation, including delays in diagnosis, patient preferences, comorbidities, and access to care. Despite these challenges, our findings highlight the clinical benefits of early intervention, particularly for pain relief and alignment. Further studies are warranted to standardize methodologies, assess long-term outcomes, and evaluate the impact of early kyphoplasty on mortality and cost efficiency in this patient population.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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