

# Factors and Strategies for Post-Vertebroplasty Residual Pain from Thoracolumbar Osteoporotic Vertebral Compression Fractures (OVCF): a systematic review.

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## Review Article

**Keywords:** Residual Pain, Vertebroplasty, Osteoporotic Vertebral Compression Fractures, Bone Cement, Zoledronic Acid

**Posted Date:** March 9th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-162171/v1>

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# Abstract

**Purpose** Insignificant pain relief (IPR) in short period after vertebroplasty is common, which often disturb doctors and affect patients. Therefore, we reviewed systematically relative articles and attempted to get meaningful evidence on factors and strategies for IPR.

**Methods** PubMed, Web of Science, Embase, CNKI, WanFang, and VIP were searched for literatures treating the osteoporotic vertebral compression fractures (OVCFs) with vertebroplasty and assessing the clinical efficacy.

**Results** 817 references were electronically retrieved, 81 full-text papers were screened and 41 studies were included. Twenty-two trials presented factors on IPR, mainly including bone cement related, operation related and patient-related factors. Nineteen studies showed strategies on residual pain, including improving osteoporosis, reforming surgical operation and add other therapies. 16 prospective, 20 retrospective and 5 meta-analyses consisted the systematic review. The data from included studies point to different results, with less risk of bias, were needed to clarify the factors and strategies for residual pain.

**Conclusions** Bone cement distribution and operation error are highly related to the post-vertebroplasty residual pain. Many therapeutic methods could improve pain and rehabilitate function but lacking more high-level evidence due to the insufficient trails.

## Introduction

The aging population is already a major social problem in developing countries in the world today. The problem mainly manifested the increasing elderly people and following health problems. Osteoporosis (OP) is a common disease in the elderly that has arouse more and more attention from the public. Bone loss, bone strength decline and bone microstructure degeneration are common features of OP. Osteoporotic fracture is one of the most serious complications. Among them, osteoporotic vertebral compression fracture (OVCF) is the most common. The back or low back pain caused by OVCF affects the daily life of the elderly seriously. Conservative treatment or prolonged bed rest cannot relieve pain effectively, and even aggravate pain. With the development of spinal minimally invasive surgery, percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) have become the gold standard for the treatment of OVCF. They both can reduce pain immediately, improve functional activities and cut down other complications[1, 2]. However, post-operative OVCF patients with residual pain were often found clinically and in related reports. Some patients who still feel pain in long-term follow-up so that they have poor quality of life. At present, there are few reports on the causes and measures of residual pain in patients after percutaneous vertebroplasty, but the conclusions are still disputed. Therefore, we are very eager to review the relevant literatures and willing to get more accurate answers in order to help patients better with the study reported increasingly. The purpose of this article is to analysis and discuss

the related trails on the causing factors and improving strategies on postoperative residual pain from osteoporotic thoracolumbar compression fractures.

## Methods

We searched 6 databases including Pubmed, Web of Science, Embase, CNKI, WanFang, and VIP in order to obtain more thorough results. We set the search terms as "osteoporotic vertebral compression fractures or OVCF" and "postoperative pain" and the retrieved document as journal literature. The published area and country are not limited, the language is English or Chinese and the publication time is from January 2016 to September 2020.

## Result

817 literatures were searched out. Firstly, removing the 764 articles that were duplicate and irrelevant passages by their title and abstract. Secondly, we removed 12 articles including 4 were simple reviews and 8 didn't have title and abstract in English. Finally, 41 studies for date extraction and result discussion. With regard to related factors, 22 articles (bone cement related: 12, operation related: 6 and patient related:4) were chosen to analyze. And about strategy, there were 19 articles (improving osteoporosis: 8, reform surgical operation: 6 and add other therapy: 5) included. 16 prospective, 20 retrospective and 5 meta-analyses consisted the systematic review together. The below flow chart can be seen thoroughly. (Fig.1)

According to the 41 studies, we sorted out and listed in six tables. In factor-related tables, we set the items as Factor, Author/Year, Operation, Study Type and Better Pain Relief, which could be found in Table1. The item of better pain relief means the better group in pain improvement. In on strategy table, we set the items as Author/Year, Study Type, Test group, Control group and Better group, which could be found in Table2.

## Discussion

### Discussion on related factors

The percentage of post-vertebroplasty residual pain ranges from 4-15%[3-5]. Overall, the clinical effectiveness is rather good. Considering that the elderly patients, only better pain and functional recovery can they enjoy their late life. If elderly people would keep healthy, our society and every family can reduce the pressure form economy and others. Some large-sample retrospective studies were implemented in recent years[3-6]. It was found that postoperative pain and bone mineral density, severe back soft tissue injury, bone cement features, lumbar facet joint violation, bone cement leakage or residual and others are mainly related from these studies[3-6], but a unified understanding has not been formed. According to the present, we explored the causes of post-operative residual pain mainly from three important factors: bone cement, operation and patient-related reason.

## Bone cement related factors

It is currently believed that the mechanism of pain relief in vertebroplasty may be related to the following three aspects. The first is bone trabecular fractures in the vertebral body are stabilized by the diffusion of bone cement to form a riveting effect between the bone trabecular and bone cement. The second is the axial pressure can be supported by filled bone cement. And the last is the pain nerve endings will be damaged by thermal energy come from bone cement after filling bone cement. Therefore, it is speculated that the distribution of bone cement has a possible relationship with postoperative residual pain. From 2018 to 2020, 5 articles [7-11] (1 prospective and 4 retrospective), 2024 cases were retrieved for in-depth research about bone cement distribution. The level evaluation of the five articles indicated the evidence is relatively low. In 2018, Liu C et al. [7] Observed the distribution of bone cement on the fracture line after PVP by MRI and CT scans. Two groups of less than 50% and more than 50% were divided on the basis of the distribution area. The patients in more than 50% group had better pain and function scores on the on the second day after surgery, but there was no significant difference between the two groups at 3 months after surgery. In Ye L et al's study[8], 26 (11.6%) patients whose compressed vertebrae were filling with insufficient bone cement had poor pain relief. It was found that these patients all had the upper fracture line without good bone cement diffusion. One large samples study was carried on by Liu H et al. in 2019[9]. 1314 OVCF patients who underwent bilateral PKP were divided into bone cement confluent distribution group and separated distribution group. The authors obtained the results finally that the confluent not the separated distribution led to better pain relief, if you would make bilateral operation, originated from the evidence of post-op follow up. Similarly, a prospective study of 201 patients with OVCF who underwent bilateral PKP by He S et al.[10] The shape of bone cement distribution was divided into two groups: "H-shaped" and "O-shaped". The patients with "H-shaped" distribution of cement had a lower pain score during the 1-year follow-up. Two above studies suggested that bilateral operation should ensure bilateral bone cement diffusion. Tan L et al. [11] pointed out clearly that the distribution should touched the upper and lower endplates of vertebral body. The last follow-up in 137 OVCF patients who underwent PVP showed pain relieve better in the situation that bone cement contacted with the upper and lower endplates. There was no difference in pain improvement when the bone cement touched one side and no side. The above studies have explained to a certain extent that the distribution of bone cement is related to postoperative residual pain. Although the evident level of these studies is not very high, we think carefully observation the position of fracture line before surgery is very important. Make sure achieve better diffusion when you operate the bilateral cement injection. The question that follows is how much volume of bone cement would reach ideal distribution and clinical efficacy.

Limited to the ethical reasons, there are just two studies[9, 12] that provided us with reference about the volume of bone cement. A large-sample controlled study by Liu H et al.[9] found that more bone cement is better for pain relief, but the best amount is not stated. Only one study with 130 cases by Sun H et al. [12] proposed that when 4-6ml of bone cement is injected with a volume fraction of 19.78%, the patient will relieve pain most quickly. If the volume fraction increased, the bone cement will increase the risk of leakage. Due to the lack of research reports, there is currently insufficient evidence on the relationship between the volume of bone cement and postoperative residual pain improvement.

Since the volume of bone cement is not clearly related to residual pain, is it related to the nature of bone cement? Early PVP surgery often caused severe complications such as acute spinal cord or nerve root compression, paraplegia, cemented pulmonary embolism, and intervertebral disc degeneration due to the leakage of bone cement especially in the cracked wall of vertebral body[13, 14]. Many scholars believed that low viscosity is an important cause of bone cement leakage until the advent of high viscosity bone cement. High-viscosity bone cement can reduce leakage, but whether it has relationship with pain relief rarely reported in the past. In the recent years, 4 four prospective studies[13-16] and one meta-analysis[17]on viscosity that maybe deal with our question were published. The level evaluation of the five articles indicated the evidence is relatively high. The 4 prospective studies, 558 case, 289 high-viscosity and 269 low- viscosity included. Guo Z et al.[14]divided 100 patients with OVCF underwent PVP into two groups, 50 cases in each group, using high-viscosity and low-viscosity bone cements. The results show that high-viscosity bone cement can relieve pain better. Contrary to the former study, three papers reported the different results. F G et al.[13]observed the clinical efficacy of high or low viscosity bone cement in 200 OVCF cases the same as Li K et al.[15]observed in 80 cases and Miao F et al.[16]. observed in 178 cases. They all drawn the same conclusion that there was no significant difference in pain, function, and quality of life with high or low viscosity bone cement. However, the above studies have shown that high-viscosity bone cement is better at preventing bone cement leakage[13, 15, 16]. There also was a high-quality meta-analysis about the topic in 2017 strengthen the controversy discuss[17]. 6 RCT studies, 554 cases underwent PVP surgery, 278 cases with high-viscosity bone cement, and 276 cases with low-viscosity bone cement, were qualified into the meta-analysis. From its results, we found the high-viscosity bone cement is better no matter in pain improvement, functional recovery and bone cement leakage. Through the literature review, we think the relationship between different viscosity bone cement and postoperative residual pain is controversial form 2016 to the present. Especially in the last two years, opinions that high viscosity cannot help pain better have been put forward. Only with same thinking can high viscosity bone cement decrease leakage.

Thus, in terms of bone cement, the residual pain has a close relationship with distribution in vertebral body. The better distribute shapes is as pattern of vertebral body or “H” shape[10]. Other factors about bone cement are still disputed. There was also an interesting study focus on different phases bone cement in PKP for curing OVCF[18]. The conclusions were that the wet-sand phase of low-viscosity bone cement is better than wire-drawing phase of that according to the clinical efficacy. Bone cement in wet-sand phase would be beneficial to distributing evenly, strengthening the injured vertebral body, alleviating the early postoperative pain, declining the refracture rate of injured and adjacent vertebral bodies. Such different views were worth for us to thinking.

### **Operation related factors**

We have reviewed thoroughly literatures on several aspects on the relationship between surgical operation and residual pain. As many meta-analyses shown, PKP and PVP have no difference in pain improvement and function recovery[19, 20]. 10 studies, from a meta-analysis with 16 studies[19], indicated no difference by comparing the pain improvement in PKP group and PVP group. We acquired

exact conclusions on unilateral versus bilateral percutaneous vertebroplasty from the following meta-analysis articles. About with PVP, 9 studies included 627 OVCF shown no difference on postoperative residual pain[20]. And about with PKP, it is generally believed that the two ways have no difference in postoperative efficacy now[21]. Another high-level meta-analysis put forward that unilateral PKP has slightly better efficacy than bilateral PKP in the short term, but no different in long-term comparison[22]. Therefore, from the above studies' result, we think there is no relationship between unilateral or Bilateral puncture with residual pain no matter with PKP or PVP.

Operative error is a role factor causing the residual pain after PKP or PVP. In the current studies, pedicle residual bone cement and facet joint violation which affected the pain alleviating were the main operative error. There were three retrospective papers talking about this topic involved 341 cases[23-25]. According to the prognosis results, 84 OVCF cases with vertebroplasty were divided into the good prognosis group and poor prognosis group by Liu J et al.[23]. The final results showed that the good prognosis group had lower pain score that was positively correlated with the internal and external residual cement score of the pedicle. In the same year, a similar study was reported again[24]. It was described again that the residual bone cement score has positive relationship with post-operative pain through CT scans of the inner and outer sides of the pedicle. It is necessary for every doctor to avoid the residual bone cement in the pedicle during surgery and remove it if happen so that patient could feel less post-operative pain.

As for facet joint violation, it was found by Li Y et al. that 15.9% (25/157) of unilateral PKP patients had different degrees of facet joint violation, and the injured patients showed higher pain and dysfunction scores in a short-term follow up of 1 month[25]. There are currently few reports on two topics. Anyway, the important details of operation need to be pay enough attention. It is common that the puncture needle would damage the surrounding normal tissues because of repeated positioning by C-arm fluoroscopy during the operation. In addition, there were earlier reports about the risk of bone cement residue or even leakage for the reason that surgeon pursued for puncture angle excessively lead to internal and external walls of the pedicle rupturing. Or maybe the puncture needle was pulled out before the bone cement was hard, then the pedicle remains in the pedicle. This requires the surgeon to improve operation skill and reduce error.

Another factor is the timing of surgery, but there is currently controversy. It is believed by Yan et al.[26] that taking the operation within 1-3 weeks after OVCF is the best for pain relief, the second is within 1 week, and the third is beyond 3 weeks. Zhou X et al.[27] found that there is no significant difference in pain relief by comparing the early (within 4 weeks) and late (more than 4 weeks) period, but the early surgery can better restore the vertebral height and reduce the occurrence of refractures.

### **Patient related factors**

Four studies[28-31] reported the patient's bone mineral density (BMD), soft tissue injury and bone marrow edema respectively. BMD is the major factor related to patient's own problem. Shen et al. [28]retrospectively analyzed 107 OVCF cases and found that lumbar BMD is an important factor in post-operative residual pain. The lower BMD t value, the higher back pain visual analogue scale (VAS). Cao J

et al.[29]found a positive relationship between patients' BMD and degree of long-term pain relied though a meta-analysis about BMD and refracture after vertebroplasty. Two other studies focused on degree of soft tissue injury and postoperative recovery in OVCF patients. Peng K et al.[30]reported the soft tissue injury of the lower back and back before surgery can significantly affect the early pain relief, and significantly delay the movement after PKP in 71 OVCF cases. Xu W et al.[31]observed the correlation between degree and ranges of preoperative bone marrow edema on MRI and postoperative efficacy. According to degree and ranges of edema, 93 OVCF cases were divided into A (0-24%), B (25-75%) and C (75-100%) three groups. The research results suggest that B group acquired best pain relief. However, there was no difference in pain improvement from 6 months to 12 months after surgery. To sum up, we should attach importance to injured degree on MRI and patient's BMD. Increasing BMD positively and treating soft tissue comprehensively are necessary in OVCF patient with residual pain.

### **Discussion on feasible strategies**

By searching the literatures, we analyzed three main strategies on the post-operative residual pain in OVCF patient. Three methods, improving osteoporosis, reforming operation and implementing other therapies, would be analyzed and discussed. The studies on improving osteoporosis and reforming surgical operation had higher qualities.

### **Improving Osteoporosis**

There have been few reports of unsatisfactory postoperative pain relief due to low bone density in recent years. However, many researchers regarded the zoledronic acid (ZOL) as the treatment for severely osteoporotic patients who had residual pain after vertebroplasty and they all get positive results. As all we known, zoledronic acid could inhabit osteoclasts differentiate and proliferate, regulate bone metabolism and reduce bone loss. In this article, 6 retrospective studies [32-37] and 2 prospective studies [38, 39]were searched out. 7 studies[32-35, 37-39] reported the effect of ZOL and one study[37] reported the effect of Teriparatide.1416 cases, 574 cases in test group and 842 cases in control group, who had residual pain in back or low back were observed. The level evaluation of the 8 articles indicated the evidence is relatively low because of more retrospective studies.

Shi C et al.[32]reported that osteoporotic thoracolumbar fractures were treated with PKP and ZOL, which was better than PKP alone or ZOL alone in terms of pain relief and functional improvement. PKP combined with ZOL in the treatment of postmenopausal OVCF patients had better postoperative pain relief, BMD and osteocalcin expression than the control group, which was reported by Huang S et al.[33] Two prospective studies also come up with same results. Huang Z et al.[38] and Zheng H et al.[39] both proposed PKP and ZOL treatment was better than the control group in pain relief in multiple stages of follow-up within 12 months. ZOL was used on the second or third day after surgery in the above studies. Hu W et al.[34]reported a controlled study of 121 OVCF patients were injected with ZOL before PVP surgery. The results showed that patients in the test group had lower pain scores after one year of follow-up. These indicated that vertebroplasty combined with ZOL would improve the residual pain in OVCF patient. Whether the ZOL will be injected preoperatively or postoperatively probably shows no difference.

In recent years, vertebroplasty combined with ZOL and osteosynthetic agents for OVCF patient also has a certain clinical efficacy. PVP combined with ZOL and vitamin K2 was used to treat patients with multi-stage OVCF, which was studied by Huang Y et al.[35] Compared with the control group, the test-group patient had better pain relief in the follow-up from 1 to 12 months after PVP. Vitamin K2 is mainly derived from meat, egg yolk and cheese. It has the two-way effect of promoting bone formation and inhibiting bone resorption and can improve the unbalanced state of bone tissue metabolism[35].

A study of PVP combined with ZOL and rosuvastatin also had an excellent result that the test group patients acquired better pain ease, function recovery and less refracture occurrence[36]. Statins were recently found to increase bone density, promote bone formation, and inhibit bone tissue absorption by reducing CTX (type I procollagen peptide) expression[40]. Rosuvastatin promotes the upregulation of BMP-2 expression in bone cells as a precondition of osteoblast formation, reproduction, and differentiation. It can also contribute to fracture healing and prevent refracture[41]. Teriparatide (TPTD) is a new anti-osteoporosis drug applied for in the near years. PKP combined with TPTD for 12 months effectively reduce postoperative residual pain, reduce new fractures, and improve lift quality of OVCF patients[37]. This is just the only study about using teriparatide.

Currently, more and more studies on anti-osteoporosis drugs improving residual pain. Combining with ZOL was reported the most and was most presentative. In 2020, Vitamin K2, statins and Teriparatide were started reporting, but the number of studies is insufficient. It is another pity that is most of related trials are retrospective, lacking RCTs or meta-analysis to provide higher-level evidence.

## **Reform surgical operation**

While the operation of PKP or PVP combined with injection of polymethyl methacrylate (PMMA) bone cement has become an essential technique for surgeons, every skill would be reformed in order to better clinical outcome. The following studies which showed the reform of surgical operation were reviewed. Xu B et al.[42]reported that the clinical effect of bone filled bag vertebroplasty for OVCF was similar to PKP, which effectively relieve pain, restore part of the vertebral body height, and significantly reduce the rate of vertebral leakage. This technique is a safe, simple and effective treatment method. Targeted puncture and low-dose bone cement was a new method put forward by Yuan L et al.[43] Compared with traditional PVP, the target PVP lower the incidence of bone cement leakage and adjacent vertebral fractures, but there was no difference in pain relief. In 2015, Noriega D et al[44] firstly reported the SpineJack device technology, also called Titanium implantable vertebral augmentation device. The special device was treated for traumatic vertebral compressive fracture patients at first, which can restore function and improve patients' life quality. The SpineJack device is stretched inside the vertebral body to restore the height of the vertebral body through a built-in titanium device, and then bone cement is injected, and the device is kept in the vertebral body for continuous action. In the next few years, Noriega D's team[45]set about the multi-center RCT that was compare SpineJack implantable device technology and PKP in OVCF patient. From the clinical efficacy, it was found that patients had lower pain scores during follow-up 6 months after surgery. This technique is non-inferior to PKP. Despite the mentioned operation was only

reported once, it was the proof that we have been exploring better way. However, there is the certain fact that which way is best. Maybe the future would give us answer.

Certainly, bone cement is the part of operation as well. Mineralized collagen polymethyl methacrylate (MC-PMMA) bone cement has better bioabsorbability and improved biocompatibility[46-48]. At present, MC-PMMA have been used and reported in three researches, but the results were mixed. Three studies[46-48] were all retrospective including 245 cases. Among of them, 133 cases in MC-PMMA group and 112 case in PMMA group. Zhu J et al[46] found the Mineralized bone cement showed the better pain relief and functional improvement in the 1-year follow-up. On the contrary, Wang X et al.[47]and Jiang W et al. [48] carried out same studies and found two kinds of bone cement had no significant different in postoperative residual pain.

Here are other improved ways about short-term pain relief. Vertebral anesthesia (into the vertebral body), a different way, reported by Mao G et al.[49] was better than conventional local anesthesia (to the surface of the periosteum) in pain relief at 12h and 24h after operation. Ying J et al.[50] considered the relation between setting temperature of bone cement and residual pain. Adding artificial bone repair material (ABRM) to bone cement reduced the setting temperature of bone cement. The most of pain relief was on the third day after surgery. However, the two studies had no difference in the improvement of long-term pain, which were not fit in our topic.

### **Add other therapies**

For the residual pain after vertebroplasty, effective treatments on pain are indispensable. This includes various therapies of Western medicine and Chinese medicine, but the level of evidence in related studies is low but could for readers' reference. Pregabalin was effective for the poor pain relief after PVP treatment, which had relative safety and certain efficacy. OVCF patients after PVP whose improvement rate were less than 25% were taken pregabalin in Liu B et al's study[51]. Li Z et al.[52] divided 62 residual pain cases after PVP into extracorporeal shock wave therapy (ESWT) group and oral analgesia group. ESWT was an effective and physically acceptable way for postoperative pain and was better than control group. Chinese Medicine theory and therapy also play a significant role in the residual pain after vertebroplasty in OVCF patient as the following studies demonstrated. Du X et al.[53] combined radiofrequency needle knife and Xianling Gubao capsules for the treatment on 30 residual pain case after PVP. They drew the conclusion that the combination of radiofrequency needle knife and Xianling Gubao capsules can effectively and quickly relieve lumbar and back pain, improve lumbar function, increase bone density and reduce the recurrence rate of osteoporotic fractures. It is worthy of clinical promotion and application. Xianling Gubao Capsule made of many kinds of herbals that can improve bone density, promoting fracture healing, effectively alleviating osteoporotic pain, and restoring patient mobility. The occurrence of residual pain after operation is closely related to blood stasis of theory of Chinese Medicine. Shentong Zhuyu decoction was reported by Li H et al.[54] can accelerate the recovery of residual pain after operation by promoting the absorption of blood stasis by the body. Shentong Zhuyu Decoction was recorded in "Yi Lin correct wrong" written by the famous doctor Wang Qingren in the Qing

Dynasty. It mainly treats the body pain syndrome caused by blood stasis blocking the meridian. Zhang B et al.[55] adopted Chinese Medicine five-tone therapy on OVCF patient after PKP. It was proven that application of five-tone therapy could alleviate pain symptoms and had a good effect. The five-tone therapy of Chinese medicine organically combines the theory of the yin and yang and the five elements in TCM with music. based on the five tones in the music, combining the five elements and the five internal organs, it regulates the patient's spirit, improves the function of patient's internal organs and reduces pain after vertebroplasty.

There are many different kinds of therapy for residual pain in OVCF patients after surgery on the basis of literature review. These treatments all display better clinical efficacy and contribute to dealing with patient's complain.

## Conclusions

Although vertebroplasty has become the standard for the treatment of OVCF, postoperative pain relief varies among different patients. Because of the difference, this article reviewed and analyzed relates factors and improvement strategies. It aims to summarize the latest research results and serve the clinic and patients. We reviewed three common factors including bone cement, surgical operation and patient's problem. The residual pain is related to the distribution of bone cement. Whether bone cement is distributed the fracture region seems more important. Yet the nature of bone cement, PKP or PVP, unilateral or bilateral puncture are not related factors. Pedicle residual bone cement and facet joint violation should be aroused more attention when puncture. Correspondingly, we reviewed three useful strategies including improving osteoporosis, reforming surgical operation and adding other therapies. For now, applying the anti-osteoporosis medications, especially ZOL, has a positive effect on pain relief and quite few adverse events. The reforming operation, such as bone bag filling skill, targeted puncture, Spinejack device, MC-PMMA bone cement and so on, were effective. However, there need to be confirmed by more trails by which provide more evidence. As for other therapy, physical therapy and Chinese medicine treatment, etc. all have certain curative effects. In our opinions, post-vertebroplasty residual pain is still a common concern. Considering the reasons of residual pain and choosing the best strategy is indispensable absolutely for us. We firmly believe that the minimally invasive spine surgery should bring better clinical efficacy in the near future.

## Declarations

### Conflict of interest (COI)

Binbin Tang, Kang Liu, Lianguo Wu, and Xiaolin Shi declare that they have no conflict of interest.

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## Tables

Table 1. *Literatures List on the factors (bone cement related-operation related-patient related) of residual pain.*

| <b>First Author/Year</b> | <b>Operation</b> | <b>Study Type</b> | <b>Better Pain Relief</b>  | <b>Factor, No.</b> |
|--------------------------|------------------|-------------------|--|--------------------|
| Liu C. [7]<br>2018       | PVP              | Prospective       | Well distribution in the fracture line area                        | 1                  |
| Ye L. [8]<br>2018        | PVP              | Retrospective     | Well distribution in the fracture line area                        | 1                  |
| Liu H. [9]<br>2019       | PKP              | Retrospective     | Confluent distribution   | 1                  |
| He S. [10]<br>2019       | PKP              | Retrospective     | “H” shape distribution   | 1                  |
| Tan L. [11]<br>2020      | PVP              | Retrospective     | Distribution as fully contacted both the upper and lower endplates | 1                  |
| Sun H. [12]<br>2018      | PVP              | Prospective       | 4-6ml was the best   | 2                  |
| Liu H. [9]<br>2019       | PKP              | Retrospective     | More volume  | 2                  |
| Guo Z. [14]<br>2017      | PVP              | Prospective       | High viscosity   | 3                  |
| Xu M. [17]<br>2017       | PVP              | Meta-analysis     | High viscosity   | 3                  |
| F G. [13]<br>2019        | PVP              | Prospective       | No difference  | 3                  |
| Li K. [15]<br>2020       | PVP              | Prospective       | No difference  | 3                  |
| Miao F. [16]<br>2020     | PVP              | Prospective       | No difference  | 3                  |
| Chen Y. [20]<br>2019     | PVP              | Meta-analysis     | No difference  | 4                  |
| Chen X. [21]<br>2018     | PKP              | Meta-analysis     | No difference  | 4                  |
| Chen Y. [22]<br>2018     | PKP              | Meta-analysis     | No difference  | 4                  |
| Liu J. [23]<br>2017      | PVP              | Retrospective     | Low score in residual  | 5                  |
| Yan S. [24]<br>2017      | PVP              | Retrospective     | Low score in residual  | 5                  |
| Li Y. [25]<br>2018       | PKP              | Retrospective     | No violation   | 6                  |
| Shen Y. [28]             | PVP              | Retrospective     | Undeclined BMD   | 7                  |

|                      |     |               |                                   |   |
|----------------------|-----|---------------|-----------------------------------|---|
| 2016                 |     |               |                                   |   |
| Cao J. [29]<br>2016  | PVP | Meta-analysis | Normal BMD                        | 7 |
| Peng K. [30]<br>2018 | PKP | Retrospective | No soft tissue injury on low back | 8 |
| Xu W. [31]<br>2018   | PVP | Prospective   | Moderate 25-75% degree            | 9 |

PVP: Percutaneous vertebroplasty. PKP: Percutaneous kyphoplasty. 1: Bone cement distribution. 2: Bone cement volume. 3: Bone cement viscosity. 4: Unilateral or bilateral puncture. 5: Pedicle Residual Bone Cement. 6: Facet Joint Violation. 7: Bone mineral density (BMD). 8: Soft Tissue Injury. 9: Bone Marrow Edema.

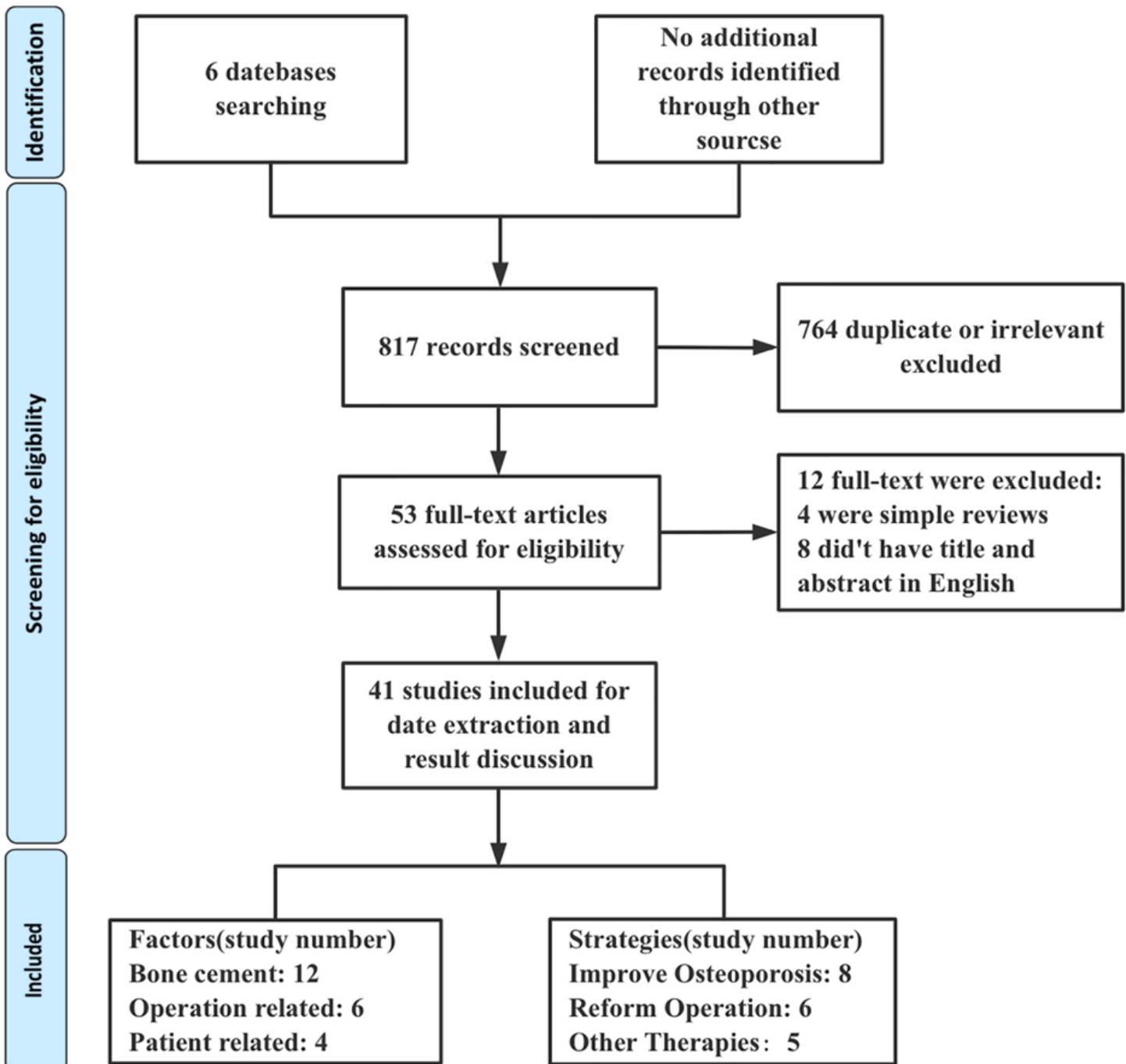
Table 2. *Literatures list on strategies (improve osteoporosis reform operation and add other therapies) on residual pain relief.*

| Author/Year          | Study type    | Test group  | Control group               | Better Group  | Strategy, No. |
|----------------------|---------------|---|-----------------------------|---------------|---------------|
| Shi C. [32] 2018     | Retrospective | PKP and ZOL   | PKP or ZOL                  | Test group    | 1             |
| Huang S. [33] 2019   | Retrospective | PKP and ZOL   | PKP                         | Test group    | 1             |
| Huang Z. [38] 2019   | Prospective   | PKP and ZOL   | PKP                         | Test group    | 1             |
| Zheng H. [39] 2019   | Prospective   | PKP and ZOL   | PKP                         | Test group    | 1             |
| Hu W. [34] 2020      | Retrospective | PVP, ZOL and Ca   | PVP and Ca                  | Test group    | 1             |
| Huang Y. [35] 2020   | Retrospective | PVP∩ZOL and V <sub>K2</sub>                             | PVP∩Ca and V <sub>D</sub>   | Test group    | 1             |
| Li H. [36] 2020      | Retrospective | PVP, ZOL and Rosuvastatin                               | PVP and Ca                  | Test group    | 1             |
| Kong M. [37] 2019    | Retrospective | PKP and 12-month TPTD                                   | PKP, Ca and V <sub>D</sub>  | Test group    | 1             |
| Xu B. [42] 2018      | Retrospective | Bone filling bag vertebroplasty                         | PKP                         | No difference | 2             |
| Yuan L. [43] 2020    | Prospective   | Low-dose targeted PVP                                   | Traditional PVP             | No difference | 2             |
| Noriega D. [45] 2019 | Prospective   | TIVAD vertebroplasty                                    | PKP                         | Observe group | 2             |
| Zhu J. [46] 2019     | Retrospective | MC-PMMA cement PKP                                      | PMMA cement PKP             | Observe group | 2             |
| Wang X. [47] 2018    | Retrospective | MC-PMMA cement PVP                                      | PMMA cement PVP             | No difference | 2             |
| Jiang W. [48] 2020   | Retrospective | MC-PMMA cement PVP                                      | PMMA cement PVP             | No difference | 2             |
| Liu B. [51] 2019     | Prospective   | Pregabalin  | /                           | Test group    | 3             |
| Li Z. [52] 2020      | Prospective   | ESWT  | Celecoxib Capsules oral     | Test group    | 3             |
| Du X. [53] 2018      | Prospective   | Radiofrequency needle knife and Xianling Gubao capsules | Radiofrequency needle knife | Test group    | 3             |
| Li H. [54] 2019      | Prospective   | Shentong Zhuyu decoction                                | /                           | Test group    | 3             |

|                   |             |  |                        |            |   |
|-------------------|-------------|--|------------------------|------------|---|
| Zhang B. [55]2019 | Prospective | TCM five-tone therapy and Conventional treatment | Conventional treatment | Test group | 3 |
|-------------------|-------------|--|------------------------|------------|---|

ZOL: Zoledronic acid. Ca: Calcium supplements. VK2: Vitamin K2. VD: Vitamin D. TPTD: Teriparatide. TIVAD: Titanium implantable vertebral augmentation device. PMMA: Polymethyl methacrylate. MC: Mineralized collagen. ESWT: Extracorporeal Shock Wave Therapy. TCM: Traditional Chinese Medicine. /: no therapy. 1: Improve osteoporosis. 2. Reform operation. 3.Add other therapies.

## Figures



## Figure 1

Flow chart of selection of systematic reviews following the PRISMA statement.