

Dear Editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate the editor and reviewer very much for the constructive suggestions and comments on our manuscript entitled “Predictive risk factors for the recollapse of cemented vertebrae after percutaneous vertebroplasty: A meta-analysis” (ID: 62934).

We have studied the reviewer’s comments carefully. According to the reviewer’s detailed suggestions, we have made a careful revision of the original manuscript. All revisions based on reviewer’s comments have been presented in the revised manuscript, which we would like to submit for your kind consideration.

Kind regards,

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Dear Editor and Reviewer,

Thank you for your letter and the reviewer's comments concerning our manuscript entitled "Predictive risk factors for the recollapse of cemented vertebrae after percutaneous vertebroplasty: A meta-analysis" (ID: 62934). Those comments are all valuable and helpful for revising and improving our paper, as well as the important guiding significance to other researches. We have studied these comments carefully and comments of the reviewer have been replied point by point, which we hope to meet with approval. The main corrections in the manuscript and the response to the reviewer's comments are as follows. (Reviewer's comments in blue)

Replies to the reviewer's comments:

Reviewer #1:

1. Response to comment: This statement is too general: Even so, the vertebral body that is strengthened via PVP is likely to collapse again. Is better to state the percentage of recollapse according to the literature.

Response: Thank you for pointing this out. We have searched electronic databases including the CENTRAL, MEDLINE, EMBASE, and PubMed for original articles or reviews published up to March 2020. To the best of our knowledge, the percentage of the cemented vertebra recollapse after PVP in OVCF patients has not ever been systematically calculated and reported. We were unable to give the accurate statistical

incidence of recollapse according to the literature review. However, we calculated the incidence of recollapse in the studies included in this meta-analysis, respectively. The recollapse rate in each study ranged from 0.6% to 63.3% and the pooled incidence was 10.1%. More details have been listed in Table 1.

2. Response to comment: How recollapse is defined in the literature and when to consider it a significant finding to be treated.

Response: We are very sorry for our negligence in explaining the accurate definition of recollapse in our meta-analysis. Recollapse, that is, an insufficiency fracture of the treated vertebra, which can be assessed through medical history, clinical symptoms, and imaging findings. The osteoporotic patients usually relieve back pain after the operation, but it may reappear with the site of prior PVP. (Heo D H , Chin D K , Yoon Y S , et al. Recollapse of previous vertebral compression fracture after percutaneous vertebroplasty[J]. Osteoporosis International, 2009, 20(3):473-480.) Progressive vertebral height loss and aggravation of kyphotic deformity can be found in X-ray imaging after PVP during follow-up period. When the treated patient reappears with intractable back pain or neurological symptoms, combined with severe kyphosis in imaging finding, it should be required further treatments after excluding new injuries. (W B, X B, Jiang, et al. Risk factors and score for recollapse of the augmented vertebrae after percutaneous vertebroplasty in osteoporotic vertebral compression fractures.[J]. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis

Foundation of the USA, 2018.) Details were added in the introduction of this manuscript.

3. Response to comment: When the authors state that the solid lump pattern of distribution of the cement is associated with vertebral body re-collapse, I think that the readers would be interested in knowing which cement distribution patterns are not associated with re-collapse. Therefore, I recommend to also state these patterns.

Response: It is truly significant to our study and we have added this part according to the Reviewer's suggestion. The distribution patterns of cement injected into the fractured vertebrae have been reported and divided into 2 patterns: solid lump and trabecular. (He D , Lou C , Yu W , et al. Cement Distribution Patterns Are Associated With Recompression in Cemented Vertebrae After Percutaneous Vertebroplasty: A Retrospective Study[J]. World Neurosurgery, 2018.) As we have discussed in the manuscript, the optimum status of injected cement through PVP is that cement interdigitates throughout the fractured vertebrae so that the loads are transferred through the cement column exactly between the vertebral endplates. The trabecular distribution pattern of the cement allows the vertebral body to withstand external forces more evenly, avoiding the stress-shielding effect. As a result, the interlocking between injected cement and bone trabecula is significant for maintaining the height of vertebral body. However, the solid lump distribution pattern without interlocking results in insufficient mechanical strength of the vertebral body, which may cause the cemented vertebrae to collapse again. Consistent with our findings, Kim et al.

reported that recollapse in the cemented vertebrae after PVP was more frequent in solid lump distribution pattern than trabecular distribution pattern. (Kim K H , Kuh S U , Park J Y , et al. What is the importance of "halo" phenomenon around bone cement following vertebral augmentation for osteoporotic compression fracture?[J]. osteoporosis international, 2012, 23(10):2559-2565.) Added portion can be found in paragraph 4 of the discussion.

4. Response to comment: In general, the discussion section is too long and must be summarized focusing in the main point and sending to the reader clear messages.

Response: Thank you for pointing this out. Based on the comments of reviewer, we have deleted the unnecessary content of discussion except for the risk factors we found and limitations. As we considered the predictive risk factors as the main points of this manuscript, details of which should be elaborated and explained clearly. In addition, we described truthfully the limitations of this meta-analysis so that readers were able to obtain the maximal amount of useful information from reading the article. We hope that the content we keep can meet with approval.

5. Response to comment: First paragraph. When the authors say that recollapse is considered a pathological fracture, probably is better to say that is considered an insufficiency fracture, because no malignancy is in the affected vertebral body.

Response: We are very sorry for our inaccurate description. As we originally described the recollapse as a pathological fracture, we thought that the causes of

pathological fractures included bone tumors, osteoporosis, and endocrine disorders, etc. And our research focused on risk factors for the cemented vertebra recollapse after PVP in OVCFs. After repeated thinking, we believed that this statement could not rule out the ambiguity caused by conditions other than osteoporosis. However, insufficiency fractures located at spine are painful, debilitating, and are common consequences of osteoporosis. When investigating the clinical characteristics of insufficiency fractures, an acute traumatic event or a previous history of malignancy is often seen as the exclusion criteria for diagnosis. (Kawaguchi S , Yamashita T , Koshio H , et al. Insufficiency fracture of the spine: a prospective analysis based on radiographic and scintigraphic diagnosis[J]. Journal of Bone & Mineral Metabolism, 2001, 19(5):312-316.) Therefore, it seems more accurate to define the recollapse as a kind of insufficiency fractures. We have replaced the relevant descriptions in the manuscript with insufficiency fractures according to the Reviewer's recommendation.

6. Response to comment: Second paragraph. The authors refer to a previous metanalysis thar included both PVP and KP. This is an opportunity to sate the main findings found in that metanalysis compared with the current work.

Response: As the Reviewer suggested, it was really important that the main findings in that meta-analysis should be compared with the current work. In short, five risk factors including fractures located at the thoracolumbar junction (T10-L2), preoperative IVC, solid lump distribution pattern of the cement, higher VHR and preoperative severe kyphosis were identified in the previous study to associate with

the cemented vertebra recollapse. While higher VHR and preoperative severe kyphosis were seemed to be not significant with the recollapse in our study. Reasons for the differences were due to the details of the two techniques. PKP with balloon may better restore the height of fractured vertebrae but at the cost of partially destroying cancellous bones. In PVP, the bone cement penetrates evenly throughout the remaining trabeculae, which makes the stress distribution of the cemented vertebrae more balanced. This interlocking between trabeculae and cement is effective in restoring vertebral stability, but not as significant for vertebral height restoration as PKP. On the other hand, preoperative severe kyphosis is usually accompanied by significant height loss of vertebral body, however, this condition may not be a standard indication for PVP. (Navarro-Navarro R , T. Fernández-Varela, Montesdeoca-Ara A , et al. Outcomes of vertebroplasty in osteoporotic vertebral fractures with limited indication[J]. Revista Espanola de Cirugia Ortopedica y Traumatologia, 2020, 64(1):4-12.) By comparing the results of the previous work with our meta-analysis, we considered that it was more appropriate to explore the risk factors associated with PVP separately.

7. Response to comment: Fourth paragraph. The authors state that The IVC is seen as a sign of avascular necrosis. I think there is not universal agreement about that, because the cleft may simply indicate the presence of intravertebral instability

Response: Thank you for pointing this out. As stated by the Reviewer, the preoperative IVC was indeed considered to be a sign of intravertebral instability,

which might be seen as the most important risk factor for recollapse. From the perspective of etiology, the formation of IVC may be related to bone ischemia and necrosis. According to our review and mastery of relevant literature, Maldague et al. first associated avascular necrosis with the IVC sign in 1978 by following up 10 patients with an IVC sign. (Maldague B E . The intravertebral vacuum cleft: a sign of ischemic vertebral collapse.[J]. Radiology, 1978, 129(1):23.) Moreover, Ratcliffe et al. also confirmed through anatomical study that the existence of IVC is associated with local avascular necrosis. (Ratcliffe J F . The arterial anatomy of the adult human lumbar vertebral body: a microarteriographic study.[J]. Journal of Anatomy, 1980, 131(Pt 1):57-79.) In our analysis, osteoporotic vertebrae are often accompanied by severe demineralization, which may increase the bone fragility, and has decreased the ability for remodeling of the fractured vertebrae. Thus, an avascular necrosis area is likely to occur presenting with an IVC sign under this condition. We discussed the probable pathological conditions leading to IVC in order to illustrate the possible reasons why preoperative IVC was associated with the cemented vertebra recollapse.

8. Response to comment: Sixth paragraph. The authors state: Thus, if predictive risk factors for recollapse are identified preoperatively, surgical fixation and restoration should be considered as the initial treatment for OVCFs. I think this statement is too simplistic and needs to be nuanced. I don't think that all vertebral fractures with a cleft or in the thoracolumbar junction could not be treated by vertebroplasty.

Response: Thank you for pointing this out and we appreciate the Reviewer's comments. We are very sorry for the simplistic description of our viewpoint. Considering the discomfort caused by the cemented vertebra recollapse for patients and the challenging of revision surgery for surgeons, the treatment of OVCFs deserves our thorough consideration. If there are predictive risk factors for recollapse preoperatively, surgical fixation and restoration can be used as the initial treatment option for patients whose physical conditions permit. If patients with poor physical condition have undergone PVP with the presence of these factors, surgeons should take the potential risk of recollapse seriously. Savage et al. proposed that the use of bracing after PVP might be an effective postoperative management to prevent the treated vertebrae recollapse. (Savage J W , Schroeder G D , Anderson P A . Vertebroplasty and Kyphoplasty for the Treatment of Osteoporotic Vertebral Compression Fractures[J]. Journal of the American Academy of Orthopaedic Surgeons, 2014, 22(10):653-664.) However, there was no level I or II evidence to support the viewpoint. Regardless of the surgical technique, regular postoperative follow-up and systematic treatment of osteoporosis are necessary. Once diagnosed, further treatment should be provided by experienced surgeons to avoid more serious consequences. More details were added in paragraph 5 of the discussion.

Special thanks to you for your valuable comments and suggestions!

We have tried our best to revise the manuscript according to the comments. These changes will not influence the content and framework of the paper. We would like to

express our great appreciation for your pertinent comments which help us both in English and in depth to improve the quality of the paper. We hope that the correction will meet with approval.

Kind regards,

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