Am J Transl Res 2024;16(12):7600-7608
www.ajtr.org /ISSN:1943-8141/AJTR0160732

Original Article

Osteoporotic thoracolumbar spine fractures in the elderly: alterations in GNRI and BMP-2 in delayed union and associated factors

Xiao Qian, Ke Pan, Chunping Liang, Huaichun Chen, Junhua Hui

Department of Orthopaedics, Liyang Hospital of Chinese Medicine, Changzhou 213300, Jiangsu, China

Received September 24, 2024; Accepted November 29, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Objective: To investigate the alterations in the Geriatric Nutritional Risk Index (GNRI) and bone morphogenetic protein 2 (BMP-2) levels and identify associated factors in older adults with delayed union of osteoporotic thoracolumbar spine fractures. Methods: From June 2021 to June 2023, 139 elderly patients with osteoporotic thoracolumbar spine fractures were selected and divided into a delayed group and a normal group according to the fracture healing status at 6 months postoperatively. GNRI and BMP-2 levels were assessed in both cohorts. Receiver operating characteristic (ROC) curves were used to determine the predictive value of GNRI and BMP-2 for delayed union. Multivariate Logistic regression was utilized to identify risk factors associated with delayed union after surgery for osteoporotic thoracolumbar spine fractures. Pearson correlation analysis was conducted to explore the relationships among independent risk factors. Finally, the Generic Quality of Life Inventory-74 (GQOL-74) was employed to assess the quality of life in both groups. Results: At 6 months post-surgery, 41 of the 139 patients had delayed union and were classified into the delayed group, while 98 cases achieved fracture healing and served as the normal group. The delayed group exhibited obviously reduced GNRI and BMP-2 levels than the normal group. ROC curve analysis indicated that the areas under the curve (AUCs) of GNRI, BMP-2, and their combination for predicting delayed union were 0.826, 0.803, and 0.883, respectively. A higher recovery rate of the injured vertebra height (OR = 1.456, 95% CI: 1.232-1.722, P < 0.001), a lower GNRI (OR = 0.590, 95% CI: 0.444-0.782, P < 0.001), and a lower BMP-2 level (OR = 0.909, 95% CI: 0.850-0.971, P = 0.005) were independent risk factors for delayed union in elderly patients undergoing surgery for osteoporotic thoracolumbar spine fractures. Pearson correlation analysis showed a negative correlation between the recovery rate of the injured vertebra height and GNRI (r = -0.640) as well as BMP-2 (r = -0.614), and a positive correlation between GNRI and BMP-2 (r = 0.751). Although the postoperative quality of life in the delayed group significantly enhanced, it remained significantly lower than that in the normal group. Conclusions: Delayed union after surgery in elderly patients with osteoporotic thoracolumbar spine fractures is strongly associated with preoperative levels of GNRI and BMP-2. The recovery rate of the injured vertebra height, GNRI, and BMP-2 are independent risk factors for delayed fracture healing. Delayed healing of osteoporotic thoracolumbar spine fractures in the elderly negatively affects the improvement of patients' quality of life.

Keywords: Osteoporotic thoracolumbar spine fractures, delayed union, geriatric nutritional risk index, BMP-2

Introduction

Osteoporosis (OP) is a prevalent condition in older adults, particularly older women, with vertebral compression fractures being the most common type, accounting for approximately 50% of all osteoporotic fractures [1, 2]. The occurrence of vertebral fractures is closely related to long-term compression and excessive strain on the vertebral body [3]. In clinical practice, vertebroplasty has become the preferred approach for treating osteoporotic vertebral compression fractures [4]. This procedure is valued for its minimal invasiveness, small incisions, low blood loss, and rapid postoperative recovery [5]. However, it is important to note that some elderly patients may encounter issues such as slow callus formation and delayed fracture healing after the operation, which may result in delayed- or non-union frac-

https://doi.org/10.62347/AFIX5363

tures [6, 7]. These patients may experience continuous vertebral collapse, local kyphosis, and prolonged chronic low back pain, with some requiring secondary surgical treatment in severe cases [8].

Malnutrition is a prevalent phenomenon among elderly OP patients, which not only leads to a decrease in bone mass and muscle strength, but also significantly increases the risk of OP [9]. Hence, accurately assessing the nutritional status of patients is of vital importance for the prevention and treatment of delayed fracture healing. The Geriatric Nutritional Risk Index (GNRI), an objective indicator of nutritional status in older adults, has been strongly linked to nutrition-related complications and adverse outcomes in older patients [10]. In a study by Kamioka H et al. [11], it was noted that GNRI can serve as an indicator of osteoporosis and the risk of associated fractures in patients with chronic liver disease. Moreover, other evidence has indicated that GNRI has remarkable predictive value for subsequent vertebral fractures in patients undergoing percutaneous vertebroplasty [12]. On the other hand, osteoclast-mediated bone resorption plays a crucial role in fracture healing, and its overactivity may lead to delayed fracture healing [13]. Bone morphogenetic protein 2 (BMP-2), a potent osteogenic factor, can facilitate the osteoclast differentiation and accelerate fracture healing [14]. In a rat model of tibial osteotomy, the incorporation of BMP-2 into the polymeric implant coating significantly enhanced bone healing [15]. Additionally, Wang et al. [16] reported that the positive effect of deer antler extract on the healing of tibial fractures in mice is related to its activation of the BMP-2/deleted in pancreatic carcinoma locus 4 (SMAD4) signaling pathway.

The roles of GNRI and BMP-2 in delayed postoperative healing in elderly patients with osteoporotic thoracolumbar spine fractures have not been extensively studied. As an innovation, this research intends to fill this gap and explore their correlations. Meanwhile, our research explores the crucial factors influencing the delayed healing of osteoporotic thoracolumbar spine fractures in the elderly patients, providing valuable insights for more effective and targeted clinical practice directions for the smooth healing of fractures in such patients.

Methods

Research population

The clinical data of 139 elderly patients with osteoporotic thoracolumbar spine fractures who underwent surgical treatment in Liyang Hospital of Chinese Medicine from June 2021 to June 2023 were retrospectively analyzed. Inclusion criteria: (1) Bone mineral density (BMD) ≤ -2.5, as measured by dual-energy X-ray absorptiometry; (2) Diagnosis of thoracolumbar fractures [17]; (3) Age ≥ 60; (4) Treatment with percutaneous vertebroplasty in our hospital; (5) Single vertebral compression fracture with an intact posterior vertebral wall; (6) Complete case data. Exclusion criteria: (1) History of thoracolumbar surgery or trauma; (2) Other bone diseases like osteoarthritis, bone tuberculosis, and bone tumors; (3) Malignancies in other parts of the body; (4) Acute or chronic infections; (5) Hematopoietic or immune system diseases; (6) Space-occupying lesions in the spinal canal or spinal nerve symptoms. The Liyang Hospital of Chinese Medicine Medical Ethics Committee approved the study.

Determination of delayed union of fractures

Delayed fracture healing is defined as the absence or minimal formation of callus, with sclerosis and gaps visible at the fracture ends on X-ray films three months after surgery. The patients were divided into a delayed union group and a normal union group based on the postoperative healing results.

Observation data

(1) Baseline data of the two groups were collected and analyzed, including age, weight, recovery rate of the injured vertebra height, BMD T-score, bone cement injection volume, gender (male/female), fracture site (thoracic/lumbar vertebra), surgical approach (unilateral/bilateral), and smoking history (with or without). The injured vertebra height was measured on X-ray films as the height of the maximum collapsed part of the injured vertebra. The recovery rate of the injured vertebra height (%) = (the height of the injured vertebra 3 months post-operation - the height of the injured vertebra pre-operation)/(the average height of the upper and lower adjacent vertebrae 3 months post-

operation - the average height of the upper and lower adjacent vertebrae pre-operation) × 100%.

(2) Preoperative serum BMP-2 levels and GNRI were collected from both groups. Serum BMP-2 levels were detected using an enzyme-linked immunosorbent assay (ELISA). Serum specimens were thawed at room temperature and BMP-2 was detected using a Spectra Max iD5 multimode microplate reader. Serum albumin (ALB) was also detected, and GNRI was calculated using the formula: GNRI = 1.489 × serum ALB + 41.7 × (actual body weight/ideal body weight); if the actual body weight exceeded the ideal body weight, it was recorded as 1; otherwise, the actual ratio was used. Ideal weight = 22 × height^2.

(3) GNRI and BMP-2 levels were compared between the delayed and normal groups. The predictive value of these variables for delayed union in elderly patients with osteoporotic thoracolumbar fracture was analyzed using receiver operating characteristic (ROC) curves.

(4) The independent risk factors influencing delayed union were identified by multivariate Logistic regression analysis.

(5) Correlations among independent risk factors were determined by Pearson correlation coefficients.

(6) The Generic Quality of Life Inventory-74 (GQOL-74), with scores ranging from 0 to 100, was used for the assessment of quality of life in patients of the two groups. The assessment covered four dimensions: physical health, mental health, material life, and social function. Higher scores indicate better quality of life.

Statistical methods

Statistical analyses were performed using the SPSS 20.0 software package. Count data were expressed as rates (%) and compared using the chi-square test (χ^2). Measurement data were presented in the form of mean ± standard deviation (Mean ± SD), and inter-group differences were assessed using the independent sample t-test (t). The ROC curve was drawn to detect the predictive implications of preoperative serum BMP-2 level and GNRI for delayed fracture healing. Independent risk factors for delayed union were identified through both univariate and multivariate analyses. The relationship between independent factors was determined through Pearson correlation. Statistical significance was defined as $P < 0.05$. The sample size in this study was determined using a sample size estimation formula. After calculation, both the delayed group (n = 41) and the normal group (n = 98) met the minimum sample size requirement of 37. The specific formula is presented below:

$$n = \frac{(z_{1-\alpha/2} + z_{\beta})^2 \times p_1(1 - p_1) + (z_{1-\alpha/2} + z_{\beta})^2 \times p_2 (1 - p_2)}{(effect\ size)^2}$$

Results

Comparison of baseline data between the two groups

When comparing the baseline data of the delayed and normal groups (**Table 1**), we found no statistical differences in age, weight, bone cement injection volume, sex, fracture site, surgical approach, smoking history, and various underlying diseases (all $P > 0.05$). However, statistically significant difference was identified in the recovery rate of the injured vertebra height and BMD T-score (both $P < 0.05$).

Comparison of GNRI and BMP-2 levels between the two groups

As shown in **Figure 1**, the GNRI of patients in the delayed and normal groups were 89.68 ± 2.94 and 93.63 ± 2.91, respectively, with the delayed group showing a significantly lower GNRI than the normal group (7.240, $P < 0.001$). The BMP-2 levels were 125.49 ± 14.26 pg/mL in the delayed group and 141.25 ± 11.44 pg/mL in the normal group, showing a notably lower BMP-2 level in the delayed group compared to the normal group (6.283, $P < 0.001$).

Predictive value of GNRI and BMP-2 in delayed union

ROC curves were plotted based on patients' GNRI and BMP-2 levels. The area under the curve (AUC) for predicting delayed union using GNRI, BMP-2, and their combination was 0.826, 0.803, and 0.883, respectively. These results indicate improved diagnostic efficiency under the combined prediction approach (**Figure 2** and **Table 2**).

Table 1. Comparison of baseline data between the two groups

	Delayed group	Normal group	t/χ^2	P
n	41	98		
Age (years)	67.34 ± 3.78	66.70 ± 4.12	0.855	0.394
Weight (kg)	61.95 ± 11.90	60.18 ± 9.99	0.899	0.370
Rate of the injured vertebra height recovery (%)	78.91 ± 6.80	67.66 ± 5.26	10.515	< 0.001
Bone mineral density T-score	-2.92 ± 0.50	-2.73 ± 0.35	2.556	0.012
Bone cement injection volume (ml)	4.15 ± 1.11	3.90 ± 1.14	1.188	0.237
Sex (male/female)	19/22	51/47	0.376	0.540
Fracture site (thoracic/lumbar vertebra)	20/21	52/46	0.212	0.645
Surgical approach (unilateral/bilateral)	16/25	33/65	0.363	0.547
Smoking history (yes/no)	5/36	16/82	0.385	0.535
Underlying diseases				
Hypertension (with/without)	12/29	27/71	0.042	0.837
Diabetes (with/without)	10/31	13/85	2.591	0.108
Coronary heart disease (with/without)	4/37	6/92	0.572	0.450
Cerebral infarction (with/without)	6/35	10/88	0.557	0.456
Thyroid disease (with/without)	18/23	28/70	3.069	0.080

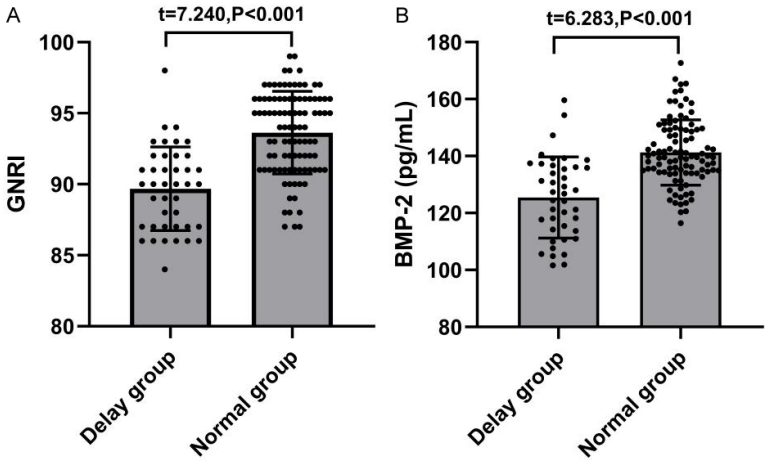

Figure 1. Comparison of GNRI and BMP-2 levels between delayed and normal groups. A. Comparison of GNRI between the delayed group (n = 41) and the normal group (n = 98). B. Comparison of BMP-2 between the delayed group (n = 41) and the normal group (n = 98). Note: GNRI, geriatric nutritional risk index; BMP-2, bone morphogenetic protein 2.

Multivariate analysis of factors associated with delayed-union fractures

Multivariate logistic regression was performed on factors showing differences in baseline data between the delayed and normal groups, including the recovery rate of the injured vertebral height, BMD T-score, GNRI, and BMP-2. BMD T-score was not identified as an independent influencing factor for delayed fracture healing (OR = 0.173, 95% CI: 0.027-1.129, P = 0.067). However, a higher recovery rate of the injured vertebra height (OR = 1.456, 95% CI: 1.232-1.722, P < 0.001), a lower GNRI (OR = 0.590, 95% CI: 0.444-0.782, P < 0.001), and a lower BMP-2 level (OR = 0.909, 95% CI: 0.850-0.971, P = 0.005) were identified as independent risk factors for delayed union in elderly patients undergoing surgery for osteoporotic thoracolumbar spine fractures (**Tables 3**, **4**).

Relationships among independent risk factors

Pearson correlation analysis clarified the relationships among the independent risk factors contributing to delayed fracture healing, namely the recovery rate of the injured vertebra height, GNRI, and BMP-2. The results indicated an inverse correlation between the recovery rate of the injured vertebra height and GNRI (r = -0.640) as well as BMP-2 (r = -0.614). A positive correlation was found between GNRI and BMP-2 (r = 0.751), as shown in **Figure 3**.

Quality of life

Quality of life was assessed using GQOL-74, as shown in **Table 5**. No significant inter-group dif-

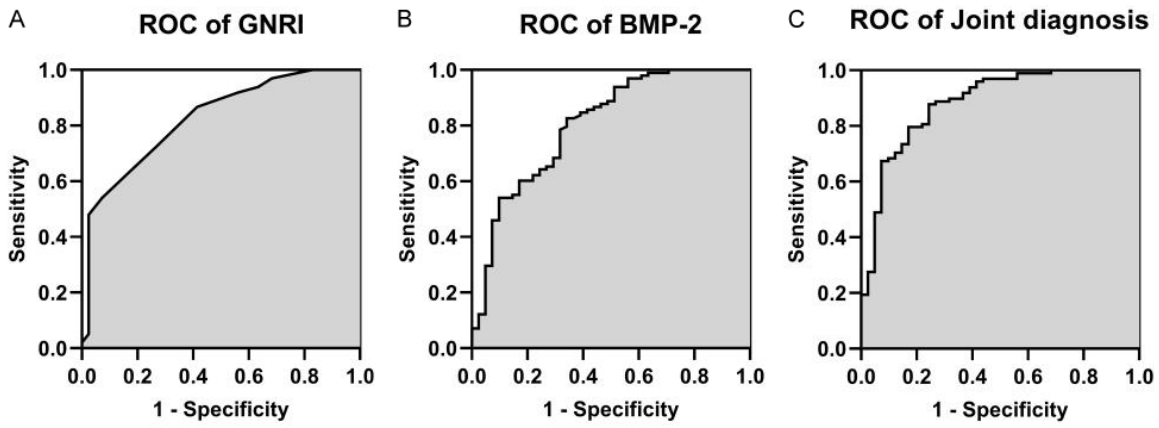

Figure 2. ROC curves of GNRI, BMP-2, and their combined use for predicting delayed union. A. ROC curve of GNRI in predicting delayed healing. B. ROC curve of BMP-2 in predicting delayed healing. C. ROC curve of combined use in predicting delayed healing. Note: ROC, receiver operating characteristic; GNRI, geriatric nutritional risk index; BMP-2, bone morphogenetic protein 2.

Table 2. ROC curve data

	AUC	95% CI	Specificity	Sensitivity	Youden index	Cut off
GNRI	0.826	0.752-0.899	92.68%	54.08%	46.76%	93.5
BMP-2	0.803	0.719-0.888	65.85%	82.65%	48.51%	132.49
Joint diagnosis	0.883	0.819-0.948	75.61%	87.76%	63.36%	0.379

Note: ROC, receiver operating characteristic; AUC, area under the curve; GNRI, geriatric nutritional risk index; BMP-2, bone morphogenetic protein 2.

Table 3. Variable assignment

Indicator	Variable	Assignment
Recovery rate of the injured vertebra height	X1	Continuous variable
BMD T-score	X2	Continuous variable
GNRI	X3	Continuous variable
BMP-2	X4	Continuous variable

Note: BMD, bone mineral density; GNRI, geriatric nutritional risk index; BMP-2, bone morphogenetic protein 2.

ferences were observed in GQOL-74 scores across all dimensions before surgery (all $P > 0.05$). The postoperative GQOL-74 scores of both groups elevated notably (all $P < 0.05$). At six months after surgery, the scores of the delayed group in four aspects, namely physical health, mental health, material life, and social function, were significantly reduced compared to the normal group (all $P < 0.05$).

Discussion

This study probed into the variations in GNRI and BMP-2 levels and their related factors in elderly patients with delayed union of osteoporotic thoracolumbar spine fractures. Osteoporosis (OP) is particularly prevalent among older adults, with vertebral compression fractures being a common complication [18]. Despite the wide application of vertebroplasty in clinical practice, delayed fracture healing remains an issue in some patients after surgery, significantly compromising patients' quality of life and rehabilitation progress [19]. Hence, identifying and understanding the factors influencing fracture healing is of great significance for improving clinical treatment outcomes.

GNRI is an important indicator for assessing the nutritional status of the elderly, with lower GNRI suggesting malnutrition, which might impact fracture healing [20]. Malnutrition is a common problem among elderly patients with OP, influencing bone mass and muscle strength and increasing the risk of fractures [21]. This study showed that the delayed group had notably lower GNRI than the normal group, indicating that malnutrition might be a crucial factor

Table 4. Multivariate Logistic regression analysis of factors affecting bone union

	B	Standard error	Wald	P	Exp (B)	95% confidence interval of EXP (B)	
						Lower bound	Upper bound
Recovery rate of the injured vertebra height	0.376	0.085	19.345	< 0.001	1.456	1.232	1.722
BMD T-score	-1.753	0.956	3.361	0.067	0.173	0.027	1.129
GNRI	-0.528	0.144	13.449	< 0.001	0.590	0.444	0.782
BMP-2	-0.096	0.034	7.892	0.005	0.909	0.850	0.971

Note: BMD, bone mineral density; GNRI, geriatric nutritional risk index; BMP-2, bone morphogenetic protein 2.

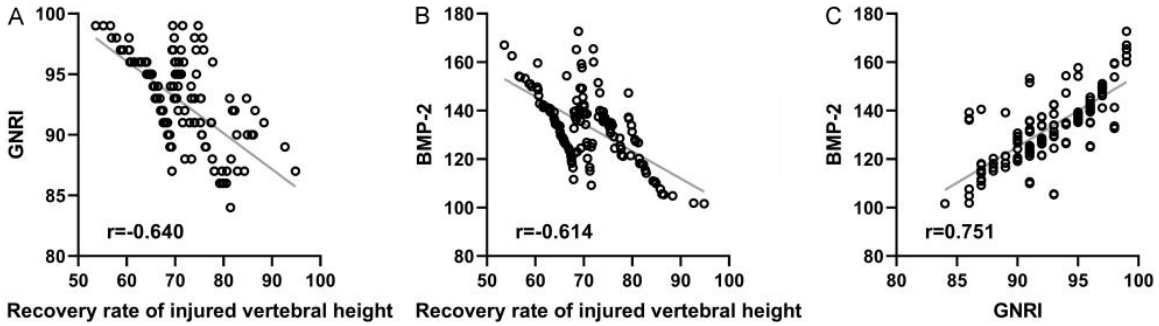

Figure 3. Pearson correlation analysis of the relationships among independent risk factors. A. Correlation analysis between the recovery rate of the injured vertebral height and GNRI. B. Correlation analysis between the recovery rate of the injured vertebral height and BMP-2. C. Correlation analysis between GNRI and BMP-2. Note: GNRI, geriatric nutritional risk index; BMP-2, bone morphogenetic protein 2.

Table 5. Comparison of quality of life between the two groups

Quality of life		Normal group (n = 98)	Delayed group (n = 41)	t	P
Physical health	Before surgery	62.54 ± 6.10	61.87 ± 7.20	0.522	0.602
	After surgery	80.05 ± 7.87**	72.28 ± 7.15*	5.670	< 0.001
Mental health	Before surgery	62.41 ± 5.79	63.72 ± 6.56	1.110	0.269
	After surgery	78.71 ± 8.27**	73.12 ± 6.44*	4.279	< 0.001
Material life	Before surgery	59.93 ± 6.96	61.87 ± 8.82	1.254	0.212
	After surgery	75.83 ± 7.59**	70.53 ± 7.61*	3.747	< 0.001
Social function	Before surgery	62.27 ± 6.84	62.93 ± 8.16	0.455	0.650
	After surgery	82.34 ± 8.25**	71.80 ± 7.61*	7.263	< 0.001

Note: *P < 0.05 and **P < 0.01 versus the preoperative level.

leading to delayed fracture healing. Malnutrition not only affects bone formation and healing but may also delay inflammation resolution and tissue repair [22, 23]. Therefore, improving the nutritional status of patients, particularly by increasing the intake of proteins and trace elements, may help to promote fracture healing.

BMP-2, an important bone growth factor that facilitates bone formation and healing, may contribute to delayed fracture healing [24]. The mechanism of BMP-2 in fracture healing mainly involves promoting the differentiation and proliferation of osteoblasts, thereby accelerating bone formation and healing [25]. This study found that the BMP-2 level was significantly lower in the delayed group than in the normal group, suggesting that BMP-2 is crucial in the healing process. A reduced BMP-2 level could lead to insufficient osteoblast activity, impairing new bone formation and delaying fracture healing. Therefore, exogenous supplementa-

tion of BMP-2 or other bone growth factors can be considered in clinical practice to promote fracture healing [26, 27].

ROC curve analysis indicated that GNRI and BMP-2 had considerable diagnostic implications in predicting delayed fracture healing, with their combined use offering even higher diagnostic efficiency. This suggests that fracture healing can be effectively predicted and monitored by tracking these two indicators, allowing for timely and targeted interventions.

Multivariate Logistic regression analysis further indicated that the recovery rate of the injured vertebra height, GNRI, and BMP-2 level were independent risk factors for delayed fracture healing. Specifically, a higher recovery rate of the injured vertebra height, a lower GNRI, and a lower BMP-2 level significantly augmented the risk of delayed fracture healing. This further underlines the significant roles of nutritional status and bone growth factors in the process of fracture healing.

The recovery rate of the injured vertebra height is one of the crucial factors influencing fracture healing [28]. In vertebroplasty, restoring the height of the injured vertebra can alleviate the compression on the surrounding tissues and enhance the local blood supply, thereby facilitating fracture healing [29]. However, an excessive restoration of the height of the injured vertebra may potentially increase the risk of delayed fracture healing. To some extent, this is related to the augmented tension of the paravertebral soft tissues in the patient's body, which subsequently increases the stress between the injured vertebra and the adjacent vertebrae and exacerbates the instability of the vertebrae [30]. Additionally, to more optimally restore the height of the injured vertebra, the balloon may be over-expanded during the surgical procedure. This is liable to generate a compressive impact on the surrounding cancellous bone and impede the dispersion of bone cement, rendering it arduous for the bone cement to effectively fill the bone defect. Consequently, vertebral collapse is more prone to occur in the subsequent stage, thereby further escalating the risk of delayed healing [31]. This study identified a statistically higher recovery rate of the injured vertebra height in the delayed group, suggesting that excessive restoration of the injured vertebra height during or after the operation might be one of the causes of delayed fracture healing. This also indicates that an excessive focus on restoring the height of the injured vertebra during the surgical procedure does not contribute to an elevation in the success rate of fracture healing. Instead, it will increase the risk of delayed healing.

The subsequent Pearson correlation analysis indicated the presence of a negative correlation between the recovery rate of the injured vertebra height and both GNRI and BMP-2, as well as a positive correlation between GNRI and BMP-2. This implies that nutritional status and bone growth factor levels are not only independent risk factors, but they may also collectively influence fracture healing through interaction. Malnutrition could result in a decreased level of BMP-2, thereby affecting bone formation and healing. Additionally, the improvement of the recovery rate of the injured vertebra height might indirectly impact the levels of GNRI and BMP-2 by enhancing the local blood supply and nutrient supply. Hence, in clinical treatment, these factors should be taken into comprehensive consideration, and multi-faceted intervention measures should be implemented to enhance fracture healing. Finally, we discovered that at six months after surgery, the delayed group had significantly lower scores in four aspects - physical health, mental health, material life, and social function, compared to the normal group. This suggests that delayed fracture healing after surgery in elderly patients with osteoporotic thoracolumbar spine fractures will hinder the improvement of patients' quality of life to some extent.

The findings of this study provide important insights for clinical practice. By monitoring the levels of GNRI and BMP-2, high-risk patients for delayed fracture healing can be predicted and identified early, allowing for individualized treatment strategies. For example, for malnourished patients, their nutritional status can be improved through nutritional support and supplementation of nutrients such as protein, vitamin D, and calcium; for patients with a low level of BMP-2, exogenous supplementation of BMP-2 or other bone growth factors can be contemplated. Preoperatively, clinical medical staff should conduct a detailed analysis of the imaging data of elderly patients with osteoporotic thoracolumbar spine fractures. Intraoperatively, an appropriate quantity of bone cement should

be precisely administered to avert the excessive restoration of the injured vertebral height due to over-injection or over-expansion. Postoperatively, patients should be guided to engage in regular rehabilitation training and ensure proper rest.

Although this study offers valuable insights, it also has some limitations. First of all, as a single-center retrospective study, this study may have selection and information bias. Second, the smaller sample size could have an impact on the generalizability of the results. Finally, this study did not explore other factors that may affect fracture healing, such as patients' living habits and comorbidities.

In conclusion, the delayed fracture healing in elderly patients with osteoporotic thoracolumbar spine fractures is closely related to the preoperative levels of GNRI and BMP-2. The recovery rate of the injured vertebra height, the GNRI, and the BMP-2 level are independent risk factors for delayed fracture healing.

Disclosure of conflict of interest

None.

Address correspondence to: Xiao Qian, Department of Orthopaedics, Liyang Hospital of Chinese Medicine, Changzhou 213300, Jiangsu, China. Tel: +86-0519-87265951; E-mail: okfast35@163.com

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