European Review for Medical and Pharmacological Sciences 2023; 27: 10868-10867

Analysis of changes in serum high t-PINP/β-CTX ratio and risk of re-fracture after vertebral osteoporotic fracture surgery

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Abstract. – OBJECTIVE: This study's aim was to investigate the expression changes of total type I procollagen amino-terminal peptide (t-PINP) and type I collagen C-terminal peptide (β-CTX) in serum after vertebral osteoporotic fracture surgery and the clinical value of predicting the risk of refracture.

PATIENTS AND METHODS: The clinical data of 100 patients with vertebral osteoporotic fractures treated in our hospital from January 2019 to January 2020 were retrospectively analyzed, and the patients were divided into the control group (patients without re-fracture, n = 68) and the observation group (patients with re-fracture, n = 32) according to whether they had re-fracture at 2-year follow-up. The risk factors of postoperative re-fracture were analyzed using Multivariate logistic regression analysis. The serum contents of t-PINP, β-CTX, osteocalcin (BGP), and calcium (Ca) were measured. Bone mineral density (BMD) was measured by bone densitometer. The correlation between the t-PINP/β-CTX ratio and the bone metabolic index was analyzed by Pearson correlation. The area under the curve (AUC), sensitivity, and specificity of t-PINP/β-CTX in predicting the risk of re-fracture were determined by the receiver operating characteristic (ROC) curve.

RESULTS: There was a significant difference in age, the number of vertebral bodies with initial fracture, and whether there was leakage of bone cement between the two groups ($p < 0.05$). Age, the number of vertebral bodies with primary fracture, and the leakage of bone cement were risk factors affecting re-fracture after operation ($p < 0.05$). Compared with those in the control group, the level of t-PINP and the ratio of t-PINP/β-CTX were higher, and the β-CTX level was lower in the observation group ($p < 0.05$). The BGP level was higher, and the levels of BMD and Ca were lower in the observation group than those in the control group ($p < 0.05$). Pearson correlation analysis showed that t-PINP had a positive correlation with BGP ($r = 0.222$, $p < 0.05$). β-CTX was positively correlated with BMD and Ca ($r = 0.230$, 0.269, $p < 0.05$). The ratio of t-PINP/ β-CTX was negatively correlated with BMD and Ca ($r = -0.621$ and -0.660, $p < 0.05$), but positively correlated with BGP ($r = 0.517$, $p < 0.05$). ROC curve analysis showed that the AUC of t-PINP, β-CTX, and the ratio of t-PINP/β-CTX in predicting the risk of re-fracture after vertebral osteoporotic fracture surgery was 0.724, 0.736, and 0.838, respectively.

CONCLUSIONS: The t-PINP/β-CTX ratio was significantly correlated with the bone metabolic indexes in patients with vertebral osteoporotic fractures. The detection of the changes in its index can help predict the risk of postoperative re-fracture, providing a new idea for clinical assessment of the risk of postoperative re-fracture.

Key Words:
Vertebral osteoporotic fracture, t-PINP/β-CTX ratio, Re-fracture risk.

Introduction

Osteoporosis is a systemic bone disease. Patients with osteoporosis are prone to fracture due to decreased bone density and bone quality, the destruction of bone microstructure, and increased bone fragility due to various reasons. Vertebral osteoporosis fracture is one of the common and serious complications of osteoporosis, which not only increases the pain of patients but also brings a certain economic burden to families and society[1]. Foreign study has shown that the incidence of vertebral osteoporosis fractures is increasing year by year, with a total of 644,500 cases of vertebral osteoporosis fractures in South Korea from 2012 to 2016, in which patients over 70 years old account for about 45% of the total patients[2]. At present, surgical treatment of vertebral osteoporosis fractures has a good effect, but the incidence of re-fracture is still high, which strongly affects the prognosis and quality of life of patients. Early prediction of the risk of postoperative re-fracture and early intervention are helpful in improving the prog-

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nosis of patients[3,4]. Proximal humerus fractures account for 6-8% of all fractures, of which approximately 85% of proximal humerus fractures occur in patients older than 50 years, and most of these fractures occur in women over 60 years of age, making these fractures the third most common osteoporotic fracture in older patients, after wrist fractures and hip fractures[5].

Bone mineral density (BMD) is an important indicator of bone strength and is a common indicator for clinical diagnosis of osteoporosis. Bone Calcitonin (BGP) and calcium (Ca) are common clinical bone metabolism indicators that are involved in the synthesis and metabolism of bone in the body, and their indicators reflect the bone metabolism state of the body. β-isomer of the C-terminal telopeptide of type I collagen (β-CTX) is a degradation product of extracellular matrix collagen fiber, whose level reflects the degradation rate of bone matrix[6]. Total type I procollagen N-terminal propeptide (t-PINP) is generated by the osteocyte precursor cells. The changes in the t-PINP level reflect the changes in the synthesis rate of type I collagen and osteogenic activity, which are widely used in osteoporosis. Among them, the t-PINP/β-CTX ratio has a certain value in the diagnosis of vertebral fractures in elderly adults and osteoporotic vertebral fractures in elderly men[7]. However, literature on the prediction of refracture after surgery for vertebral osteoporotic fractures is limited.

In this study, patients with vertebral osteoporotic fractures undergoing surgery were selected to analyze the change of serum t-PINP/β-CTX ratio after surgery and the clinical value of predicting the risk of refracture.

Patients and Methods

General Materials

The clinical data of 100 patients with vertebral osteoporotic fractures treated in our hospital from January 2019 to January 2020 were retrospectively analyzed. Inclusion criteria: (1) All patients met the diagnostic criteria of osteoporosis[8]. (2) The vertebral fracture was confirmed by X-ray, computed tomography (CT), and magnetic resonance imaging (MRI) diagnosis. (3) The patients and family members had good compliance and signed the informed consent. They could cooperate with the examination and treatment.

Exclusion criteria: (1) The patient's fracture was caused by falling from a building, violence, etc. (2) The important organs of patients had severe dysfunction. (3) The patients combined with bone tumor. (4) The patients had neurological disease or neuropathy.

The patients were grouped as the control group (no fracture patients, n = 68) and the observation group (fracture patients, n = 32) based on whether there were re-fractures during the follow-up of 2 years. The operation of this study was ratified by the Ethics Committee of our hospital.

Outcome Measures

Clinical data

General clinical data, such as age, sex, body mass index (BMI), basic diseases, and Cobb angle changes detected by electronic computed tomography were collected and compared between the two groups. The surgical data, including the number of vertebrae for initial fractures, the amount of bone cement injection, and the leakage of bone cement were collected from the two groups.

Serum Indicators

The fasting venous blood from the patients in the two groups was collected, and centrifuged at 3,000 r/min for 10 min. The supernatant was carefully separated and stored at -80°C to avoid repeated freezing and thawing. The levels of t-PINP and β-CTX, and the content of osteocalcin (BGP) were examined by electrochemiluminescence assay. The content of calcium (Ca) in serum was determined by the biochemical method. In electrochemiluminescence immunoassay, the procalcitonin detection kit (catalog number: 5056888200) was purchased from Shenzhen Jianzhu Technology Co., Ltd. (Shenzhen, China), the t-PINP assay kit (catalog number: CL06631) was purchased from Shanghai Yaji Biotechnology Co., Ltd. (Shanghai, China), and the β-CTX assay kit (catalog number: E-EL-R1405) was purchased from Shanghai Kelei Biotechnology Co., Ltd. (Shanghai, China). A 50 μL serum sample, one copy of biotinylated hCT-specific monoclonal antibody, and ruthenium complex-labeled hCT-specific monogram lowering antibody were taken for the first incubation. Streptomycin was added to coat the bead particles, the reaction solution was sucked into the measuring cells, and the magnetic beads were adsorbed on the surface of the electrode by magnetic action. The electrodes were energized to induce chemiluminescence, and the photomultiplier recorded the luminous intensity. The calibration curve of Roche E2010 electrochemiluminescence immunoanalyzer was used to obtain the final detection results.

Biochemical method

With the calcium kit purchased from Shanghai Xinfan Biotechnology Co., Ltd., (catalog number: ZDSJ244, Shanghai, China), the measurement parameters were input in strict accordance with the instructions in the kit, and routine measurements were performed in the order of calibration, quality control and sample determination. The change value of absorbance was measured at 660 nm using Toshiba TBA-FX8 automatic biochemical analyzer, and the concentration of calcium ions was calculated.

Bone mineral density (BMD) detection

The preoperative levels of BMD in the two groups were measured with the UBS-3000plus full-automatic ultrasonic bone densitometer purchased from Shanghai Shengshou Medical Equipment Co., Ltd. (Shanghai, China).

Follow-Up

The two groups had an average follow-up of (1.52 ± 0.36) years and were divided into the control group (patients without refracture, n = 68) and the observation group (patients with refracture, n = 32) according to whether they had refractured.

Statistical Analysis

SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used to analyze the experimental data. The measurement data, such as the age, t-PINP, t-PINP/β-CTX ratio, and β-CTX were represented in () and compared using the *t*-test. The gender and other enumeration data were shown in (%), and compared with χ^2 test. The correlation between the ratio of t-PINP/β-CTX and the bone metabolic index was analyzed by Pearson correlation analysis. Multivariate logistic regression analysis was used to analyze the risk factors affecting postoperative re-refracture in patients with vertebral osteoporosis fractures. The area under the curve (AUC), sensitivity, and specificity of all included indicators were analyzed using the receiver operating characteristic (ROC) curve. $p < 0.05$ was considered statistically significant.

Results

Comparison of Clinical Data

There were statistically significant differences in the age, number of vertebral bodies with initial fracture, and whether there was leakage of bone cement ($p < 0.05$, Table I).

Table I. Comparison of clinical data ($\bar{x} \pm s$).

Indicators	The control group (n = 68)	The observation group (n = 32)	χ^2/t	p
Gender (cases)				
Male	21 (30.88%)	12 (37.50%)	0.431	0.511
Female	47 (69.12%)	20 (62.50%)		
Age (year)	65.56 ± 12.86	71.45 ± 10.46	2.261	0.026
BMI value (kg/m^2)	22.69 ± 2.16	21.96 ± 2.45	1.510	0.134
Basic disease			0.043	0.979
coronary heart disease	16 (23.53)	7 (21.88)		
hypertension	14 (20.59)	6 (18.75)		
Diabetes	8 (11.76)	4 (12.50)		
Trauma history			0.106	0.744
Yes	15 (22.06)	8 (25.00)		
No	53 (77.94)	24 (75.00)		
Fracture site			0.033	0.983
Thoracic segment	12 (17.65)	6 (18.75)		
Thoracolumbar	38 (55.88)	18 (56.25)		
Lumbar segment	18 (26.47)	8 (25.00)		
Number of vertebral bodies with initial fracture	1.45 ± 0.42	2.55 ± 1.03	7.597	< 0.001
Cobb angle change (°)	17.17 ± 1.07	16.78 ± 1.06	1.705	0.091
The amount of bone cement injection (ml/vertebra)	3.92 ± 0.62	4.08 ± 0.25	1.404	0.164
Leakage of bone cement			11.822	0.001
Yes	5 (7.35)	11 (34.38)		
No	63 (92.65)	21 (65.63)		

Multivariate Logistic Regression Analysis on the Risk Factors of Postoperative Re-Fracture in Patients with Vertebral Osteoporosis Fracture

A multivariate logistic regression analysis model was established with the incidence of postoperative re-fracture of patients with vertebral osteoporosis fracture as the dependent variable and the statistically significant factors in Table I as the independent variable. The results showed that age, the number of vertebral bodies with initial fracture, and the leakage of bone cement were the risk factors affecting re-fracture after operation ($p < 0.05$, Table II).

Comparison of Bone Metabolism

The BGP level was higher, and the levels of BMD and Ca were lower in the observation group than those in the control group ($p < 0.05$, Table III).

Comparison of t-PINP/β-CTX Ratio

Compared with the control group, the level of t-PINP and the ratio of t-PINP/β-CTX were higher, and the β-CTX level was lower in the observation group ($p < 0.05$, Table IV).

Correlation Analysis Between t-PINP/β-CTX Ratio with Bone Metabolic Index

Pearson correlation analysis showed that t-PINP had a positive correlation with BGP (r = 0.222, $p < 0.05$). β-CTX was positively correlated with BMD and Ca (r = 0.230, 0.269, $p < 0.05$). The ratio of t-PINP/β-CTX was negatively correlated with BMD and Ca (r = 0.621 and -0.660, $p < 0.05$), and positively correlated with BGP (r = 0.517, $p < 0.05$, Table V and Figure 1).

Analysis of the Value of t-PINP/β-CTX Ratio in Predicting the Risk of Re-Fracture After Vertebral Osteoporotic Fracture

ROC curve analysis showed that the AUC of t-PINP, β-CTX, and the ratio of t-PINP/β-CTX in predicting the risk of re-fracture after vertebral osteoporotic fracture surgery was 0.724, 0.736, and 0.838, respectively (Table VI and Figure 2).

Discussion

With the aging of society in recent years, the incidence of osteoporosis has been increasing year by year. Patients with osteoporosis experience high morbidity, a long disease course, difficulty in treatment, and numerous complications. Vertebral osteoporosis fractures can also occur[9]. Previous study[10] has shown that the prevalence rate of vertebral fracture in more than 50% of women is as high as 15%, and the prevalence increases with age, posing a serious threat to the health and even life of patients. Osteoporosis vertebral fracture has become the focus of medical scholars' research.

Table II. Multivariate logistic regression analysis on the risk factors of postoperative re-fracture in patients with vertebral osteoporosis fracture.

Factors	B	SE	Wald	p	OR	95% CI
Age	0.755	0.623	3.412	0.023	2.352	1.752-3.566
The number of vertebral bodies with initial fracture	0.525	0.241	4.706	0.005	3.532	1.635-5.642
The leakage of bone cement	0.635	0.341	3.448	0.024	3.434	1.425-6.535

Table III. Comparison of bone metabolism ($\bar{x} \pm s$).

Groups	Cases	BMD (SD)	BGP (ng/ml)	Ca (mmol/l)
The control group	68	-2.78 ± 0.56	4.05 ± 1.26	1.98 ± 0.25
The observation group	32	-4.29 ± 0.82	6.22 ± 1.03	1.32 ± 0.24
t		10.778	8.492	12.471
p		< 0.001	< 0.001	< 0.001

Osteocalcin (BGP), Bone mineral density (BMD).

Table IV. Comparison of t-PINP/β-CTX ratio ($\bar{x} \pm s$).

Groups	Cases	t-PINP (ng/ml)	β-CTX (ng/ml)	t-PINP/β-CTX ratio
The control group	68	56.23 ± 13.63	0.46 ± 0.21	122.24 ± 20.63
The observation group	32	64.59 ± 8.56	0.35 ± 0.08	184.54 ± 23.16
t		3.182	2.861	13.541
p		< 0.001	0.005	< 0 .001

Osteocalcin (BGP), Bone mineral density (BMD).

Table V. Correlation analysis between t-PINP/β-CTX ratio with bone metabolic index.

Correlation		t-PINP	β-CTX	t-PINP/β-CTX ratio
BMD	*r*	-0.165	0.230	-0.621
	p	0.102	0.021	< 0.001
BGP	*r*	0.222	-0.114	0.517
	p	0.026	0.259	< 0.001
Ca	*r*	-0.187	0.269	-0.660
	p	0.063	0.007	< 0.001

Type I procollagen amino-terminal peptide (t-PINP), type I collagen C-terminal peptide (β-CTX), calcium (Ca).

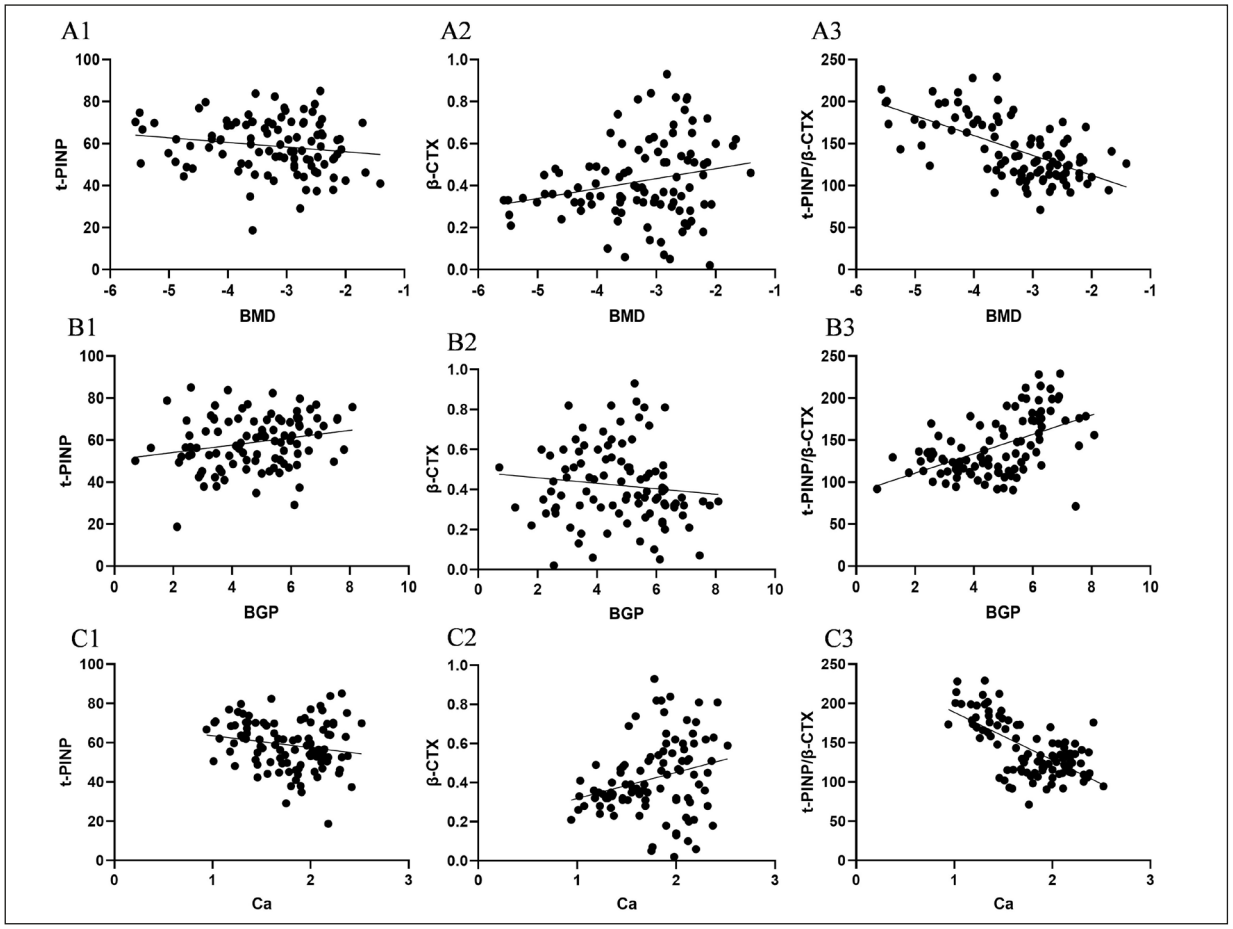

Figure 1. Correlation analysis between t-PINP/β-CTX ratio with bone metabolic index. **A1-A3**, Correlation between BMD and t-PINP/β-CTX ratio; **B1-B3**, Correlation between BGP and t-PINP/β-CTX ratio; **C1-C3**, Correlation between Ca and t-PINP/β-CTX ratio.

Table VI. Analysis of the value of the t-PINP/β-CTX ratio in predicting the risk of re-fracture after a vertebral osteoporotic fracture.

Indicators	AUC	95% CI	*p*-value	Sensitivity	Specificity
t-PINP	0.724	0.623-0.826	0.021	80.60%	59.40%
β-CTX	0.736	0.640-0.832	0.018	82.93%	60.59%
t-PINP/β-CTX ratio	0.838	0.753-0.924	0.012	77.45%	85.46%

Type I procollagen amino-terminal peptide (t-PINP), type I collagen C-terminal peptide (β-CTX), Area Under the Curve (AUC).

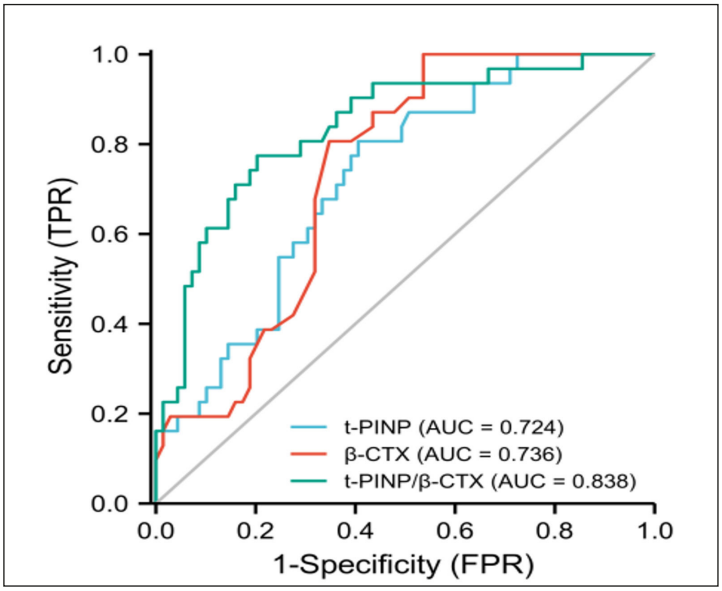

Figure 2. ROC curve analysis about the value of t-PINP/β-CTX ratio in predicting the risk of re-fracture after vertebral osteoporotic fracture.

The multivariate logistic regression analysis in this study revealed that the risk factors for the occurrence of fracture after the surgery in patients with vertebral osteoporosis fracture were age, the number of vertebral bodies with primary fracture, and leakage of bone cement ($p < 0.05$). It indicated that with the increase of age, bone density decreases rapidly, bone fragility increases, and vertebral osteoporotic fractures can occur with little or no external force. Therefore, it was recommended that elderly patients with vertebral osteoporotic fractures should pay attention to anti-osteoporosis therapy after surgery to prevent bone loss and reduce the risk of re-fracture. There was a significant correlation between the number of vertebral bodies in the initial fracture and bone loss, with a higher number of vertebral fractures indicating more severe bone loss and degeneration. The leakage of bone cement in the intervertebral space can increase pressure on the proximal intermediate plate and can easily lead to fracture of adjacent vertebral tubercles, thus increasing the risk of fracture recurrence.

At present, the common way to treat osteoporotic vertebral fractures is kyphoplasty, which relieves the compression of surrounding tissues and nerves by improving the biological characteristics of the vertebral body. It has a good effect in the treatment of osteoporotic vertebral fractures, but the high incidence of postoperative refracture is still a difficult concern for orthopedic surgeons. Early prediction of the risk of postoperative fracture recurrence in patients with osteoporosis and effective intervention are essential to improve the quality of life of patients with osteoporosis[11,12]. The International Osteoporosis Foundation (IOF) points out that t-PINP and β-CTX can be used as serum markers of bone transformation in bone metabolism. t-PINP is a product during type I collagen synthesis, and type I collagen is an important component of bone tissue, accounting for 90% of bone tissue[13]. Therefore, changes in t-PINP levels reflect the process of bone formation. When osteoporosis occurs in the body, bone resorption increases, so t-PINP levels are also elevated to

varying degrees[14]. β-CTX is an important collagen fiber degradation product in the extracellular matrix. It is the most widely studied and used bone resorption marker, whose level reflects the absorptive activity of osteoclasts in the body[15-16]. Zhong et al[15] showed that postmenopausal women with osteoporosis have significantly higher β-CTX levels than the normal population. In this study, the level of t-PINP and the t-PINP/β-CTX ratio was higher, and β-CTX level was lower in the observation group than those in the control group. It was suggested that changes in the level of t-PINP, β-CTX, and t-PINP/β-CTX ratio had a certain relationship with the postoperative re-fracture of osteoporosis patients. Pearson correlation analysis found that t-PINP, β-CTX, and t-PINP/β-CTX ratio was closely correlated with BMD, Ca, and BGP, which further indicated that t-PINP, β-CTX, and t-PINP/β-CTX ratio were involved in bone metabolism and had a close relationship with post-operative re-fracture of osteoporotic vertebral fracture patients.

The incidence rate of re-fracture after vertebral osteoporotic fracture surgery is high, which not only greatly reduces the life quality but also increases the disability rate, even endangering the lives of patients[18-19]. Therefore, early prediction of the risk of re-fracture is very important. Post-fracture bone reconstruction is a process by which osteoblast-mediated new bone formation and osteoclast-mediated bone resorption are coupled to each other. Osteoblast and osteoclast activity reflects bone metabolic processes. The t-PINP/ β-CTX ratio reflects the balance between bone formation and resorption and can be used to predict the risk of re-fracture in patients with osteoporosis after surgery[20]. ROC curve analysis in the study showed that the AUC of t-PINP, β-CTX, and the t-PINP/β-CTX ratio in predicting the risk of re-fracture after vertebral osteoporotic fracture surgery was 0.724, 0.736, and 0.838, respectively. The above results implied that t-PINP, β-CTX, and the t-PINP/β-CTX ratio had certain predictive values in re-fracture after operation in patients with osteoporotic vertebral fracture, among which the predictive value of the t-PINP/β-CTX ratio was higher. Thus, the t-PINP/β-CTX ratio was helpful for doctors to implement targeted intervention treatment in the early stage and had certain significance in improving the quality of life of patients.

However, the sample size in this study was small, and the samples were all from patients treated in our hospital. Thus, the conclusion of the study might be biased to a certain extent. Besides, the follow-up time was relatively short, and an unqualified sample size might be included. In the future, a prospective study with a multi-center and large sample size will be conducted to analyze the predictive value of the t-PINP/β-CTX ratio in postoperative re-fracture risk in patients with vertebral osteoporotic fracture.

Conclusions

In summary, the t-PINP/β-CTX ratio is significantly correlated with bone metabolism indexes in patients with vertebral osteoporotic fractures, and detecting the changes in its indexes can help predict the risk of postoperative refracture and provide a new idea for clinical evaluation of postoperative refracture risk.

Informed Consent

Informed consent was obtained from all individual participants included in the study. The patients participating in the study all agreed to publish the research results.

Ethics Approval

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University (20190107-01).

Authors' Contributions

XB L confirmed the authenticity of all the raw data and edited the manuscript, HY collected data and processed the data. XBL and LJH conducted the statistics. ZBX reviewed and revised the article. All authors read and approved the final manuscript.

Funding

No funding was received for this paper.

Conflict of Interest

The authors declare that they have no competing interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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