CORRELATION ANALYSIS OF SERUM CCL4, TRACP-5B AND HPDR2 LEVELS WITH ADVERSE OUTCOMES IN POSTMENOPAUSAL OSTEOPOROSIS (PMOP)

ANALIZA KORELACIJE NIVOA SERUMSKOG CCL4, TRACP-5B I HPDR2 SA NEPOVOLJNIM ISHODIMA U POSTMENOPAUZALNOJ OSTEOPOROZI (PMOP)

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Summary

Background: To determine the predictive efficacy of measuring fibroblast growth factor 23 (HPDR2) in postmenopausal individuals with osteoporosis, tartrate-resistant acid phosphatase 5b (TRACP-5b), and serum macrophage inflammatory protein-1 β (CCL4) for fractures.
Methods: The osteoporosis group consisted of 242 postmenopausal individuals with osteoporosis who were admitted to the hospital between January 2023 and January 2025. There were two groups: 108 patients with fractures and 134 without. The decreased bone mass group (164 patients) and the control group (130 patients) consisted of postmenopausal women diagnosed with decreased bone mass and normal bone mass, respectively, at the hospital during the same time period. The levels of serum CCL4, TRACP-5b and HPDR2 in each group were compared. The predictive value of serum CCL4, TRACP-5b, and HPDR2 detection for fractures in postmenopausal patients with osteoporosis was assessed using univariate and multivariate analyses of fracture risk factors. The relationships between the levels of serum CCL4, TRACP-5b, and HPDR2 and fracture severity were analysed.

Kratak sadržaj

Uvod: Cilj je bio da se ispita prediktivna vrednost merenja fibroblastnog faktora rasta 23 (HPDR2), tartarat-rezistentne kiseline fosfataze 5b (TRACP-5b) i serumskog makrofagnog inflamatornog proteina-1β (CCL4) za nastanak preloma kod osoba u postmenopauzi sa osteoporozom.
Metode: Grupu sa osteoporozom činile su 242 osobe u postmenopauzi sa osteoporozom koje su hospitalizovane u periodu od januara 2023. do januara 2025. godine. Od toga je 108 pacijentkinja imalo prelom, a 134 nisu imale. Grupa sa smanjenom koštanom masom (164 pacijentkinje) i kontrolna grupa (130 pacijentkinja) obuhvatile su postmenopauzalne žene sa dijagnostikovanom smanjenom koštanom masom, odnosno normalnom koštanom masom, u istom periodu. Upoređeni su nivoi serumskog CCL4, TRACP-5b i HPDR2 među grupama. Prediktivna vrednost detekcije serumskog CCL4, TRACP-5b i HPDR2 za nastanak preloma analizirana je univarijantno i multivarijantno u odnosu na faktore rizika. Takođe je analizirana povezanost nivoa serumskog CCL4, TRACP-5b i HPDR2 sa težinom preloma.

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Results: The levels of serum CCL4, TRACP-5b and HPDR2 in the osteoporosis group were significantly greater than those in the decreased bone mass group and the control group (P<0.01), and the reduced bone mass group's serum CCL4, TRACP-5b, and HPDR2 levels were considerably higher than the control group's (P<0.01). The fracture group had significantly greater serum levels of HPDR2, TRACP-5b, and CCL4 than the non-fracture group (P<0.01). Multivariate analysis revealed that serum CCL4>719.75 pg/mL, TRACP-5b>6.90 U/L and HPDR2>247.35 pg/mL were risk factors for fractures in postmenopausal patients with osteoporosis (P<0.01). Serum levels of CCL4, TRACP-5b, and HPDR2 are highly effective at predicting fractures in patients with osteoporosis (P<0.01). The combined detection sensitivity of the three indicators was 90.0%, the specificity was 89.7%, and the area under the curve (AUC) was 0.949. The AUC was significantly greater than that of CCL4 (Z=3. 415, P<0.01), TRACP-5b (Z=3.814, P<0.01), and HPDR2 (Z=3.986, P<0.01) were detected as individual indicators. However, the AUC of each indicator did not change statistically significantly (P>0.05).

Conclusions: Serum CCL4, TRACP-5b and HPDR2 are involved in the occurrence and development of postmenopausal osteoporosis. The detection of their levels has high value in predicting fractures in postmenopausal osteoporosis patients.

Keywords: inflammatory protein-1β, tartrate-resistant acid phosphatase 5b, fibroblast growth factor 23, osteoporosis, fracture

Rezultati: Nivoi serumskog CCL4, TRACP-5b i HPDR2 u grupi sa osteoporozom bili su značajno viši u poređenju sa grupom sa smanjenom koštanom masom i kontrolnom grupom (P<0.01), dok su u grupi sa smanjenom koštanom masom ovi nivoi bili značajno viši nego u kontrolnoj grupi (P<0.01). Grupa sa prelomom imala je značajno više vrednosti HPDR2, TRACP-5b i CCL4 u odnosu na grupu bez preloma (P<0.01). Multivarijantna analiza je pokazala da su serumski CCL4>719,75 pg/mL, TRACP-5b>6,90 U/L i HPDR2>247,35 pg/mL faktori rizika za prelome kod postmenopauzalnih pacijentkinja sa osteoporozom (P<0.01). Nivoi serumskog CCL4, TRACP-5b i HPDR2 imaju visoku prediktivnu vrednost za nastanak preloma kod pacijentkinja sa osteoporozom (P<0.01). Kombinovana detekcija tri indikatora imala je senzitivnost 90,0%, specifičnost 89,7% i površinu ispod krive (AUC) od 0,949. Ovaj AUC je bio značajno ve i od AUC pojedinačnih detekcija CCL4 (Z=3,415, P<0.01), TRACP-5b (Z=3,814, P<0.01) i HPDR2 (Z=3,986, P<0.01), ali razlike između pojedinačnih indikatora nisu bile statistički značajne (P>0.05).

Zaključak: Serumski CCL4, TRACP-5b i HPDR2 učestvuju u nastanku i progresiji postmenopauzalne osteoporoze. Određivanje njihovih nivoa ima veliku vrednost u predikciji preloma kod pacijentkinja sa postmenopauzalnom osteoporozom.

Ključne reči: inflamatorni protein-1β, tartarat-rezistentna kiselinska fosfataza 5b, fibroblastni faktor rasta 23, osteoporoza, prelom

Introduction

Osteoporosis mostly occurs in elderly individuals, and menopause is an important risk factor (1). After menopause, women experience a decrease in estrogen levels, leading to postmenopausal osteoporosis. The incidence of this disease ranges from 34.25% to 39.20%. Postmenopausal osteoporosis leads to an increase in fracture fragility, making fractures highly likely to occur (2). This can cause adverse events such as lower back pain and hunchback, seriously threatening the life and health of postmenopausal women. Early prediction of the risk of fractures is of great clinical importance for improving the prognosis of postmenopausal patients with osteoporosis (3). The activity of osteoclasts and bone metabolism are closely associated with the inflammatory cytokine interleukin-1β (CCL4). Osteoclasts are the primary source of tartrate-resistant acid phosphatase 5b (TRACP-5b), a typical marker of osteoporosis whose level indicates osteoclast function (4). Osteocytes release fibroblast growth factor 23 (FGF23), which plays a key role in regulating blood calcium levels and maintaining bone homeostasis (5).

The systemic metabolic bone disease known as postmenopausal osteoporosis (PMOP) is characterised by decreased bone mass and degradation of bone microstructure (6). Fragility fractures are the leading cause of disability and death among older women, imposing a heavy social and economic burden. In clinical practice, bone mineral density (BMD) is the primary factor used to assess this condition. However, its ability to predict fracture risk lags, and it is difficult to comprehensively reflect the dynamic changes in bone metabolism and the heterogeneity of disease progression. In recent years, serum biomarkers have emerged as a research hotspot for predicting fracture risk and prognosis because of their potential for noninvasive, dynamic monitoring of bone turnover (7–9). CCL4 is involved in the inflammatory response related to osteoporosis and osteoclast activation. Anti-tartrate acid phosphatase 5b (TRACP-5b) is a direct specific marker of osteoclast activity, whereas the equilibrium of bone mineralisation is impacted by fibroblast growth factor 23 (HPDR2) and controls phosphorus metabolism (10). In individuals with PMOP, these three elements may have a significant role in the pathological process of bone loss and fracture risk (11). However, research on the combined assessment of the above markers for adverse prognostic risk factors (such as new fractures, rapid bone mass loss, poor treatment outcomes, etc.) in PMOP patients (especially those at high risk of fractures) is still insufficient (12).

Therefore, this study aimed to systematically analyse the correlation between the levels of serum CCL4, TRACP-5b and HPDR2 and the occurrence of adverse outcomes in postmenopausal osteoporosis

patients, to identify more sensitive and earlier comprehensive predictive indicators and provide a new theoretical basis and clinical translation direction for risk stratification, individualised intervention and prognosis assessment.

Materials and Methods

General information

The osteoporosis group consisted of 242 postmenopausal patients with osteoporosis who were admitted to our hospital between January 2023 and December 2025. Diagnostic criteria: The patient's vertebral body's bone mass was measured. Dual-energy X-ray absorptiometry was used to measure the hip and lumbar areas' bone mineral densities (BMD). A dual-energy X-ray densitometer (Discovery Wi model, Hologic, USA) was used, and the system automatically obtained the T value. A T value of -1 indicates normal bone mass. A T value greater than -2.5 and less than -1 indicates decreased bone mass. A T value of -2.5 indicates osteoporosis. A group of 108 patients with fractures and 134 patients without fractures were created from the patients. All patients in the fracture group had thoracolumbar compression fractures. Their ages ranged from 55 to 80 years, with an average of 65.23 ± 5.94 years. The participants' menopausal ages ranged from 47 to 59 years, with an average of 52.07 ± 2.95 years.

The fractures are grouped according to their severity: vertebral compression greater than 40% is classified as Grade III. Vertebral compression of 25% to 40% is classified as Grade II. Vertebral compression less than 25% was classified as Grade I. Twelve Grade I instances, twenty-four Grade II cases, and eighteen Grade III cases were in the fracture group. The patients in the non-fracture group ranged in age from 53 to 80, with an average age of 65.18 ± 5.02 years. The age at menopause ranged from 44 to 60 years, with an average of 51.64 ± 4.19 years. A total of 164 women who visited our hospital during the same period and were diagnosed with decreased bone mass were selected and included in the decreased bone mass group. Their ages ranged from 51 to 75 years, with an average of 63.85 ± 4.89 years. The participants' menopausal ages ranged from 44 to 60 years, with an average of 51.79 ± 4.08 years. One hundred thirty menopausal women who underwent physical examinations in our hospital during the same period and had normal bone mass were selected and included in the control group. The participants' ages ranged from 53 to 74 years, with an average of 64.61 ± 4.28 years. The participants' menopausal ages ranged from 41 to 63 years, with an average of 50.75 ± 4.14 years.

Inclusion and exclusion criteria

Inclusion criteria: both the osteoporosis group and the decreased bone mass group satisfied the appropriate diagnostic criteria. The menopausal period should last at least 1 year. The research subjects cooperated with the follow-up and were in good mental condition.

Exclusion criteria: osteoporosis caused by other diseases, such as endocrine disorders, etc.; pathological fracture; immune or haematological diseases; congenital bone metabolism abnormalities; previous history of traumatic fractures; and intellectual decline and mental disorders. There was no statistically significant difference in the baseline data across research groups (P>0.05), and the groups were comparable. Each research participant signed an informed consent form, and the hospital ethics committee approved [No. SYSU-FAH-2022-022].

Detection methods

After each group of research subjects was enrolled, 5 mL of fasting elbow venous blood was drawn and placed in anticoagulant tubes. The blood was centrifuged at 3,000 r/min for approximately 10 minutes. The supernatant was placed at -70 °C for serological index detection. The level of estradiol (E2) was determined via the chemiluminescence method. The enzyme-linked immunosorbent assay was used to measure serum levels of CCL4, TRACP-5b, and HPDR2. The supplier of the reagent kit was Shanghai Lianmai Bioengineering Co., Ltd.

(1) Serum macrophage inflammatory protein-1 β (CCL4): Detected by Enzyme-Linked Immunosorbent Assay (ELISA). Use the Human CCL4 Quantikine ELISA Kit (Catalogue number: DMB00B, R&D Systems, Inc., Minneapolis, MN, USA).

(2) Serum anti-tartrate acid phosphatase 5b (TRACP-5b): Detected by enzyme immunoassay based on monoclonal antibody. Use BoneTRAP® Assay (Catalogue number: 31-BTRAPHU-E01, Immunodiagnostic Systems Ltd. (IDS), Boldon, UK).

(3) Serum fibroblast growth factor 23 (HPDR2): Detected by enzyme-linked immunosorbent assay (ELISA). Use Human HPDR2 (C-Term) ELISA Kit (Catalogue number: 60-6800, Immutopics International, San Clemente, CA, USA).

Observation indicators

The levels of serum CCL4, TRACP-5b and HPDR2 in each group were measured. The determinants of fractures in patients with osteoporosis were analysed using both univariate and multivariate methods, and the efficacy of serum CCL4, TRACP-5b, and HPDR2 in predicting fractures was evaluated.

Relationship between the levels of serum CCL4, TRACP-5b and HPDR2 in the fracture group and the severity of fractures.

Statistical analysis methods

The data were collected in Excel 2006 and processed and analysed using SPSS 21.0. When expressed as $\bar{x}\pm s$, the measurement data follow a normal distribution. The SNK-q method was used for pairwise comparisons among several groups, analysis of variance for comparisons among numerous groups, and a t-test for comparisons between two groups. Rates or counts are used to convey count data, and the χ^2 test was employed to compare groups. Binary logistic regression was performed to determine whether fractures occurred in patients with osteoporosis. Utilising receiver operating characteristic (ROC) curves, the effectiveness of serum CCL4, TRACP-5b, and HPDR2 detection in fracture prediction was examined.

Results

Comparison of the serum CCL4, TRACP-5b and HPDR2 levels among the groups

The levels of serum CCL4, TRACP-5b and HPDR2 in the osteoporosis group were significantly greater than those in the decreased bone mass group and the control group (P<0.01), and the levels of serum CCL4, TRACP-5b and HPDR2 in the decreased bone mass group were significantly greater than those in the control group (P<0.01). See Table I.

Univariate analysis of fractures in postmenopausal osteoporosis patients

Serum E2, CCL4, TRACP-5b, and HPDR2 levels were significantly higher in the fracture group than in the non-fracture group (P<0.01). However, for height, weight, hip BMD, lumbar BMD, menopausal age, and age, the two groups did not differ significantly (P>0.05; see Table II).

Table I Comparison of serum MIP-1 b, TRACP-5b, and HPDR2 levels among different groups.

Group	n	CCL4 (pg/mL)	TRACP-5b (U/L)	HPDR2 (pg/mL)
Control group	130	120.02±34.46	3.21±0.71	137.82±39.99
Bone mass decline group	164	240.51±91.49	4.70±1.52	161.15±44.19
Osteoporosis group	242	704.47±116.35	5.70±2.21	225.02±60.24
F		1018.683	44.047	75.054
P		<0.001	<0.001	<0.001

Table II Univariate analysis of fractures in postmenopausal osteoporosis patients.

Item	Fracture group (n=108)	Non-fracture group (n=134)	t	P
Age (years)	65.23±5.94	65.18±5.02	0.057	0.950
Menopausal age (years)	52.07±2.95	51.64±4.19	0.639	0.529
Height (cm)	159.97±6.46	156.43±7.08	0.373	0.715
Body weight (kg)	60.12±6.56	59.82±6.10	0.253	0.806
Hip BMD (g/cm²)	0.64±0.13	0.51±0.13	1.429	0.150
Waist BMD (g/cm²)	0.61±0.01	0.61±0.02	0.055	0.952
E (pg/mL)	18.46±2.98	17.31±2.72	2.009	0.040
CCL4 (pg/mL)	780.97±101.03	642.71±88.02	8.034	<0.001
TRACP-5b (U/L)	7.16±2.41	4.60±1.35	6.541	<0.001
HPDR2 (pg/mL)	257.24±55.60	199.24±50.72	5.984	<0.001

Table III The efficacy of serum E2, MIP-1 b, TRACP-5b, and HPDR2 detection in predicting fractures in patients with osteoporosis.

Indicator	Truncation value	Sensitivity (%)	Specificity (%)	AUC	95%CI
E	17.83 pg/mL	64.1	59.4	0.619	0.526~0.707
CCL4	719.75 pg/mL	70.7	83.9	0.840	0.773~0.909
TRACP-5b	6.90 U/L	55.9	98.8	0.815	0.734~0.871
HPDR2	247.35 pg/mL	55.9	86.9	0.783	0.698~0.853
CCL4+TRACP-5b+HPDR2	–	90.0	89.7	0.949	0.882~0.972

Table IV Multivariate analysis of factors affecting fracture occurrence in postmenopausal osteoporosis patients.

Indicator	β	SE	Wald χ^2	P	OR	95%CI
E	0.161	0.123	1.985	0.152	1.186	0.939~1.499
CCL4	0.026	0.009	15.047	<0.001	1.026	1.014~1.038
TRACP-5b	0.740	0.221	10.714	0.001	2.113	1.342~3.292
HPDR2	0.027	0.001	10.474	0.001	1.027	1.002~1.032

Table V Relationship between serum MIP-1β, TRACP-5b, and HPDR2 levels and fracture severity in patients with osteoporosis.

Severity of fracture	n	CCL4 (pg/mL)	TRACP-5b (U/L)	HPDR2 (pg/mL)
Level I	24	654.45±40.59	5.94±0.01	190.35±10.28
Level II	48	756.43±37.53	7.04±0.67	243.10±21.93
Level III	36	898.03±46.61	9.89±1.26	320.54±35.71
F		132.082	98.682	98.7592
P		<0.001	<0.001	<0.001

The efficacy of serum CCL4, TRACP-5b and HPDR2 detection

The diagnostic value of the combined indicators for predicting fractures in patients with osteoporosis was significantly higher than that of E2 (P<0.01). Logistic regression analysis was used to evaluate factors associated with the occurrence of fractures in osteoporosis, and the following predictive model was obtained:

Y = 0.02 × XCCL4 + 0.74 × XTRACP-5b + 0.02 × XHPDR2 – 25.77.

The combined detection method demonstrated a sensitivity of 90.0% and a specificity of 89.7%. The area under the ROC curve (AUC) reached 0.949, which was significantly higher than that of MIP-1β (Z=3.415, P<0.01), TRACP-5b (Z=3.814, P<0.01), and HPDR2 (Z=3.986, P<0.01) when assessed individually. However, there was no statistically significant difference in AUC among the three single indicators (P > 0.05) (*Table III*).

Multivariate analysis of fractures in postmenopausal osteoporosis patients

The threshold values in the ROC curve analysis were utilised for assignment, and the factors that showed statistically significant differences in the univariate analysis were included in the multivariate study: E2 >17.80 pg/mL was 2, 17.80 pg/mL was 1; CCL4 >719.72 pg/mL was 2, 719.72 pg/mL was 1; TRACP-5b >6.97 U/L was 2, 6.97 U/L was 1; and HPDR2 >247.32 pg/mL was 2, 247.32 pg/mL was 1. Binary logistic regression was re-run. The results revealed that CCL4>719.75 pg/mL, TRACP-5b>6.90 U/L and HPDR2>247.35 pg/mL were risk

factors for fractures in postmenopausal osteoporosis patients (P<0.01), see *Table IV*.

Relationships between the serum levels of CCL4, TRACP-5b and HPDR2 and the severity of fractures in patients with osteoporosis

Patients with Grade II fractures had significantly higher levels of serum CCL4, TRACP-5b, and HPDR2 than patients with Grade I fractures (P<0.01), while those with Grade III fractures had levels higher than those with Grade II or Grade I fractures (see *Table V*).

Discussion

Patients with osteoporosis have increased bone fragility, leading to a significantly increased risk of fractures (13). This disease is common among middle-aged and elderly menopausal women. After menopause, due to the decline in ovarian function, estrogen levels decrease, bone metabolic balance is disrupted, and calcium and phosphorus metabolism becomes disordered, leading to osteoporosis (14–16). Clinical research (17) has shown that osteoporosis is an independent risk factor for lumbar fractures. The course of the disease is relatively slow, the onset is sudden, and the degree of harm is serious. Most patients cannot walk after the onset of the disease, which is inconvenient for daily life and seriously affects the life and health of postmenopausal women (18). The diagnosis of lumbar fractures relies mainly on X-ray films and CT scans, and by the time the fractures are detected through imaging, they are already irreversible (19). Therefore, scholars are seeking early warning indicators of fractures in patients with osteoporosis to provide a basis for further intervention measures for these patients.

CCL4 has a connection to bone metabolism and exhibits strong chemotactic effects on various cells (20). Osteoclast migration is a key factor in the development of osteoporosis. The elevated CCL4 levels in patients with osteoporosis indicate a significant increase in osteoclast activity. These findings indicate that the higher the serum CCL4 level is, the greater the risk of fracture (21). Moreover, this study revealed that serum CCL4 levels increased with increasing fracture severity, indicating that CCL4 levels are an indicator of fracture severity in patients with osteoporosis (22). Bone destruction and absorption are dynamic processes that require osteoclasts to differentiate and activate before migrating to the absorption site (23). An in vitro study revealed that adding the CCL4 antibody to the culture medium significantly reduced the number of migrated osteoclasts. In the same study (24) on multiple myeloma, CCL4 was found to activate osteoclasts, indicating that serum CCL4 plays an important role in osteoclast activation (25). This study revealed that when the serum CCL4 concentration is 719.75 pg/mL, its sensitivity in pre-

dicting fractures in patients with osteoporosis is 70.7%, its specificity is 83.9%, and its AUC is 0.840, indicating that the serum CCL4 concentration has certain value in predicting fractures in patients with osteoporosis.

TRACP-5b is a cytokine secreted by osteoclasts that can reflect the bone metabolism status of the body and the biological activity of osteoclasts in the early stage (26). The results of this investigation showed that the osteoporosis group's serum TRACP-5b level was substantially higher than that of the control group and the bone mass decrease group. The serum TRACP-5b level in the fracture group was significantly greater than that in the non-fracture group. Multivariate analysis revealed that Patients with postmenopausal osteoporosis were at risk for fractures if their TRACP-5b was greater than 6.97 U/L. The above results indicate that an increase in serum TRACP-5b levels can reflect osteoclast activation. Research has shown that during bone resorption, osteoclasts are activated and secrete large amounts of TRACP-5b, which participates in bone metabolism and calcium degradation processes (27–30). This study revealed that when the serum TRACP-5b concentration is 6.97 U/L, its sensitivity in predicting fractures in patients with osteoporosis is 55.9%, and its specificity is 98.8%. Its AUC is 0.815, indicating that serum TRACP-5b concentration has high predictive value for fractures in patients with osteoporosis.

HPDR2 is a cytokine secreted by osteocytes and osteoblasts (31). It mainly regulates the level of phosphates in the body by inhibiting the sodium phosphorus cotransporter and suppressing the reabsorption of phosphates by renal tubules. HPDR2 can reduce the level of 1,25 (OH)2D3 in the blood by inhibiting -hydroxylase and activating 24-hydroxylase, thereby decreasing intestinal phosphorus absorption (32). In addition, HPDR2 can indirectly affect the activity of the calcium phosphorus cotransporter by influencing parathyroid hormone synthesis and secretion, thereby regulating phosphorus reabsorption by the kidneys (33–36). This study also revealed that serum HPDR2 levels increase with increasing fracture grade, suggesting that serum HPDR2 can be used to gauge fracture severity. The serum HPDR2 concentration of 247.32 pg/mL is highly effective in predicting fractures in patients with osteoporosis, with a sensitivity of 55.9%, a specificity of 86.9%, and an AUC of 0.783. Moreover, this study revealed that the combined detection of serum CCL4, TRACP-5b, and HPDR2 has greater predictive value for fractures in patients with osteoporosis (37). The sensitivity is 90.0%, the specificity is 89.7%, and the AUC is 0.949, which is significantly higher than that of single index detection. This indicates some complementarity among these three indicators. However, the exact mechanism remains to be further researched.

Conclusion

TRACP-5b, HPDR2, and serum CCL4 are implicated in the development and incidence of osteoporosis. When predicting fractures in patients with osteoporosis, identifying these three signs is highly valuable.

Authors' contribution

Kejia Zhu and Jiaqu Sun both contributed equally to this work.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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