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ORIGINAL ARTICLE

Postoperative expressions of TRACP5b and CA125 in patients with breast cancer and their values for monitoring bone metastasis

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Summary

Purpose: *To explore the diagnostic values of serum tartrate-resistant acid phosphatase 5b (TRACP5b) and serum carbohydrate antigen 125 (CA125) for bone metastasis of breast cancer.*

Methods: *118 patients pathologically diagnosed with breast cancer in the second People's Hospital of Lianyungang from September 2014 to June 2017 were selected. Among them, 60 patients who were confirmed with bone metastasis by whole-body bone imaging combined with clinical manifestations and other imaging methods were included in a bone metastasis group, and 58 patients who were confirmed without bone metastasis were included in a non-bone metastasis group. Another 61 patients who were pathologically confirmed with benign breast lesion formed a benign lesion group. Enzyme-linked immunosorbent assay (ELISA) was used to detect TRACP5b level and electrochemiluminescence (ECL) was used to detect CA125 level.*

Results: *The expression levels of TRACP5b and CA125 in the bone metastasis group were significantly higher than those in the non-bone metastasis and benign lesion groups ($p<0.05$), and the expression levels in the non-bone metastasis group were higher than those in the benign lesion group ($p<0.05$). In bone metastasis of breast cancer, the expression level of TRACP5b was correlated with the number of tumor nodules, lymph node metastasis, tumor local infiltration and TNM staging ($p<0.05$), while the expression level of CA125 was correlated with the number of tumor nodules, lymph node metastasis and TNM staging ($p<0.05$). Logistic regression analysis showed that TNM staging, estrogen receptor (ER), TRACP5b, and CA125 were risk factors for bone metastasis of breast cancer patients.*

Conclusion: *In conclusion, TRACP5b and CA125 may be involved in the occurrence and progression of bone metastasis of breast cancer. Detection of TRACP5b and CA125 has good sensitivity and specificity in diagnosing bone metastasis of breast cancer, so TRACP5b and CA125 may become new biomarkers for diagnosing the disease.*

Key words: *bone metastasis, breast cancer, CA125, expression, TRACP5b*

Introduction

Breast cancer is a leading cause of cancer death among females, and its incidence and mortality rank first and sixth respectively in all cancers in females in China [1]. With large-scale physical examination for females and the advancement of comprehensive treatment, the prognosis of the disease has been greatly improved in recent years [2]. Breast cancer is prone to hematogeneous dissemination, so there are many patients with distant metastasis [3], of which bone is considered as a common metastatic site [4]. After bone metastasis, the patients usually suffer from complications such as hypercalcemia,

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nerve compression and fractures, which seriously affects the patient quality of life and their families [5]. In addition, the 5-year survival rate of the patient with bone metastasis is only about 20% [6]. Therefore, prognostic markers stratifying patients according to the risk of recurrence or death should be identified and verified, which may help optimize treatment to improve patients' conditions and quality of life.

Serum tartrate-resistant hydrochloric acid phosphatase 5b (TRACP5b) is a bone resorption marker mainly derived from osteoclasts [7]. Its expression increases in patients with non-small cell lung cancer [8], Paget's disease [9] and osteoporosis [10]. According to another study, TRACP5b level in patients with multiple bone metastases is significantly higher than that in patients with early breast cancer and patients with visceral metastasis. These studies suggest that TRACP5b may be an suitable marker for monitoring bone metastasis of breast cancer [11]. Carbohydrate antigen 125 (CA125) is one of the specific tumor markers [12], which is often found in pleura, endometrium, tubal endothelium and endocervix of adults. It has a high positive detection rate in endometrial cancer, pancreatic cancer, ovarian cancer and breast cancer. The expression level of CA125 is closely related to tumor burden in patients and increases as the disease progresses. Patients with wider metastasis and more lesions have a higher expression level of it. Therefore, CA125 is a sensitive index for the judgment of tumor metastasis [13-15].

In this study, the postoperative expression levels of serum TRACP5b and CA125 in patients with bone metastasis of breast cancer were investigated to explore good markers for the prediction of disease in early stage, so as to guide early detection of bone metastasis, carry out early detection and treatment, and improve patients' survival and quality of life.

Methods

General information

Altogether, 118 patients pathologically diagnosed with breast cancer in the second People's Hospital of Lianyungang from September 2014 to March 2015 were selected. These patients were suspected to be with bone metastases or had obvious symptoms of bone metastasis, such as local bone pain, cachexia, abnormal serum alkaline phosphatase, and multiple lesions in bone imaging by X-ray, CT or MRI. There were 60 patients who met the above conditions in the bone metastasis group, and they were aged 31-70 years old (mean 51.24±11.57). The other 58 patients who were confirmed without bone metastasis formed the non-bone metastasis group, and they were 29-70 years old (mean 53.68±12.64) years old. Another 61 patients who were pathologically confirmed with benign breast lesion constituted the benign lesion group, and they were aged 26-68 years old (mean 52.37±11.23).

Inclusion criteria: Patients confirmed with breast cancer by pathological examination of specimens after operation; 20-60 years old; patients examined within 3 years after radical operation; patients with smooth operation and thorough lymph node dissection who had no severe complications.

Exclusion criteria: Patients with abnormal PET-CT imaging caused by abscesses and active infection; patients with a history of thyroid diseases, fractures, osteoarthritis and osteoporosis; patients with other organ metastases; patients who had recently taken drugs affecting bone metabolism; patients who received hormone therapy; patients with autoimmune diseases; patients

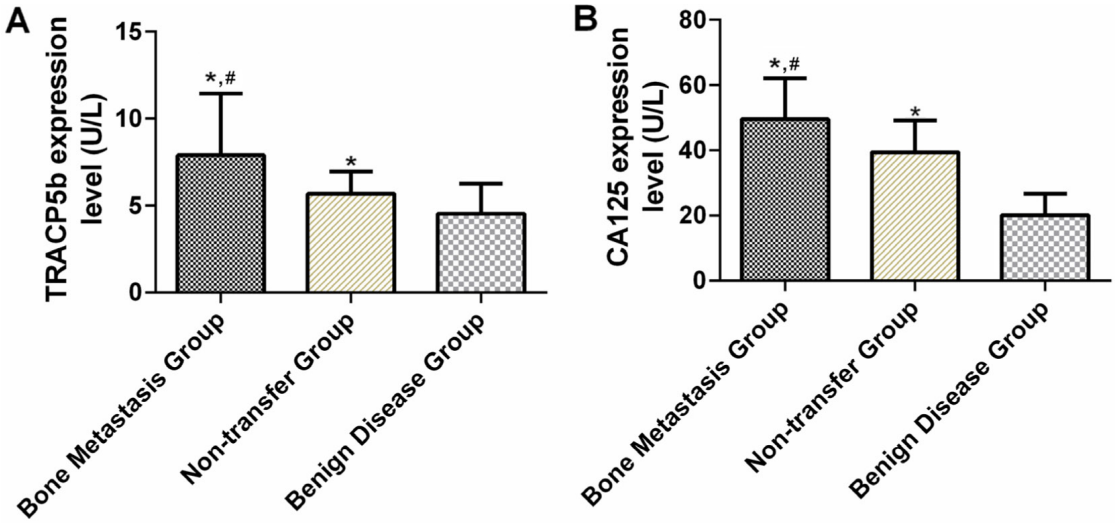

Figure 1. Comparison of expression levels of TRACP5b and CA125. **A** is the comparison of the expression level of TRACP5b between the bone metastasis, non-bone metastasis and benign lesion groups. **B** is the comparison of the expression level of CA125 between the bone metastasis, non-bone metastasis and benign lesion groups. *indicates $p<0.05$ compared with the benign lesion group. #indicates $p<0.05$ compared with the non-bone metastasis group

Table 1. Comparison of expression levels of TRACP5b and CA125 (x±sd)

Groups	*n*	*TRACP5b (U/L)*	*CA125 (U/L)*
Bone metastasis group	60	7.88±3.56*,#	49.51±12.57*,#
Non-bone metastasis group	58	5.67±1.29*	39.38±9.75*
Benign lesion group	61	4.53±1.71	20.08±6.63
F		30.260	137.100
P		<0.001	<0.001

*indicates p<0.05 compared with the benign lesion group. #indicates p<0.05 compared with the non-bone metastasis group

Table 2. Correlation of expression levels of TRACP5b and CA125 with clinicopathological parameters of breast cancer (x±sd)

Clinicopathological features	*n*	*TRACP5b (n=118)*	*t value*	*p value*	*CA125 (n=118)*	*t value*	*p value*
Age (years)			0.188	0.063		0.2535	0.800
<60	72	6.059±2.137			43.515±11.125		
≥60	46	6.713±1.251			46.029±10.173		
Primary sites			0.618	0.538		0.1653	0.8690
Left	61	6.658±2.954			45.558±12.954		
Right	57	6.954±2.158			45.186±11.365		.
Tumor nodules			5.258	<0.001		2.656	0.009
Solitary nodules	53	5.459±1.688			41.395±10.966		
≥2	65	7.895±3.007			47.163±12.324		
Lymph node metastasis			3.849	<0.001		2.013	0.0464
Yes	67	7.692±3.015			47.068±12.695		
No	51	5.903±1.646			42.558±11.156		
Local tumor infiltration			2.551	0.012		1.932	0.056
Yes	66	7.254±3.135			46.565±12.369		
No	52	6.024±2.018			42.469±10.114		
TNM staging			3.866	<0.001		4.21	<0. 001
Stages I + II	78	6.045±1.899			41.118±11.120		
Stage III	40	7.963±3.481			50.283±12.103		
ER			0.938	0.350		0.08405	0.933
Negative	62	6.394±2.454			44.856±11.265		
Positive	56	6.863±2.966			45.035±11.587		
HER2			0.607	0.545		1.026	0.307
Negative	21	6.439±2.095			45.655±11.818		
Positive	97	6.667±1.903			43.453±11.106		
PR			0.387	0.700		1.203	0.232
Negative	30	6.738±2.248			46.558±11.599		
Positive	88	6.569±2.452			43.895±12.129		
Histological type			3.259	0.042		1.351	0.263
Non-invasive carcinoma	21	5.899±2.157			43.457±10.134		
Early invasive carcinoma	35	6.419±2.036			45.423±11.115		
Invasive carcinoma	62	7.114±1.983			47.749±11.203		

ER: estrogen receptor, PR: progesterone receptor, HER-2: human epidermal growth factor receptor 2

Table 3. Diagnostic values of TRACP5b and CA125 for bone metastasis of breast cancer

Diagnostic indexes	*AUC*	*95%CI*	*Standard error*	*Cut-off value*	*Sensitivity (%)*	*Specificity (%)*
TRACP5b	0.741	0.609-0.813	0.052	6.79(U/L)	81.26	71.33
CA125	0.715	0.585-0.775	0.036	45.32(U/L)	75.51	65.00
TRACP5b+CA125	0.758	0.669-0.848	0.046	0.401	88.17	73.12

with severe heart, liver and kidney disease; patients with other malignant tumors; patients with severe infectious diseases.

Main instruments and reagents

An electrochemiluminescence immunoassay analyzer (Roche, USA, cobase411); CA125 diagnostic kit (Thermo Scientific, USA, MA174328); TRACP5b enzyme-linked immunosorbent assay kit (Ek-Bioscience, Shanghai, EK-H11117); a Thermo Multiscan FC basic microplate reader (Thermo Fisher, USA, 51119080).

Detection methods

Venous blood was taken before performing a bone scintigraphy scan. In the morning, 5 mL of fasting venous blood was collected from the three groups of patients, placed in vacuum blood collection tubes, and centrifuged at 3000 r/min for separation. Enzyme-linked immunosorbent assay (ELISA) was used to detect serum TRACP5b. The required plate was taken out from the aluminium foil bag after it was placed at room temperature for 20 min, and the remaining plates were sealed with ziplock bags and put back into the refrigerator at 4°C. Standard wells and sample wells were set up. Standard wells were added with 50 μL of standard sample with different expressions, and sample wells were added with 50 μL of the samples to be tested, but blank wells were added with nothing. Except for the blank wells, each standard well and sample well was added with 100 μL of horse radish peroxidase (HRP)-labeled detection antibodies. The reaction wells were sealed with microplate sealers and the plate was incubated in a water bath kettle or incubator at 37°C for 60 min. Then, the antibody in wells was discarded and the plate was dried with absorbent papers. Each well was added with 350 μL of phosphate buffered saline (PBS) and allowed to stand for 1 min. Then, the washing liquid was shaken off and the plate was dried with absorbent papers. The plate was washed for 5 times. Each well was added with 50 μL of substrates A and B, and then incubated at 37°C for 15 min in the dark. After that, each well was added with 50 μL of stop solution. An ELISA reader was used to measure the optical density (OD) values of each well at 450 nm within 15 min. Electrochemiluminescence (ECL) was used to detect serum CA125. Internal quality control was conducted during detection and the results were under control, with steps carried out in strict accordance with the kit instructions.

Statistics

SPSS22.0 (IBM Corp, Armonk, NY, USA) was used to analyze the data. Count data were expressed by [n(%)] and measurement data were expressed by mean±standard deviation (x±sd). The comparison of measurement data between groups was tested by t-test and the comparison of count data between groups was tested by chi-square test (x^2). Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic values of TRACP5b and CA125 for bone metastasis of breast cancer. Univariate and multivariate analyses were performed using logistic regression and $p<0.05$ showed statistically significant difference.

Results

Expression levels of serum TRACP5b and CA125

The expression levels of TRACP5b and CA125 in the bone metastasis group were significantly higher than those in the non-bone metastasis and benign lesion groups ($p<0.05$), and the expression levels in the non-bone metastasis group were higher than those in the benign lesion group ($p<0.05$). More details are shown in Table 1 and Figure 1.

Correlation of expression levels of TRACP5b and CA125 with clinicopathological parameters of breast cancer

In patients with breast cancer, the expression level of TRACP5b was not correlated with age, primary sites, estrogen receptors, human epidermal growth factor receptors and progesterone receptors ($p>0.05$), but correlated with the number of tumor nodules, lymph node metastasis, histological type, tumor local infiltration and TNM staging ($p<0.05$). The expression level of CA125 was not correlated with age, primary sites, tumor local infiltration, ER, PR and HER ($p>0.05$), but correlated with the number of tumor nodules, histological type, lymph node metastasis and TNM staging ($p<0.05$). More details are shown in Table 2.

Diagnostic values of TRACP5b and CA125 for bone metastasis of breast cancer

ROC curves of TRACP5b and CA125 expressions for diagnosing bone metastasis of breast cancer were plotted. The AUC of TRACP5b for diagnosing bone metastasis of breast cancer was 0.741 (95%CI: 0.609-0.813); the cut-off value was 6.79

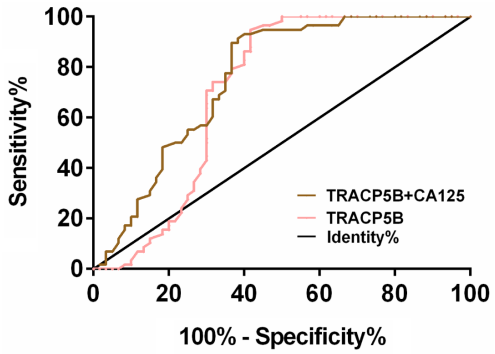

Figure 2. ROC curves of TRACP5b and CA125 for diagnosing bone metastasis of breast cancer. The AUC of TRACP5b for diagnosing bone metastasis of breast cancer was 0.741, the cut-off value was 6.79 U/L, the sensitivity was 71.33% and the specificity 81.26%. The AUC of CA125 was 0.715 (95%CI: 0.585-0.775), the cut-off value was 45.32 U/L, the sensitivity was 75.51% and the specificity 45.32%. The AUC of TRACP5b and CA125 was 0.758, the cut-off value was 0.401, the sensitivity was 73.12% and the specificity 88.17%.

(U/L); the sensitivity was 81.26%, and the specificity 71.33%. The AUC of CA125 was 0.715 (95%CI: 0.585-0.775); the cut-off value 45.32 (U/L); the sensitivity was 75.51%, and the specificity was 45%. The AUC of TRACP5b and CA125 was 0.758 (95%CI: 0.669-0.848); the cut-off value was 0.401; the sensitivity was 88.17%, and the specificity 60.00%. More details are shown in Table 3 and Figure 2.

Univariate analysis of bone metastasis in breast cancer patients

Clinical data of patients in the bone metastasis group and the non-bone metastasis group were collected to perform univariate analysis. The results showed that there was no difference in age, smoking history, drinking history, body mass index (BMI), place of residence, menopausal status,

Table 4. Univariate analysis

Categories	*Bone metastasis group (n=60)*	*Non-bone metastasis group (n=58)*	*t /x²*	*p*
Age (years)	51.24±11.57	53.68±12.64	0.630	0.276
History of smoking, n (%)		1	0.309	0.579
Yes	29 (48.33)	31 (53.45)		
No	31 (51.67)	27 (46.55)		
History of drinking, n (%)			0.273	0.601
Yes	39 (65.00)	35 (60.34)		
No	21 (35.00)	23 (39.66)		
Body mass index (kg/m²)	20.16±3.31	21.21±2.43	1.959	0.053
Place of residence, n (%)			0.002	0.964
Countryside	37 (61.67)	36 (62.07)		
City	23 (38.33)	22 (37.93)		
AST (U/L)	19.07±7.14	18. 58±7.25	0.370	0.712
ALT (U/L)	22.51±9.47	21.39±10.09	0.622	0.535
Menopause, n (%)				
Yes	4 (6.67)	3 (5.17)	0.118	0.731
No	56 (93.33)	55 (94.83)		
Past medical history, n (%)			0.087	0.958
Hypertension	6 (10)	4 (6.9)		
Diabetes	4 (6.67)	2 (3.45)		
Menopause	6 (10)	4 (6.9)		
Lymph node metastasis, n (%)			8.694	0.003
Yes	42 (70)	25 (43.1)		
No	18 (30)	33 (56.9)		
PR, n (%)			0.545	0.460
Positive	43 (71.67)	45 (77.59)		
Negative	17 (28.33)	13 (22.41)		
HER-2, n (%)			3.237	0.072
Positive	49 (81.67)	39 (67.24)		
Negative	11 (18.33)	19 (32.76)		
ER, n (%)			9.879	0.002
Positive	50 (83.33)	33 (56.9)		
Negative	10 (16.67)	25 (43.1)		
Ki-67, n (%)			3.705	0.054
Positive	38 (63.33)	27 (46.55)		
Negative	22 (36.67)	32 (55.17)		
TNM staging, n (%)			8.150	0.004
Stages I+II	47 (78.33)	31 (53.45)		
Stage III	13 (21.67)	27 (46.55)		
TRACP5b (U/L)	7.88±3.56	5.67±1.29	4.453	<0.01
CA125 (U/L)	49.51±12.57	39.38±9.75		

Table 5. Assignment

Factor	*Value*
TNM staging	Stages I+II=1, Stage III=0
Lymph node metastasis	Yes=1, No=0
ER	Positive=1, Negative=0
TRACP5b	Continuous data variables using raw data analysis
CA125	Continuous data variables using raw data analysis

Table 6. Multivariate analysis

Factor	*B*	*S.E*	*Wals*	*Sig.*	*Exp (B)*	*95% CI of Exp (B)*	
						lower limit	*upper limit*
TNM staging	1.375	0.694	3.015	0.029	3.487	0.855	17.527
ER	0.792	0.276	8.121	0.003	2.321	1.169	3.817
TRACP5b	1.449	0.732	5.189	0.001	3.178	1.205	14.581
CA125	1.404	0.372	4.387	0.002	1.695	1.027	2.928

B: constant term, SE: standard error, Wals: chi-square value, sig: p value, Exp (B): odds ratio, 95% CI of Exp (B), 95% confidence interval of odds ratio.

medical history, PR, HER- 2 and Ki - 67 between the two groups ($p>0.05$); there were however statistical differences in TNM staging, ER, lymph node metastasis, TRACP5b and CA125 between the two groups ($p<0.05$; Table 4).

Multivariate analysis of bone metastasis in breast cancer patients

TNM stage, ER, lymph node metastasis, TRACP5b and CA125 were assigned values (Table 5). Multivariate logistic regression analysis was performed, and the results showed that age was not a risk factor for bone metastasis in breast cancer patients, while TNM stage, ER, TRACP5b and CA125 were risk factors for bone metastasis in breast cancer patients (Table 6).

Discussion

Nowadays, breast cancer has become the most common malignant tumor among women, with annually increasing incidence [16]. Invasive recurrence and metastasis after operation remain main factors that potentially affect the patients' quality of life and prognosis [17]. Bone is the most common metastatic site of breast cancer, and the risk of bone metastasis is much higher than that of lung cancer or liver cancer [18]. Bone metastases are not apparent in the early stage, and when they progress to the middle and advanced stages symptoms appear, like ostealgia. At that time, the patients have missed the opportunity for cure [19]. Therefore, it is vital for the improvement of patients' survival time and quality of life to find good markers to predict bone metastasis in the early stage after breast cancer operation [20].

TRACP5b is one of the two subtypes of type 5 acid phosphatase isoenzyme, and TRACP5b with enzyme activity is only derived from the secretion by osteoclasts [21]. Previous studies have found that TRACP5b is an accurate marker for osteoclast number [22]. Changes in bone resorption are usually related to changes in osteoclast number, which indicates that TRACP5b secreted by osteoclasts is an effective marker for bone resorption [23]. By detecting the expression levels of TRACP5b and CA125 in the serum of the 3 groups, it was found that the expression levels of TRACP5b and CA125 in the bone metastasis group were significantly higher than those in the non-metastasis group and the benign lesion group. The serum levels of TRACP5b and CA125 in patients in the non-metastasis group were significantly higher than those in the benign group. Moreover, the expression level of TRACP5b was correlated with the number of tumor nodules, lymph node metastasis, local tumor infiltration and TNM staging, and the expression level of serum CA125 was correlated with the number of tumor nodules, lymph node metastasis and TNM staging. In a follow-up of 151 patients with early breast cancer conducted by Chao et al, changes of TRACP5b level in 8 patients with bone metastasis were earlier than those in imaging [24]. Koizumi and colleagues have found that TRACP5b increases when there is tiny bone metastasis of breast cancer, while NTx and PINP significantly increase only when there is extensive bone metastasis [25]. This shows that TRACP5b can be used for the early diagnosis of bone metastasis

of breast cancer, and its diagnostic value is higher than that of NTx and PINP. Derived from coelomic epithelium during embryonic development, CA125 is a specific marker for ovarian cancer and is also expressed in breast cancer, endometrial cancer, pancreatic cancer and cervical cancer [26]. CA125 has been reported most often as a marker for pleural involvement with metastatic breast cancer. In a study by Berruti et al, CA125 level was higher in 84% of patients with metastatic breast cancer [27], which is similar to our study. It was suggested that TRACP5b and CA125 may be involved in the development and progression of bone metastasis of breast cancer, and they are expected to become therapeutic targets and biomarkers for the disease. In this study, the AUC of serum TRACP5b for diagnosing bone metastasis of breast cancer was 0.741, the sensitivity was 81.26% and the specificity 71.33%. The AUC of CA125 was 0.715 (95%CI:0.585-0.775), the sensitivity was 75.51% and the specificity 45%. The AUC of TRACP5b and CA125 was 0.758 (95%CI: 0.669-0.848), the sensitivity was 88.17% and the specificity 73.12%. Therefore, TRACP5b and CA125 have diagnostic values for bone metastasis of breast cancer.

In this study the risk factors of bone metastasis of breast cancer were analyzed and the results showed that TNM staging, ER, TRACP5b and CA125 were independent risk factors for bone metastasis of breast cancer, suggesting that TRACP5b and CA125 may play an important role in the occurrence and progression of bone metastasis of breast cancer.

This study confirms the diagnostic values of TRACP5b and CA125 for bone metastasis of breast cancer, but it still has limitations. Firstly, the regulatory mechanisms of TRACP5b and CA125 in bone metastasis of breast cancer were not explored. Secondly, the prognosis and monitoring treatment of the disease were not studied. These deficiencies need to be further supplemented in future studies.

In summary, TRACP5b and CA125 may be involved in the occurrence and progression of bone metastasis of breast cancer, and they may become new biomarkers for the diagnosis of this condition.

Conflict of interests

The authors declare no conflict of interests.

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