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Clinical value of KiSS-1 and MMP-2 expression levels in breast cancer tissue in evaluating prognosis of elderly breast cancer patients after modified radical mastectomy

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Abstract

We attempted to clarify clinical value of KiSS-1 and MMP-2 levels in breast cancer (BC) tissue in evaluating prognosis of elderly BC patients after modified radical mastectomy (MCM). The data of 192 elderly female BC patients receiving MCM in our hospital from January 2018 to December 2022 were collected. According to prognosis, patients received division into poor prognosis group (n = 43) and good prognosis group (n = 149). The serum CEA level and KiSS-1 and MMP-2 levels in BC tissue received measurement in both groups. The predictive value of KiSS-1 and MMP-2 alone and jointly in adverse prognosis of elderly BC patients after MCM received assessment. Results showed that No statistical significance was exhibited between both groups in general data ($P > 0.05$). The serum CEA level and MMP-2 expression in BC tissue in poor prognosis group exhibited elevation relative to those in good prognosis group, and KiSS-1 expression in BC tissue in poor prognosis group exhibited depletion relative to that in good prognosis group, indicating statistical significance ($P < 0.05$). The high-level KiSS-1 might be a protective element for adverse prognosis of elderly BC patients after MCM, and high-level CEA and MMP-2 might be an independent risk element for adverse prognosis of elderly BC patients after MCM ($P < 0.05$). KiSS-1 and MMP-2 alone and jointly predicted AUC of adverse prognosis in elderly BC patients after MCM were 0.93, 0.802 and 0.958, with certain predictive values; when cutoff values of KiSS-1 and MMP-2 were 6.15 and 2.26, the predictive value was the best. In conclusion, KiSS-1 and MMP-2 levels in BC tissue possess relation to adverse prognosis of MCM. KiSS-1 and MMP-2 levels in elderly BC patients before surgery may be detected in the future to assist in prognosis evaluation of elderly BC patients after MCM.

Keywords: : Breast cancer; Modified radical mastectomy; KiSS-1; MMP-2; Prognosis

1. Introduction

Modified radical mastectomy (MCM) is the most commonly applied operation for therapy of breast cancer (BC) at present [1-3]. It can not only relieve tumor space-occupying effect, prolong survival period of patients, but also preserve pectoral muscles, with a good appearance post-operation [4-6]. Nevertheless, 10%-30% of BC patients may have local recurrence and distant metastasis within 2-3 years after MCM, which will elevate risk of adverse prognosis [7]. Simultaneously, because elderly BC patients are more complicated with underlying diseases, their immunity is quite low, and risk of adverse prognosis exhibits upregulation [8, 9]. Thus, it is particularly crucial to determine prognosis of elderly BC patients after MCM and indicators that may have relation to prognosis to guide early intervention of BC.

Currently, imaging often receives application for determining recurrence and metastasis of BC to evaluate patients' prognosis; changes in lesion can receive observation, while results obtained are only current manifestations and cannot quantitatively analyze risk of tumor recurrence and metastasis, which have limitations upon application. KiSS-1 metastasis suppressor (KiSS-1) is a newly discovered tumor suppressor gene [10]. It has been demonstrated that KiSS-1 has close relation to BC, ovarian cancer and other malignancies, and deficiency of this gene may elevate risk of tumor metastasis [11-13]. As a vital member of MMP family, matrix metalloproteinase-2 (MMP-2) can not only degrade extracellular matrix, and facilitate tumor cell growth, but also induce tumor cell immune tolerance [14, 15]. Combined with mechanism of KiSS-1 and MMP-2, they may possess relation to prognosis of elderly BC patients after MCM, whereas their specific association has not been clarified.

In view of this, our research focused on association of KiSS-1 and MMP-2 levels in BC tissue and prognosis of elderly BC patients after MCM.

2. Materials and methods

2.1. General data

The data of elderly female BC patients receiving MCM in our hospital from January 2018 to December 2022 was

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collected. The general data included age, body mass index (BMI), comorbidities underlying diseases [hypertension, with systolic pressure ≥ 140 mm Hg and diastolic pressure ≥ 90 mm Hg; diabetes, with fasting blood glucose (FBG) ≥ 7.0 mmol/L and (or) 2h-postprandial blood glucose (2hPBG) ≥ 11.1 mmol/L], American Anesthesiologist Association (ASA) grading [16] (I-III), maximum tumor diameter, pathological types (infiltrating carcinoma and non-infiltrating carcinoma), TNM staging [17] (stages I-II), regional lymph node metastasis (axillary lymph node metastasis at levels I and II on the same side, or internal mammary lymph node metastasis on the same side, etc., through imaging examination). Inclusion criteria: (1) BC diagnosis met relevant diagnostic criteria in the Guidelines and Specifications for Diagnosis and Treatment of Breast Cancer (2015 Edition) of the Chinese Anti-Cancer Association [18], and received confirmation by surgery and pathology; (2) age ≥ 63 years old; (3) unilateral BC; (4) with indication of MCM (TNM staged in stage I and II of BC, and tumor did not involve pectoral fascia), and it was the first time to receive MCM; (5) complete preservation of pathological tissue sections; (6) completion of 1-year follow-up; (7) all patients' medical records, relevant examination data, and follow-up data were complete. Exclusion criteria: (1) Those with other malignancies such as gastric cancer and cervical cancer; (2) those with congenital heart disease, liver and kidney failure and other important organ diseases; (3) those with infectious pneumonia; (4) those with immune system diseases or abnormal coagulation function; (5) those with distant metastasis of tumors; (6) those who received radiotherapy, chemotherapy, immunosuppressive drugs and other related therapies before surgery. According to inclusion and exclusion criteria, 192 patients received enrollment as research subjects. Included patients aged 63-73 years old; pathological types: 130 cases of infiltrating carcinoma and 62 cases of non-infiltrating carcinoma.

2.2. Instruments and reagents

Fluorescence quantitative polymerase chain reaction (PCR) analyzer; low-speed centrifuge; Trizol reagent kit; 2 × Mic, DNA Ladder reagents; CEA reagent kit.

2.3. Methods

(1) Prognostic evaluation and grouping: Patients who underwent MCM received follow-up for 1 year, and CT or MRI examinations received performance every 3 months during follow-up period, and if examination results were normal, CT or MRI examinations received performance every 6 months. Patient mortality, tumor recurrence (CT or MRI depicted new lesions at the resection site of original lesion), and distant metastasis (CT or MRI depicted mediastinal lymph node metastasis, chest wall metastasis, lung metastasis, etc.) during 1-year follow-up period. Patients who died had tumor recurrence or had distant metastasis were included in poor prognosis group, while others were included in good prognosis group.

(2) Detection of serum carcinoembryonic antigen (CEA) level: The 5mL of fasting peripheral venous blood received collection before operation, followed by centrifugation at a radius of 10 cm and a speed of 4000 r/min for 10 min to collect upper serum. CEA received detection through electrochemiluminescence method and corresponding reagent kit. The testing process was carried out in strict accordance with instructions of reagent kit.

(3) Detection of KiSS-1 and MMP-2 levels in BC tissue: BC tissue specimens (approximately 100 mg) were taken and ground in liquid nitrogen bath. After 1 mL of Trizol reagent was received in addition, total RNA was extracted from tissue through Trizol reagent kit, followed by reverse transcription reaction. The reverse transcription reaction system consisted of a total of 20 μL, including 1.5 μL of RNA, 1 μL of Rever TraAce, 1 μL of Rnase inhibitor, 2 μL of 10 mmol/L dNTPs, 9.5 μL of Rhase Free H_2O, 1 μL of Random Peimer and 4 μL of 5 × RT buffer. Then they received incubation at 30℃ for 10 min, reverse transcription reaction at 42℃ for 20 min, and inactivation at 99℃ for 5 min. Finally, they received centrifugation at 1200 r/min for 10 min through a low-speed centrifuge at 4℃ with a radius of 6 cm to extract cDNA from specimens. Specimens were taken for PCR amplification. Reaction conditions: Reaction received conduction at 94℃ for 2 min, at 94℃ for 45 s, at 60℃ for 30 s, and at 72℃ for 30 s, total of 40 cycles, and finally extension received conduction at 72℃ for 7 min. After the reaction was completed, KiSS-1 and MMP-2 levels received analysis with the $2^{-\Delta\Delta Ct}$ method.

2.4. Statistical analysis

SPSS 27.0 statistical software received application for data processing. Counting data received expression in frequency and rate, and comparison received conduction through χ^2 test. Measurement data conforming to normal distribution received representation by x±s, and intergroup comparison received conduction through independent sample t-test; measurement data conforming to skewed distribution received representation by M (P 25, P 75), and intergroup comparisons received conduction through rank sum test. The correlation of KiSS-1 and MMP-2 levels in BC tissue received assessment through the Spearman linear correlation test. The influencing elements of adverse prognosis of elderly BC patients after MCM received evaluation through the Logistic regression model. The receiver operator characteristic (ROC) curve received drawing, area under curve (AUC) received calculation, and predictive value of KiSS-1 and MMP-2 alone and jointly for adverse prognosis of elderly BC patients after MCM received analysis. AUC > 0.900 indicated high predictive performance, AUC > 0.700-0.900 indicated certain predictive performance, and AUC between 0.500-0.700 indicated poor predictive performance. The difference was statistically significant with $P < 0.05$.

3. Results

3.1. Prognosis of MCM in elderly BC patients

The prognosis of 192 elderly BC patients was poor in 43 cases, accounting for 22.40% (43/192), including 10 cases of death, 26 cases of recurrence and 7 cases of distant metastasis.

3.2. Comparison of general data between both groups

According to prognosis, patients received division into poor prognosis group (n = 43) and good prognosis group (n = 149). No statistical significance was exhibited between both groups in general data, including age, BMI, comorbidities with underlying diseases, ASA grading, maximum tumor diameter, pathological types, TNM staging, and regional lymph node metastasis ($P > 0.05$; Table 1).

3.3. Comparison of serum CEA level and KiSS-1 and MMP-2 expression in BC tissue between both groups

The serum CEA level and MMP-2 expression in BC tissue in poor prognosis group exhibited elevation relative to those in good prognosis group, and KiSS-1 expression in BC tissue in poor prognosis group exhibited depletion relative to that in good prognosis group, indicating statistical significance ($P < 0.05$; Table 2).

3.4. Analysis on correlation of KiSS-1 and MMP-2 expression in BC tissue

Spearman correlation test demonstrated that KiSS-1 level possessed negative correlation with MMP-2 level in BC tissue ($r = -0.320$, $P < 0.05$; Figure 1).

3.5. Analysis of influencing elements of adverse prognosis in elderly BC patients after MCM

The Logistic regression model was established through taking indicators CEA, KiSS-1, and MMP-2 among elderly BC patients with different prognoses as independent variables (all were continuous variables), and prognosis of elderly BC patients after MCM (1 = poor prognosis, 0 = good prognosis) as dependent variables. As a result, abnormal expression of serum CEA, KiSS-1 and MMP-2 in BC tissue possessed relation to prognosis of MCM. The high-level KiSS-1 might be a protective element for adverse prognosis of elderly BC patients after MCM (OR = 0.084, $P < 0.05$), and high-level CEA and MMP-2 might be an independent risk element for adverse prognosis of elderly BC patients after MCM (OR = 7.333, 83.197, $P < 0.05$; Table 3).

3.6. Predictive value of KiSS-1 and MMP-2 alone and jointly in adverse prognosis of elderly BC patients after MCM

ROC curve received drawing through taking KiSS-1 and MMP-2 levels in BC tissue as test variables, and prognosis of elderly BC patients after MCM as state variables (1 = poor prognosis, 0 = good prognosis). As a result, KiSS-1 and MMP-2 alone and jointly predicted AUC of adverse prognosis in elderly BC patients after MCM were 0.93, 0.802 and 0.958, respectively, all of which were over 0.800, with certain predictive values; when cutoff values of KiSS-1 and MMP-2 were 6.15 and 2.26, respectively, the predictive value was the best (Figure 2 and Table 4).

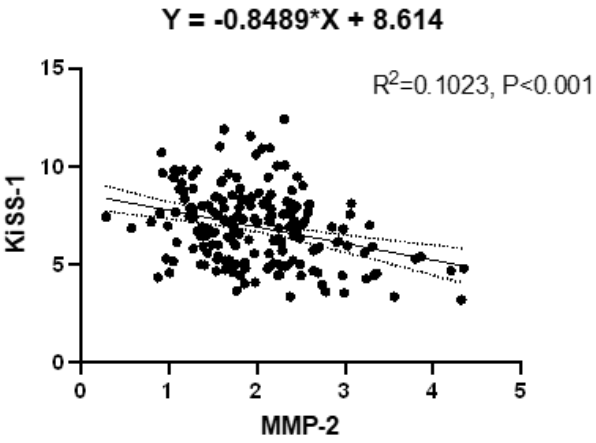

Fig. 1. Correlation of KiSS-1 and MMP-2 expression in BC tissue.

Table 1. General data in both groups.

Groups	N	Age (years)	BMI (kg/m^2)	Comorbidities underlying diseases [n (%)]		ASA grading [n (%)]		
				Hypertension	Diabetes	I	II	III
Poor prognosis group	43	68.48±1.75	21.02±1.02	19 (44.19)	13 (30.23)	12 (27.91)	18 (41.86)	13 (30.23)
Good prognosis group	149	68.53±1.74	21.04±1.03	41 (27.52)	35 (23.49)	36 (24.16)	70 (46.98)	43 (28.86)
t/χ^2		0.652	0.209	0.257		0.843		
P		0.518	0.836	0.612		0.656		

Groups		Maximum tumor diameter [M (P_{25}, P_{75}), cm]	Pathological types [n (%)]		TNM staging [n (%)]		Regional lymph node metastasis [n (%)]	
			Infiltrating carcinoma	Non-infiltrating carcinoma	I	II	Presence	Absence
Poor prognosis group	43	2.91 (2.34, 3.40)	28 (65.12)	15 (34.88)	20 (46.51)	23 (53.49)	21 (48.84)	22 (51.16)
Good prognosis group	149	2.77 (2.20, 3.30)	102 (68.46)	47 (31.54)	73 (48.99)	76 (51.01)	57 (38.26)	92 (61.74)
χ^2/Z		1.805	0.202		0.08		2.462	
P		0.071	0.653		0.777		0.117	

Table 2. Serum CEA level and KiSS-1 and MMP-2 expression in BC tissue in both groups.

Groups	N	CEA (ng/mL)	KiSS-1	MMP-2
Poor prognosis group	43	13.62±2.17	4.76±0.96	2.42±0.84
Good prognosis group	149	9.76±1.83	7.54±1.82	1.78±0.59
t		8.991	10.204	5.838
P		< 0.001	< 0.001	< 0.001

Table 3. Influencing elements of adverse prognosis in elderly BC patients after MCM.

Factors	B	SE	Wald	P	OR	95% CI of OR
Constant	-19.63	6.894	8.104	0.004	/	/
CEA	1.992	0.596	11.181	< 0.001	7.333	2.281-23.573
KiSS-1	-2.482	0.794	9.775	0.002	0.084	0.018-0.396
MMP-2	4.421	1.327	11.093	< 0.001	83.197	6.168-1122.128

Table 4. KiSS-1 and MMP-2 alone and jointly predicted in adverse prognosis of elderly BC patients after MCM.

	AUC	SE	P	95% CI	Cutoff value	Youden index	Sensitivity	Specificity
KiSS-1	0.93	0.017	< 0.001	0.896-0.964	6.15	0.796	0.977	0.819
MMP-2	0.802	0.041	< 0.001	0.722-0.882	2.26	0.47	0.698	0.772
KiSS-1+MMP-2	0.958	0.013	< 0.001	0.932-0.983	/	0.792	0.953	0.839

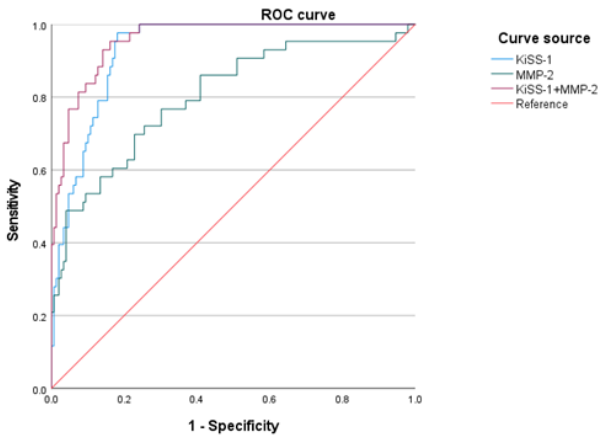

Fig. 2. KiSS-1 and MMP-2 alone and jointly predicted in adverse prognosis of elderly BC patients after MCM.

4. Discussion

BC, as a common malignancy in women, has an incidence of 24%; epidemiological investigation illustrates that BC incidence has exhibited elevation year by year in recent years [19]. Currently, clinical therapy for BC mostly adopts MCM to remove tumor focus and curb disease progression, whereas tumor recurrence and metastasis may still occur post-surgery, leading to adverse prognosis of patients [20].

CEA, a common serum marker for diagnosis and prognosis evaluation of BC, is majorly secreted by endoderm cells; elevated serum level indicates high risk of tumor recurrence and metastasis [21]. Nevertheless, specificity of serum CEA level in evaluating prognosis of BC is unfavorable, and it is vulnerable to inflammation, thus its application has limitations [22]. Thus, it is necessary to seek other new markers to evaluate prognosis of elderly BC patients after MCM. Herein, we discovered that MMP-2 expression in BC tissue in poor prognosis group exhibited elevation relative to those in good prognosis group, and KiSS-1 expression in BC tissue in poor prognosis group exhibited depletion relative to that in good prognosis group, suggesting that KiSS-1 and MMP-2 can also be applied for evaluating prognosis of elderly BC patients after MCM.

KiSS-1, a tumor metastasis suppressor gene, was first isolated from melanoma cell line. In recent years, research has demonstrated that KiSS-1 level exhibits deficiency in tumor tissue with metastasis [23]. The residue peptide encoded by KiSS-1 gene can bind to G protein-coupled receptor 54 (GPR54), facilitate hydrolysis of phosphatidylinositol diphosphate and calcium ion activity, and accelerate release of arachidonic acid and p38 phosphorylation of mitogen-activated protein kinase, thereby repressing tumor cell proliferation [24]. Additionally, residue peptide encoded by KiSS-1 gene binding to GPR54 can also activate phospholipase C, facilitate excretion of intracellular calcium ions, and thus repress tumor cell replication and invasion [25]. MMP, a crucial degrading enzyme in the body, not only has function of degrading extracellular matrix but also modulates expression of growth factors and participates in tumor occurrence and development [26]. MMP-2 is a key enzyme in MMP family getting involved in extracellular matrix degradation. MMP-2 can be converted into type IV collagenase after being activated, thus exerting a role in destroying extracellular matrix barrier and facilitating cell proliferation [27]. During BC development, MMP-2 can utilize principle of matrix degradation to enhance tumor cell metastasis and can provide favorable conditions for vascular endothelial cell proliferation and angiogenesis [28]. Referring to above research findings, combined with action mechanism of KiSS-1 and MMP-2, we speculated that they may possess relation to prognosis of elderly BC patients after MCM.

Herein, we discovered that high-level KiSS-1 might be a protective element for adverse prognosis of elderly BC patients after MCM and high-level MMP-2 might be an independent risk element for adverse prognosis of elderly BC patients after MCM, validating that abnormal expression of KiSS-1 and MMP-2 in elderly BC possesses relation to prognosis of MCM. The possible reason may be that KiSS-1 downregulation in BC tissue can reduce production of amino acid residue peptide (metastatin), and amino acid residue peptide can repress tumor cell proliferation and differentiation and trigger tumor cell apoptosis. Thus, low-level KiSS-1 may attenuate its influence on suppressing tumor cell metastasis and recurrence, leading to unfavorable prognosis of MCM for BC patients [29]; MMP-2 upregulation in BC tissue can destroy tumor cell barrier and basilar membrane, and accelerate tumor angiogenesis, thus facilitating tumor cell recurrence and metastasis and affecting prognosis of patients after MCM [30]. Herein, we discovered that KiSS-1 and MMP-2 in BC tissue have excellent value in predicting risk of adverse prognosis in elderly BC patients after MCM; when their cutoff values were 6.15 and 2.26, respectively, the best predictive effect could be obtained; moreover, with KiSS-1 downregulation and MMP-2 upregulation, risk of adverse prognosis in patients exhibited elevation. These findings suggested that for elderly BC patients with low-level KiSS-1 and high-level MMP-2 in preoperative BC tissue, clinical ad-

juvant chemotherapy and radiotherapy should receive reasonable selection according to actual situation of patients after MCM to repress tumor cell recurrence and metastasis and improve prognosis of patients. Additionally, AUC of KiSS-1 and MMP-2 jointly predicting adverse prognosis after MCM for elderly BC patients exhibited elevation relative to that detection alone, thus in clinical practice, combined observation of KiSS-1 and MMP-2 can be considered for benefiting patients as a whole. Also, we discovered that KiSS-1 level in BC tissue possessed negative association with MMP-2. This result may have relation to ability of KiSS-1 to block MMP pathway, whereas its specific mechanism still needs to be clarified in the future. Additionally, though Logistic regression model confirmed that abnormal expression of CEA possesses relation to prognosis of elderly BC patients after MCM, due to its limitations, predictive value of CEA for adverse prognosis of elderly BC patients after MCM did not receive analysis, and our research only recorded prognosis of BC patients within 1-year follow-up, thus it has limitations, and it still needs to extend follow-up time and conduct prospective cohort research in the future to verify our findings.

In conclusion, KiSS-1 and MMP-2 levels in BC tissue possess relation to adverse prognosis of MCM. KiSS-1 and MMP-2 levels in elderly BC patients before surgery may be detected in the future to assist in prognosis evaluation of elderly BC patients after MCM.

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