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The value of CA15-3, CCL20 and NK cells in predicting recurrence of HER-2 positive breast cancer after breast-conserving surgery

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Abstract: Objective To analyze the risk factors of recurrence of human epidermal growth factor receptor 2 (HER-2) positive breast cancer patient after breast- conserving surgery, and to explore the value of carbohydrate antigen 15-3 (CA15-3), CC chemokine ligand 20 (CCL20), and natural killer (NK) cells in predicting postoperative recurrence. **Methods** A total of 96 patients with HER- 2 positive breast cancer who underwent breast- conserving surgery in Rizhao People's Hospital Affiliated to Jining Medical University from June 2021 to June 2023 were selected as the research subjects. According to the recurrence status 6 months after surgery, the patients were divided into recurrence group (n=21) and non-recurrence group (n=75). Univariate and multivariate logistic regression analyses were used to identify the risk factors for recurrence of HER - 2 positive breast cancer after breast - conserving surgery. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of CA15 - 3, CCL20 and NK cells for recurrence of HER-2 positive breast cancer after breast-conserving surgery. **Results** There were no significant differences in age, tumor diameter, menstrual status, clinical stage, histological grade and tumor family history between the two groups (P>0.05). The axillary lymph node metastasis rate, serum CA15-3, CCL20 and NK cell levels in the recurrence group were higher than those in the non-recurrence group (P<0.05). ROC curve analysis showed that the area under the curve (AUC) of CA15-3, CCL20 and NK cells combined to predict the recurrence after breast-conserving surgery for HER- 2 positive breast cancer was 0.999, with a sensitivity of 97.33% and a specificity of 100.00%. The efficacy of combined prediction was better than that of individual index prediction. Conclusion Axillary lymph node metastasis, elevated serum CA15-3, CCL20 and NK cell levels are risk factors for recurrence of HER-2 positive breast cancer after breast-conserving surgery. CA15-3, CCL20 and NK cells all have certain predictive value for recurrence after breast - conserving surgery for HER - 2 positive breast cancer, and combined detection of the three indexes can improve their predictive efficacy.

Keywords: Breast cancer, Human epidermal growth factor receptor 2 positive; Breast-conserving surgery; Carbohydrate antigen 15-3; CC chemokine ligand 20; Natural killer cell; Breast cancer recurrence; Predictive value

Breast cancer accounts for approximately 18% of all female malignant tumors, with a continuously rising incidence rate and a progressively younger onset age [1-2].

Human epidermal growth factor receptor 2 (HER-2)-positive breast cancer, a common molecular subtype, is characterized by large tumor volume, high lymph node metastasis rate, advanced histological grade and poor overall prognosis [3-4]. For early and locally advanced HER-2-positive breast cancer, breast-conserving surgery is routinely performed to resect lesion tissues while maximally preserving breast cosmetic appearance and volume [5]. However, affected by multiple clinicopathological factors, patients still face a certain postoperative recurrence risk after breast-conserving surgery, leading to adverse long-term outcomes [6]. Therefore, targeted postoperative intervention and preventive strategies are urgently required to reduce recurrence risk in this patient population. Clarifying independent risk factors and establishing an early predictive model for postoperative recurrence are critical to guiding individualized clinical prevention and treatment for HER-2-positive breast cancer patients undergoing breast-conserving surgery. Cancer antigen 15-3 (CA15-3) is a classic serological biomarker with important clinical value in the early diagnosis and prognostic evaluation of breast cancer. Nevertheless, single detection of CA15-3 exhibits limited efficacy in predicting postoperative tumor recurrence [7]. Accordingly, it is necessary to explore novel biomarkers with superior predictive performance.

C-C motif chemokine ligand 20 (CCL20), a key member of the chemokine superfamily, has been confirmed to be closely involved in breast cancer recurrence and distant metastasis [8]. Natural killer (NK) cells are essential innate immune cells that secrete multiple chemokines and cytokines to exert anti-tumor effects via immune surveillance and immune clearance. Accumulating studies have demonstrated that NK cells are tightly correlated with breast cancer initiation and progression, serving as a promising prognostic biomarker for breast cancer patients [9]. This study aimed to investigate the combined

predictive efficacy of CA15-3, CCL20 and NK cells for postoperative recurrence in HER-2-positive breast cancer patients after breast-conserving surgery. Relevant results are reported as follows.

1 Subjects and Methods

1.1 Study Subjects

Patients diagnosed with HER-2-positive breast cancer who underwent breast-conserving surgery at Rizhao People's Hospital Affiliated to Jining Medical University from June 2021 to June 2023 were retrospectively enrolled.

Inclusion criteria: (1) Meeting the diagnostic criteria for HER-2-positive breast cancer specified in the *Chinese Anti-Cancer Association Guidelines and Specifications for Breast Cancer Diagnosis and Treatment (2019 Edition)* [10]; (2) Age ≥ 18 years old; (3) First-time confirmed malignant diagnosis without prior anti-tumor treatment; (4) Expected survival duration longer than 6 months; (5) Receiving standardized breast-conserving surgery with unified surgical protocols; (6) Routine postoperative detection of serum CA15-3, CCL20 and peripheral blood NK cell levels; (7) Complete clinical and pathological baseline data; (8) Signed informed consent provided by patients or their legal guardians.

Exclusion criteria: (1) Complicated with other primary malignant tumors; (2) TNM stage beyond stage I–II; (3) Presence of severe mental disorders or cognitive dysfunction; (4) Loss to follow-up or refusal of regular postoperative follow-up; (5) Preoperative confirmed distant metastasis.

A total of 96 eligible patients were finally enrolled. According to 6-month postoperative follow-up outcomes, all participants were divided into the recurrence group (n=21) and the non-recurrence group (n=75). This study was approved by the Medical Ethics Committee of Rizhao People's Hospital (Approval No: KYSQ054-2024).

1.2 Clinical Data Collection

A hospital-designed standardized questionnaire was used to collect baseline information, including age, tumor diameter, menstrual status, clinical stage, histological grade, family history of malignant tumors, and axillary lymph node metastasis status.

1.3 Biomarker Detection Methods

Fasting peripheral venous blood (approximately 5 mL) was collected on the second postoperative day. Blood samples were centrifuged at 1800 g for 10 minutes, and the supernatant was isolated for subsequent detection. Serum CA15-3 concentration was measured by electrochemiluminescence immunoassay. Serum CCL20 level was quantified using enzyme-linked immunosorbent assay. The percentage of NK cells in peripheral blood lymphocytes was detected by flow cytometry with a FACS Calibur analyzer (Becton Dickinson, USA).

1.4 Statistical Analysis

SPSS 22.0 software was used for all statistical analyses. Normally distributed continuous data were expressed as $\bar{x}\pm s$, and intergroup differences were compared using the independent sample t-test. Categorical variables were presented as case numbers and percentages [n(%)], and the chi-square test was adopted for intergroup comparison. Multivariate logistic regression analysis was performed to identify independent risk factors for postoperative recurrence. Receiver operating characteristic (ROC) curves were plotted using MedCalc software to evaluate the single and combined predictive efficacy of CA15-3, CCL20 and NK cells. A P value < 0.05 was defined as statistically significant.

2 Results

2.1 Univariate Analysis of Postoperative Recurrence

No significant differences were observed in age, tumor diameter, menstrual status, clinical stage, histological grade and tumor family history between the two groups (P>0.05). Compared with the non-recurrence group, the recurrence group presented significantly higher axillary lymph node metastasis rate, elevated serum CA15-3 and CCL20 levels, and abnormal NK cell proportions (P<0.05) (**Table 1**).

Tab.1 Univariate analysis of recurrence after breast-conserving surgery in HER-2 positive breast cancer [case(%)]

Factor	Recurrence group (n=21)	Non-recurrence group (n=75)	χ^2/t value	P value
Age			0.314	0.575
≥35 years	15(71.43)	58(77.33)		
<35 years	6(28.57)	17(22.67)		
Menopausal status			0.016	0.900
Postmenopausal	9(42.86)	31(41.33)		
Premenopausal	12(57.14)	44(58.67)		
Tumor diameter			0.987	0.320
>2.0 cm	16(76.19)	64(85.33)		
≤2.0 cm	5(23.81)	11(14.67)		
Clinical stage			0.274	0.600
Stage I	6(28.57)	26(34.67)		
Stage II	15(71.43)	49(65.33)		
Axillary lymph node metastasis	12(57.14)	18(24.00)	8.388	0.004
Histological grade			1.655	0.437
Grade 1	2(9.52)	12(16.00)		
Grade 2	8(38.10)	35(46.67)		
Grade 3	11(52.38)	28(37.33)		
Family history of tumor	11(52.38)	34(45.33)	0.327	0.567

CA15-3 (U/mL, $\bar{x}\pm s$)	56.55±15.49	33.46±9.38	8.526	<0.001
CCL20 (pg/mL, $\bar{x}\pm s$)	110.42±24.73	80.69±15.66	6.698	<0.001
NK cells (%, $\bar{x}\pm s$)	22.36±3.65	16.87±3.74	5.976	<0.001

2.2 Multivariate Logistic Regression Analysis

Variables with statistical significance in univariate analysis were included in the multivariate logistic regression model as independent variables, and postoperative recurrence was set as the dependent variable.

Variable assignment details are shown in **Table 2.** The results indicated that axillary lymph node metastasis, elevated serum CA15-3, increased CCL20 level and abnormal NK cell percentage were independent risk factors for postoperative recurrence in HER-2-positive breast cancer patients after breast-conserving surgery (P<0.05) (**Table 3**).

2.3 Predictive Efficacy of Three Biomarkers for Postoperative Recurrence

ROC curve analysis revealed that the area under the curve (AUC) of CA15-3, CCL20, NK cells alone, and their combined detection were 0.900, 0.842, 0.853 and 0.999, respectively (**Table 4, Figure 1**).

Tab.2 Assignment table of each variable

Factor	Variable name	Assignment
Postoperative recurrence	Y	0=no, 1=yes
Axillary lymph node metastasis	X1	0=no, 1=yes
CA15-3	X2	Raw value input
CCL20	X3	Raw value input
NK cells	X4	Raw value input

Tab.3 Multivariate analysis of recurrence after breast-conserving surgery in HER-2 positive breast cancer patients

Factor	β	SE	Wald $\chi2$	P value	OR	95%CI
Axillary lymph node metastasis	0.949	0.324	8.579	<0.001	2.583	1.369~4.875
CA15-3	0.984	0.231	18.145	<0.001	2.675	1.701~4.207
CCL20	0.854	0.407	4.403	0.009	2.349	1.058~5.216
NK cells	0.783	0.312	3.24	0.012	2.188	1.188~4.031

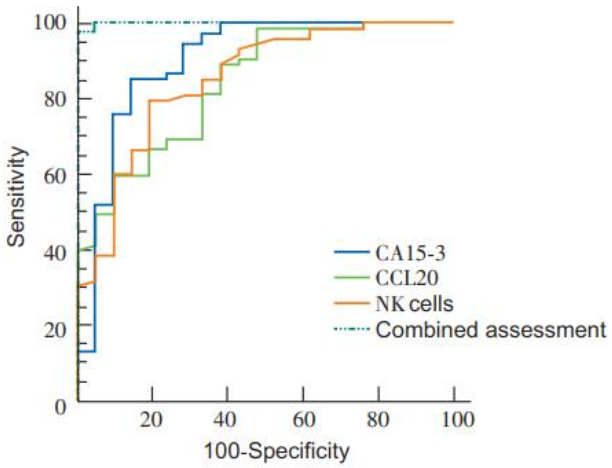

Fig.1 ROC curve of the combined prediction of 3 indicators for recurrence after breast-conserving surgery in HER-2 positive breast cancer patients

Tab.4 Predictive efficacy of three indexes for recurrence in HER2-positive breast cancer patients after breast-conserving surgery

Variable	AUC	95%CI	Cut-off value	Sensitivity (%)	Specificity (%)	SE	P value
CA15-3	0.900	0.822~0.952	43.9 U/mL	85.33	85.71	0.048	<0.001
CCL20	0.842	0.754~0.909	99.0 pg/mL	89.33	61.9	0.048	<0.001
NK cells	0.853	0.766~0.917	19.90%	80	80.95	0.048	<0.001
Combined assessment	0.999	0.960~1.000	—	97.33	100.00	0.016	<0.001

3 Discussion

Breast-conserving surgery is a standard curative strategy for early HER-2-positive breast cancer. Nevertheless, due to the high invasive biological behavior and poor inherent prognosis of HER-2-positive subtypes, the postoperative recurrence rate remains unsatisfactory [11]. Early and accurate prediction of recurrence risk is therefore a core research hotspot in clinical breast oncology. Conventional serological tumor markers such as CA15-3 have moderate predictive value for postoperative recurrence and metastasis, whereas their clinical application is limited by insufficient specificity, as these indicators may also increase under multiple benign physiological and pathological conditions [12]. Combined detection of multiple biomarkers is widely recommended to improve predictive accuracy and diagnostic efficiency.

As a crucial inflammatory chemokine, CCL20 participates in tumor cell proliferation, invasion and distant metastasis, and is closely implicated in the progression of multiple malignancies including breast cancer and hepatocellular carcinoma [13]. Previous studies have verified that CCL20 overexpression is strongly associated with postoperative recurrence risk in triple-negative breast cancer [14]. NK cells play a central regulatory role in innate anti-tumor immunity. Quantitative and functional abnormalities of NK cells are closely correlated with tumor initiation, progression and immune escape [15]. A previous study by Li Yueting *et al.* [16] confirmed that altered NK cell levels were related to breast cancer postoperative recurrence, supporting its potential role as a prognostic serological indicator.

Results of univariate and multivariate logistic regression analysis showed that axillary lymph node metastasis, elevated postoperative serum CA15-3, CCL20 and NK cell levels were independent risk factors for

postoperative recurrence in HER-2-positive breast cancer patients after breast-conserving surgery. Studies have demonstrated that axillary lymph node metastasis is an independent risk factor for recurrence following breast-conserving surgery in breast cancer patients [17], which is consistent with the findings of the present study. Lymph nodes serve as the major route for tumor cell dissemination from the primary lesion to distant sites; accordingly, patients with axillary lymph node metastasis present an increased risk of postoperative tumor recurrence. In addition, lymph node metastasis combined with lymphovascular invasion or extracapsular nodal invasion can further elevate the likelihood of postoperative recurrence [18]. CA15-3 is a tumor marker closely associated with breast cancer, and its elevated level is generally correlated with disease progression and tumor recurrence. CCL20 recruits and activates leukocyte subsets involved in tumor progression and metastasis; its upregulation may facilitate the migration and invasion of tumor cells, thereby increasing the risk of postoperative recurrence. Elevated NK cell levels reflect the activation of the immune system and enhanced anti-tumor responses, and may also indicate the presence of immune escape mechanisms, enabling tumor cells to evade immune surveillance and ultimately promoting disease recurrence.Luo Jie *et al.* [19] confirmed that CCL20 overexpression increases the risk of local recurrence after breast-conserving surgery. Ma Miaomiao *et al*. [9] found that breast cancer patients with high NK cell expression rates exhibit poor prognosis. This study further explored the predictive value of CA15-3, CCL20 and NK cells for postoperative recurrence in HER-2-positive breast cancer patients undergoing breast-conserving surgery. ROC curve analysis revealed that at the optimal cut-off values of 43.9 U/mL for CA15-3, 99.0 pg/mL for CCL20, and 19.9% for NK cells, the combined detection of the three indicators yielded an AUC of 0.999, a sensitivity of 97.33%, and a specificity of 100.00% for predicting postoperative recurrence. The combined predictive efficacy was significantly superior to that of single indicators, suggesting that the combination of CA15-3, CCL20 and NK cells can improve the predictive performance for recurrence in this patient population.

In conclusion, axillary lymph node metastasis and elevated serum levels of CA15-3, CCL20 and NK cells are independent risk factors for postoperative recurrence in HER-2-positive breast cancer patients after breast-conserving surgery. Combined detection of these biomarkers can effectively improve the predictive value for postoperative recurrence.

Conflict of Interest: None

Reference

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·乳腺癌专题·论著·

CA15-3、CCL20联合NK细胞预测HER-2阳性乳腺癌保乳手术后复发的价值

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摘要：目的 分析人类表皮生长因子受体2(HER-2)阳性乳腺癌患者保乳手术后复发的危险因素，探讨糖类抗原15-3(CA15-3)、C-C趋化因子配体20(CCL20)、自然杀伤(NK)细胞联合预测其术后复发的价值。**方法** 以2021年6月至2023年6月于济宁医学院附属日照市人民医院行保乳手术的HER-2阳性乳腺癌患者96例为研究对象，依据术后6个月的复发情况将其分为复发组(n=21)及未复发组(n=75)。采用单因素及多因素logistic回归分析影响HER-2阳性乳腺癌保乳手术后复发的危险因素，采用受试者工作特征(ROC)曲线分析CA15-3、CCL20及NK细胞对HER-2阳性乳腺癌保乳术后复发的预测价值。**结果** 两组年龄、肿瘤直径、月经状态、临床分期、组织学分级、肿瘤家族史比较差异均无统计学意义(P>0.05)。复发组的腋窝淋巴结转移率、血清CA15-3、CCL20水平及NK细胞水平均高于未复发组(P<0.05)。ROC曲线分析结果显示，CA15-3、CCL20及NK细胞联合预测HER-2阳性乳腺癌保乳术后复发的曲线下面积(AUC)为0.999，灵敏度为97.33%，特异度为100.00%。联合预测的效能均优于各指标单独预测。**结论** 术后腋窝淋巴结转移、血清CA15-3、CCL20及NK细胞水平升高是HER-2阳性乳腺癌保乳术后复发的危险因素；CA15-3、CCL20及NK细胞对HER-2阳性乳腺癌保乳术后复发均具有一定的预测价值，三种指标联合检测可提升其预测效能。

关键词： 乳腺癌，人类表皮生长因子受体2阳性；保乳手术；糖类抗原15-3；C-C趋化因子配体20；自然杀伤细胞；乳腺癌复发；预测价值
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The value of CA15-3, CCL20 and NK cells in predicting recurrence of HER-2 positive breast cancer after breast-conserving surgery

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Abstract: Objective To analyze the risk factors of recurrence of human epidermal growth factor receptor 2 (HER-2) positive breast cancer patients after breast-conserving surgery, and to explore the value of carbohydrate antigen 15-3 (CA15-3), C-C chemokine ligand 20 (CCL20), and natural killer (NK) cells in predicting postoperative recurrence. **Methods** A total of 96 patients with HER-2 positive breast cancer who underwent breast-conserving surgery in Rizhao People's Hospital Affiliated to Jining Medical University from June 2021 to June 2023 were selected as the research subjects. According to the recurrence status 6 months after surgery, the patients were divided into recurrence group (n=21) and non-recurrence group (n=75). Univariate and multivariate logistic regression analyses were used to identify the risk factors for recurrence of HER-2 positive breast cancer after breast-conserving surgery. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of CA15-3, CCL20 and NK cells for recurrence of HER-2 positive breast cancer after breast-conserving surgery. **Results** There were no significant differences in age, tumor diameter, menstrual status, clinical stage, histological grade and tumor family history between the two

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groups (P>0.05). The axillary lymph node metastasis rate, serum CA15-3, CCL20 and NK cell levels in the recurrence group were higher than those in the non-recurrence group (P<0.05). ROC curve analysis showed that the area under the curve (AUC) of CA15-3, CCL20 and NK cells combined to predict the recurrence after breast-conserving surgery for HER-2 positive breast cancer was 0.999, with a sensitivity of 97.33% and a specificity of 100.00%. The efficacy of combined prediction was better than that of individual index prediction. **Conclusion** Axillary lymph node metastasis, elevated serum CA15-3, CCL20 and NK cell levels are risk factors for recurrence of HER-2 positive breast cancer after breast-conserving surgery. CA15-3, CCL20 and NK cells all have certain predictive value for recurrence after breast-conserving surgery for HER-2 positive breast cancer, and combined detection of the three indexes can improve their predictive efficacy.

Keywords: Breast cancer, human epidermal growth factor receptor 2 positive; Breast-conserving surgery; Carbohydrate antigen 15-3; C-C chemokine ligand 20; Natural killer cell; Breast cancer recurrence; Predictive value

乳腺癌发病率约占女性恶性肿瘤的18%，且呈逐年升高趋势，发病群体趋于年轻化[1-2]。原癌基因人类表皮生长因子受体2（human epidermal growth factor receptor 2，HER-2）阳性是乳腺癌的常见亚型，具有肿块大、淋巴结转移率高、组织学分级高、预后较差等特点[3-4]。对于早期及局部进展期HER-2阳性乳腺癌，临床通常行保乳手术，在去除病灶组织的同时最大程度保留患者的乳房体积[5]。然而，受多种因素影响，保乳术后患者仍存在一定的复发风险，导致不良预后[6]。故对于保乳手术患者术后仍有必要采取有效的防治措施以降低其术后复发风险。明确影响HER-2阳性乳腺癌患者保乳术后复发的危险因素，早期预测其复发风险是指导临床及早采取有效防治措施的关键。糖类抗原15-3（cancer antigen 15-3，CA15-3）是一种在乳腺癌早期诊断、预后评估中具有重要价值的标志物，但该指标单独检测对乳腺癌术后复发的预测效能不够理想[7]。因此，需要探索新的预测价值的更高的指标。C-C基序趋化因子配体20（C-C motif chemokine ligand 20，CCL20）是趋化因子家族的重要成员之一，目前已被证实与乳腺癌的复发、转移等密切相关[8]。自然杀伤（natural killer，NK）细胞是天然免疫细胞，可分泌趋化因子和细胞因子，通过免疫清除、监视作用发挥抗肿瘤效果。有研究指出，NK细胞与乳腺癌的发生、发展密切相关，可作为乳腺癌患者的潜在预后评估指标[9]。本研究探讨CA15-3联合CCL20、NK细胞预测HER-2阳性乳腺癌保乳术后复发的效能，现报道如下。

1　对象与方法

1.1　研究对象　以2021年6月至2023年6月于济宁医学院附属日照市人民医院行保乳手术的HER-2阳性乳腺癌患者为研究对象。纳入标准：（1）符合《中国抗癌协会乳腺癌诊治指南与规范（2019年版）》[10]中HER-2阳性乳腺癌诊断标准；（2）年龄≥18岁；（3）均为首次确诊；（4）预计生存时间在6个月以上；（5）均行相同方案的保乳手术；（6）术后均常规检测CA15-3、CCL20、NK细胞水平；（7）一般资料完整；（8）患者或家属对研究知情。排除标准：（1）合并其他部位恶性肿瘤；（2）TNM分期非Ⅰ～Ⅱ期；（3）存在精神疾病；（4）拒绝接受随访或失访；（5）术前明确未转移。依据上述纳入及排除标准，本研究共纳入96例患者，依据6个月的随访结果将其分为复发组（n=21）及未复发组（n=75）。本研究经日照市人民医院医学伦理委员会审批（审批号：KYSQ054-2024）。

1.2　资料收集　采用医院自制的基本情况调查问卷，收集患者的年龄、肿瘤直径、月经情况、临床分期、组织学分级、肿瘤家族史、腋窝淋巴结转移等资料。

1.3　指标检测方法　患者术后次日采集其空腹静脉血约5 mL，以1 800 g离心10 min后收集上层清液，以电化学发光免疫分析法测定血清CA15-3水平，以酶联免疫吸附法测定血清CCL20水平，采用FACS Calibur型流式细胞分析仪（美国Becton Dickinson公司）测定NK细胞在外周血淋巴细胞中的百分比水平。

1.4　统计学方法　使用SPSS 22.0软件处理数据。符合正态分布的计量资料以$\bar{x}\pm s$表示，行t检验；计数资料以例（%）表示，行χ^2检验。以多因素logistic回归分析HER-2阳性乳腺癌保乳术后复发的危险因素；以MedCalc软件制作受试者工作特征（receiver operating characteristic，ROC）曲线，分析CA15-3、CCL20及NK细胞对HER-2阳性乳腺癌保乳术后复发的预测效能。P<0.05为差异有统计学意义。

2　结　果

2.1　HER-2阳性乳腺癌保乳术后复发的单因素分析　两组患者年龄、肿瘤直径、月经状态、临床分期、组织学分级、肿瘤家族史比较差异均无统计学意义

（P>0.05）。复发组的腋窝淋巴结转移率、血清CA15-3、CCL20水平及NK细胞水平均高于未复发组（P<0.05）。见表1。

2.2　HER-2阳性乳腺癌保乳术后复发的多因素分析　将单因素分析中差异有统计学意义的因素作为自变量，术后复发作为因变量，纳入多因素logistic回归分析，各变量赋值情况见表2。结果显示，腋窝淋巴结转移、CA15-3、CCL20、NK细胞水平升高是HER-2阳性乳腺癌保乳术后复发的独立危险因素（P<0.05）。见表3。

2.3　3项指标对HER-2阳性乳腺癌保乳术后复发的预测效能　ROC曲线分析结果显示，CA15-3、CCL20、NK细胞单独及3项联合预测HER-2阳性乳腺癌保乳术后复发的曲线下面积（area under the curve，AUC）分别为0.900、0.842、0.853、0.999。见表4和图1。

表1　HER-2阳性乳腺癌保乳术后复发的单因素分析［例(%)］

Tab.1　Univariate analysis of recurrence after breast-conserving surgery in HER-2 positive breast cancer　［case(%)］

因素	复发组（n=21）	未复发组（n=75）	χ^2/t值	P值
年龄				
≥35岁	15(71.43)	58(77.33)	0.314	0.575
<35岁	6(28.57)	17(22.67)		
月经状态				
绝经	9(42.86)	31(41.33)	0.016	0.900
未绝经	12(57.14)	44(58.67)		
肿瘤直径				
>2.0 cm	16(76.19)	64(85.33)	0.987	0.320
≤2.0 cm	5(23.81)	11(14.67)		
临床分期				
Ⅰ期	6(28.57)	26(34.67)	0.274	0.600
Ⅱ期	15(71.43)	49(65.33)		
腋窝淋巴结转移	12(57.14)	18(24.00)	8.388	0.004
组织学分级				
1级	2(9.52)	12(16.00)		
2级	8(38.10)	35(46.67)	1.655	0.437
3级	11(52.38)	28(37.33)		
肿瘤家族史	11(52.38)	34(45.33)	0.327	0.567
CA15-3(U/mL，$\bar{x}\pm s$)	56.55±15.49	33.46±9.38	8.526	<0.001
CCL20(pg/mL，$\bar{x}\pm s$)	110.42±24.73	80.69±15.66	6.698	<0.001
NK细胞(%，$\bar{x}\pm s$)	22.36±3.65	16.87±3.74	5.976	<0.001

表2　各变量赋值表

Tab.2　Assignment table of each variable

因素	变量名	赋值
术后复发	Y	0=否，1=是
腋窝淋巴结转移	X1	0=否，1=是
CA15-3	X2	原值代入
CCL20	X3	原值代入
NK细胞	X4	原值代入

表3　HER-2阳性乳腺癌保乳术后复发的多因素分析

Tab.3　Multivariate analysis of recurrence after breast-conserving surgery in HER-2 positive breast cancer patients

因素	β	SE	Wald χ^2	P值	OR值	95%CI
腋窝淋巴结转移	0.949	0.324	8.579	<0.001	2.583	1.369~4.875
CA15-3	0.984	0.231	18.145	<0.001	2.675	1.701~4.207
CCL20	0.854	0.407	4.403	0.009	2.349	1.058~5.216
NK细胞	0.783	0.312	3.240	0.012	2.188	1.188~4.031

表4　3项指标对HER-2阳性乳腺癌保乳术后复发的预测效能

Tab.4　Predictive efficacy of three indexes for recurrence in HER-2-positive breast cancer patients after breast-conserving surgery

变量	AUC	95%CI 下限	95%CI 上限	截断值	灵敏度（%）	特异度（%）	SE	P值
CA15-3	0.900	0.822	0.952	43.9 U/mL	85.33	85.71	0.048	<0.001
CCL20	0.842	0.754	0.909	99.0 pg/mL	89.33	61.90	0.048	<0.001
NK细胞	0.853	0.766	0.917	19.9%	80.00	80.95	0.048	<0.001
联合评估	0.999	0.960	1.000		97.33	100.00	0.016	<0.001

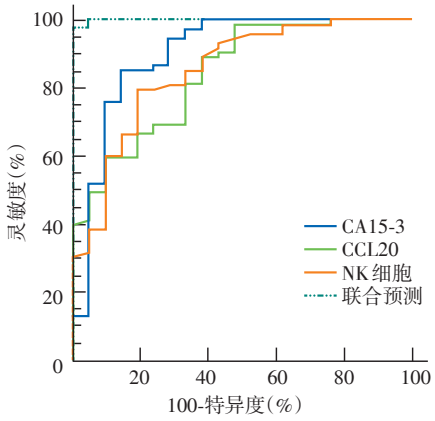

图1　3项指标联合预测HER-2阳性乳腺癌保乳术后复发的ROC曲线图

Fig.1　ROC curve of the combined prediction of 3 indicators for recurrence after breast-conserving surgery in HER-2 positive breast cancer patients

3　讨　论

保乳手术是早期HER-2阳性乳腺癌患者的标准治疗方式之一，但因HER-2阳性乳腺癌的肿瘤侵袭性较强，预后较差，保乳术后的复发率较高[11]。故早期准确预测HER-2阳性乳腺癌保乳术后的复发风险仍是临床研究的热点。常规血清标志物，如CA15-3等对其术后复发、转移等具有重要的预测价值，但此类指标的特异度较差，在其他生理、病理条件下也可能升高[12]。故临床常联合其他指标以提高预测价值。

CCL20是一种趋化因子，主要参与肿瘤细胞增殖、转移等过程，与乳腺癌、肝癌等多种恶性肿瘤的复发、转移密切相关[13]。有研究证实，CCL20与三阴性乳腺

癌患者的术后复发风险密切相关[14]。NK 细胞在机体的免疫反应过程中发挥着重要的作用，其数量及活性改变与肿瘤的发生、发展密切相关[15]。李玥婷等[16]研究显示，NK 细胞水平升高与乳腺癌术后复发有一定关系，提示其可作为乳腺癌术后复发的预测指标。

经单因素及 logistic 多因素分析结果显示，腋窝淋巴结转移、术后血清 CA15-3、CCL20 及 NK 细胞水平升高是 HER-2 阳性乳腺癌患者保乳术后复发的独立危险因素。研究显示，腋窝淋巴结转移是乳腺癌患者保乳术后复发的独立危险因素[17]，本研究结果与之相似，淋巴结是肿瘤细胞从原发部位向其他部位扩散的主要途径，故腋窝淋巴结转移者术后肿瘤复发的风险也增加；此外，淋巴结转移伴有淋巴管侵犯或淋巴结包膜外侵犯也会增加术后复发的可能性[18]。CA15-3 是一种与乳腺癌密切相关的肿瘤标志物，其水平升高通常与乳腺癌的进展或复发相关。CCL20 能吸引和激活与肿瘤进展和转移有关的白细胞亚群，其水平升高可能促进肿瘤细胞的迁移和侵袭，从而增加术后复发的风险。而 NK 细胞水平的升高反映了免疫系统的激活和抗肿瘤反应的增强，也可能反映机体免疫逃逸机制的存在，使得肿瘤细胞能够逃避免疫系统的攻击，从而增加复发的风险。罗洁等[19]研究证实，CCL20 的过表达可增加保乳术后局部复发的风险。马苗苗等[9]研究发现，NK 细胞阳性表达率较高的乳腺癌患者预后较差。本研究进一步分析 CA15-3、CCL20、NK 细胞对 HER-2 阳性乳腺癌患者保乳术后复发的预测价值，ROC 曲线显示当 CA15-3 最佳截断值为 43.9 U/mL，CCL20 最佳截断值为 99.0 pg/mL，NK 细胞最佳截断值为 19.9%时，三者联合预测 HER-2 阳性乳腺癌保乳术后复发的 AUC 为 0.999，灵敏度为 97.33%，特异度为 100.00%，显著优于单指标的预测价值，说明 CA15-3 联合 CCL20 及 NK 细胞可提升对 HER-2 阳性乳腺癌保乳术后复发的预测效能。

综上所述，腋窝淋巴结转移、血清 CA15-3、CCL20、NK 细胞水平升高是 HER-2 阳性乳腺癌患者保乳术后复发的独立危险因素，联合检测可提高对 HER-2 阳性乳腺癌患者保乳术后复发的预测价值。

利益冲突　无

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