



# The expression and clinical significance of signal transducer and activator of transcription 3, tumor necrosis factor $\alpha$ induced protein 8-like 2, and runt-related transcription factor 1 in breast cancer patients

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**Background:** This study explored the expression and clinical significance of signal transducer and activator of transcription 3 (STAT3), tumor necrosis factor  $\alpha$  induced protein 8-like 2 (TIPE2), and runt-related transcription factor 1 (RUNX1) in breast cancer tissue.

**Methods:** From October 2014 to October 2017, 68 breast cancer patients (68 breast cancer tissue specimens) who underwent a radical mastectomy in our hospital were set as the observation group and the corresponding normal tissue 3 cm away from the cancer tissue was selected as the control group. The expression levels of STAT3, TIPE2, and RUNX1 in the two groups were compared via immunohistochemical staining. Multiple logistic regression was then used to analyze the related risk factors affecting the 2-year prognosis of breast cancer patients. The receiver operating characteristic (ROC) curve was then plotted and the area under the ROC curve was calculated. The predictive values of STAT3, TIPE2, and RUNX1, and the predictive value of the three transcription factors combined on the 2-year prognostic survival of breast cancer patients were determined.

**Results:** (I) In the observation group, the positive expression of STAT3 and the negative expression of TIPE2 and RUNX1 were significantly higher than those in the control group ( $P < 0.05$ ). (II) Of the 68 patients, 51 survived within 2 years and 17 patients died. Positive STAT3 expression, negative TIPE2 expression, negative RUNX1 expression, poor histological differentiation, TNM stage III–IV, and distant metastasis were all identified as factors that can affect the 2-year prognosis of breast cancer patients ( $P < 0.05$ ). (III) The ROC curve analysis examining the 2-year prognostic survival of breast cancer patients showed that the area under the curve achieved the largest value when the predictive values of STAT3, TIPE2, RUNX1 were combined.

**Conclusions:** The levels of STAT3, TIPE2, and RUNX1 expression in breast cancer tissues were significantly different from that in adjacent normal tissues. This suggested that the combined detection of STAT3, TIPE2, and RUNX1 may improve the rate of early breast cancer diagnosis. Furthermore, STAT3, TIPE2, and RUNX1 may be useful in evaluating the prognosis of the patients with breast cancer.

**Keywords:** Signal transducer and activator of transcription 3 (STAT3); tumor necrosis factor  $\alpha$  induced protein 8-like 2 (TIPE2); runt-related transcription factor 1 (RUNX1); breast cancer

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## Introduction

Breast cancer is the most common of all female malignant tumors, and the incidence has been rising in recent years. At present, there are many treatments for breast cancer, including radiotherapy, chemotherapy, surgical resection, and combined treatment with Chinese and Western medicine, all of which can have certain therapeutic effects. However, due to the low rates of early breast cancer diagnosis, the prognosis of most patients is not ideal. Therefore, in-depth research on the mechanisms, diagnosis, and treatment of breast cancer is of great significance for improving the prognosis of patients and their overall survival.

Signal transducer and activator of transcription 3 (STAT3) is a bifunctional protein that exists in the cytoplasm and is coupled to the tyrosine phosphorylation signaling pathway which is involved in cell proliferation, apoptosis, and other processes (1). Research shows that STAT3 can be used as a potential therapeutic target for triple-negative breast cancer (2). miR-634 is able to regulate STAT3 and enhance the sensitivity of breast cancer cells to radiation (3). miR-124 reverses the doxorubicin resistance of breast cancer stem cells through STAT3/HIF-1 signaling pathways (4). Tumor necrosis factor  $\alpha$  induced protein 8-like 2 (TIPE2) is a recently discovered inflammatory regulator (5,6) that has a low level of expression in patients with malignant tumors such as colon cancer and thyroid cancer. However, the relationship between TIPE2 and breast cancer is unclear. Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) induces TIPE2 inhibits proliferation and tumorigenesis in breast cancer cells (7). TIPE2 suppresses breast cancer tumorigenesis, growth and metastasis possibly via regulation of the AKT and p38 signaling pathways (8). TIPE2 inhibits breast cancer development and metastasis possibly via promoting CD8<sup>+</sup> T and NK cell-mediated antitumor immune responses (9). Runt-related transcription factor 1, (RUNX1) is located on chromosome 21p22 and contains 9 exons. It has been reported to be closely related to the occurrence of malignant tumors (10). The novel interplay between YAP, RUNX1 and RUNX3 and its significance in breast cancer progression can serve as a prognostic tool to predict cancer recurrence (11). miR-378-mediated suppression of Runx1 alleviates the aggressive phenotype of triple-negative MDA-MB-231 human breast cancer cells (12). In this study, the

expression levels, as well as the clinical significance of STAT3, TIPE2, and RUNX1 in breast cancer tissues, were explored. We present the following article in accordance with the STARD reporting checklist (available at <http://dx.doi.org/10.21037/gs-21-108>).

## Methods

### General information

Breast cancer patients who underwent radical mastectomy for breast cancer in our hospital from October 2014 to October 2017 were enrolled in this study. This study was approved by the Sichuan Provincial People's Hospital (East Hospital), University of Electronic Science and Technology of China (No. 20180529). All patients agreed to participate in this study and signed an informed consent form. The research complies with the requirements of the Declaration of Helsinki (as revised in 2013). The following inclusion criteria were applied: (I) patients were diagnosed with breast cancer by pathological examination combined with in-hospital laboratory examination (13); (II) the clinical data and imaging data were complete; and (III) patients showed good treatment compliance and could cooperate with medical staff to complete the follow-up. The following patients were excluded from the study: (I) patients with other malignant tumors; (II) patients with cognitive impairment; and (III) patients who had been administered drugs that can affect the levels of STAT3, TIPE2, and RUNX1 prior to the start of the study. According to the inclusion and exclusion criteria, the study eventually included 68 patients (68 breast cancer tissue specimens) as the observation group, and the corresponding normal healthy tissue 3 cm away from the cancer tissue was selected as the control group.

### Study method

#### Measurement of STAT3, TIPE2, RUNX1 levels

Immunohistochemical staining was used to determine the expression levels of STAT3, TIPE2, and RUNX1 following standard protocols. Specifically, specimens were embedded in paraffin blocks and 4  $\mu$ m thick sections were baked in a constant temperature box at 75 °C for over 6 hours.

Specimens were removed and allowed to cool naturally before dewaxing using xylene and an ethanol gradient (100%, 90%, and 75%). Hydrogen peroxide solution (3%) was then used to eliminate the endogenous peroxidase activity. After dewaxing, the specimens were placed in sodium citrate buffer for heat repair (15 minutes), and following natural cooling, a goat serum blocking solution was added dropwise in the wet box to prevent non-specific binding. After settling for 20 minutes, the rabbit anti-human TIPE2 polyclonal antibody (1:400), rabbit anti-human RUNX1 monoclonal antibody (1:400), and rabbit anti-human STAT3 monoclonal antibody (1:400) were added dropwise. A phosphate buffered saline (PBS) solution was used for the negative control. The specimens were then placed in a 4 °C incubator overnight. Thereafter, the specimens were re-warmed, washed with PBS, and a biotin-labeled goat anti-rabbit IgG and horseradish enzyme-labeled streptavidin were added dropwise. After incubating for 20 minutes at room temperature, a diaminobenzidine color solution was added. Samples were then rinsed with tap water and counterstained with hematoxylin, before dehydration and sealing with neutral resin. The rabbit anti-human TIPE2 polyclonal antibody, rabbit anti-human STAT3 monoclonal antibody, and rabbit anti-human RUNX1 monoclonal antibody were all purchased from Abcam, UK.

### Western blot analysis

The protein was extracted respectively. After quantitative analysis by BCA method, the sample buffer was added. After protein boiling, the sample was loaded and electrophoresis was carried out. The protein expression levels of STAT3, TIPE2, RUNX1 were detected, and the gray value of the item was analyzed by image studio software. The ratio of the gray value of the target protein band to the gray value of the internal reference band was used as the expression amount of the target protein, each group repeated three times, and the follow-up statistical analysis was carried out.

### Judgment criteria

A total of 5 fields of view were randomly chosen and observed by 3 pathologists under an optical microscope. Each field contained at least 100 intact tumor cells. The determination criteria for positive STAT3, TIPE2, RUNX1 staining (14) were based on the proportion of positive cells in the tissue cells and the degree of staining. Specifically, the scoring system for the proportion of positive cells was as follows: 0 points for  $\leq 5\%$ , 1 point for  $>5-25\%$ , 2 points for  $>25-50\%$ , 3 points for  $>50-75\%$ , and 4 points for  $>75\%$ .

The scoring system for the staining intensity was as follows: 0 points for undyed, 1 point for light yellow, 2 points for brown, and 3 points for tan. Staining index = proportion of positive cells score + staining intensity score. A staining index  $>3$  was classified as high expression and a staining index  $\leq 3$  was classified as low expression.

### Follow-up results

The follow-up period of this study was 2 years. Follow-up commenced after the patient underwent a radical mastectomy and ended with the conclusion of this study (October 2019) or death of the patient. The follow-up time ranged from 7 to 24 months, with an average follow-up time of  $15.11 \pm 2.87$  months. Follow-up methods included a visit to the hospital for review or telephone consultation.

### Statistical analysis

SPSS22.0 software was used for statistical analysis. Measurement data were presented as mean  $\pm$  standard deviation ( $\bar{x} \pm S$ ) and analyzed using the *t*-test. Count data were expressed as n (%), and assessed using the  $\chi^2$  test. Multivariate logistic regression analysis was used to assess the related risk factors affecting the 2-year prognosis of breast cancer patients. The receiver operating characteristic (ROC) curve was plotted and the area under the ROC curve was calculated. The predictive value of STAT3, TIPE2, RUNX1, and the combined value of the three factors on the 2-year prognostic survival of breast cancer patients was analyzed. The difference was considered statistically significant when  $P < 0.05$ .

## Results

### *A comparison of STAT3, TIPE2, and RUNX1 expression levels in breast cancer tissue and healthy tissue*

Expression of STAT3 was significantly higher in the observation group compared to the control group. In contrast, the expression of TIPE2 and RUNX1 was significantly lower in the observation group compared to control group ( $P < 0.05$ ) as shown in *Table 1* and *Figures 1,2*.

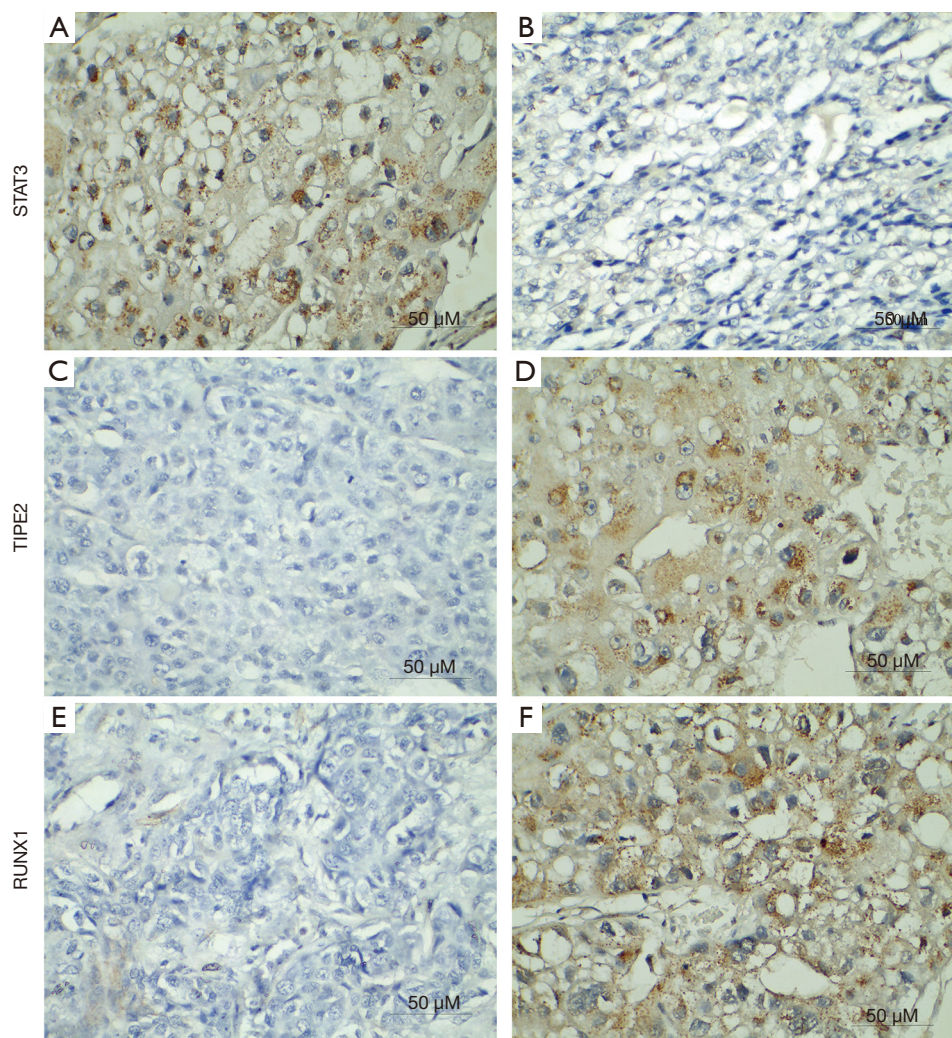
### *Univariate analysis of the 2-year survival of breast cancer patients*

Of the 68 patients, 51 survived within the 2-year follow-

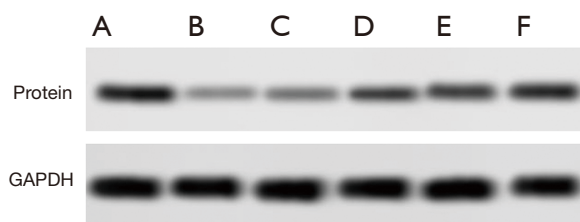
**Table 1** A comparison of STAT3, TIPE2 and RUNX1 levels in the two groups [n (%)]

Groups	STAT3		TIPE2		RUNX1	
	Positive rate	Negative rate	Positive rate	Negative rate	Positive rate	Negative rate
Observation group (n=68)	42 (61.76)	26 (38.24)	22 (32.35)	46 (67.65)	19 (27.94)	49 (72.06)
Control group (n=68)	8 (11.76)	60 (88.24)	45 (66.18)	23 (33.82)	55 (80.88)	13 (19.12)
$\chi^2$	36.562		15.562		38.417	
P	<0.001		<0.001		<0.001	

STAT3, signal transducer and activator of transcription 3; TIPE2, tumor necrosis factor  $\alpha$  induced protein 8-like 2; RUNX1, runt-related transcription factor 1.



**Figure 1** Immunohistochemical staining of STAT3, TIPE2, RUNX1 in breast cancer tissue ( $\times 500$  magnification). (A) Positive expression of STAT3 in breast cancer tissue; (B) negative expression of STAT3 in healthy tissue; (C) positive expression of TIPE2 in breast cancer tissue; (D) negative expression of TIPE2 in healthy tissue; (E) positive expression of RUNX1 in breast cancer tissue; (F) negative expression of RUNX1 in healthy tissue. Brown indicates positive protein expression. STAT3, signal transducer and activator of transcription 3; TIPE2, tumor necrosis factor  $\alpha$  induced protein 8-like 2; RUNX1, runt-related transcription factor 1.



**Figure 2** Western blot of STAT3, TIPE2, RUNX1 in breast cancer tissue. (A) Positive expression of STAT3 in breast cancer tissue; (B) negative expression of STAT3 in healthy tissue; (C) positive expression of TIPE2 in breast cancer tissue; (D) negative expression of TIPE2 in healthy tissue; (E) positive expression of RUNX1 in breast cancer tissue; (F) negative expression of RUNX1 in healthy tissue.

up period. However, 17 patients died. Univariate analysis demonstrated that age, tumor diameter, and histological type did not affect the 2-year prognosis and survival of breast cancer patients ( $P > 0.05$ ). In contrast, positive STAT3 expression, negative TIPE2 expression, negative RUNX1 expression, poor histological differentiation, TNM stage III–IV, and distant metastasis were all factors that affected the 2-year prognosis and survival of breast cancer patients ( $P < 0.05$ ) as shown in *Table 2*.

#### ***Multivariate analysis of the 2-year prognosis and survival of breast cancer patients***

Multivariate analyses revealed that positive STAT3 expression, negative TIPE2 expression, negative RUNX1 expression, poor histological differentiation, TNM stage III–IV, and distant metastasis were all independent risk factors that can affect the 2-year prognosis of breast cancer patients ( $P < 0.05$ ; *Table 3*).

#### ***The predictive value of STAT3, TIPE2, and RUNX1 status, and the combined value of the three factors in the 2-year prognostic survival of breast cancer patients***

The ROC curve was used to analyze the predictive value of STAT3, TIPE2, and RUNX1 levels, and the combined detection of the three factors on the 2-year prognostic survival of breast cancer patients. The area under the curve of STAT3, TIPE2, and RUNX1 expression, as well as the combination of the 3 factors were 0.806, 0.760, 0.688, and 0.910, respectively. The area under the curve achieved the largest value when all 3 proteins were combined as showed

in *Table 4* and *Figure 3*.

## **Discussion**

The biogenesis and development of breast cancer are associated with changes in multiple genes, including the activation of oncogenes and the loss of tumor suppressor gene function, which result in unregulated cell proliferation, differentiation, and inhibition of apoptosis (15–18). Current clinical efforts are devoted to identifying highly-specific breast cancer-related genes. The combined detection of multiple breast cancer-related genes may lead to improved rates of early breast cancer diagnosis, targeted therapy, and prognostic risk assessment, all of which have important clinical significance for the prognosis of patients with breast cancer.

STAT3 is an important gene involved in the self-renewal of human embryonic stem cells, and it is mostly expressed in epithelial malignant tumors (19). Studies have shown that STAT3 can promote tumor cell proliferation and metastasis, and inhibit anti-tumor immune responses (20), all of which are closely related to the prognosis of tumor patients. The results of this current study demonstrated that the expression of STAT3 and TIPE2 in breast cancer tissues are quite different. The positive rate of STAT3 expression was significantly higher than that of adjacent normal tissues, while the positive rate of TIPE2 expression was significantly lower than that of adjacent normal tissues. This is consistent with previous reports (21) and suggested that these two proteins may be important indicators for the early detection of breast cancer. Studies have also shown that upregulation of STAT3 expression can promote the proliferation of cancer stem cells and inhibit their differentiation (22,23). IL-6/STAT3 signaling hijacks estrogen receptor  $\alpha$  enhancers to drive breast cancer metastasis (24). Inhibition of STAT3 signaling pathway by natural product pectolarigenin attenuates breast cancer metastasis (25). Not surprisingly, the results of our study also revealed that higher rates of positive STAT3 expression were associated with poorer prognosis of the patient. Therefore, these results suggested that inhibiting the expression of STAT3 may effectively prevent the proliferation and differentiation of tumor cells, thereby improving the prognosis of patients.

In recent years, the relationship between TIPE2 protein expression and early malignant tumor cell proliferation has gradually attracted attention. Some studies reported that in the process of early malignant tumor cell proliferation, TIPE2 plays a role in reducing inflammation (26). Tumor

**Table 2** Univariate analysis of the two-year prognosis and survival of breast cancer patients

Clinical features	Cases (n=68)	2-year prognosis		$\chi^2$ value	P value
		Survived (n=51)	Deceased (n=17)		
STAT3					
Positive	42	27	15	5.522	0.019
Negative	26	24	2		
TIPE2					
Positive	22	20	2	4.390	0.036
Negative	46	31	15		
RUNX1					
Positive	19	19	0	8.798	0.003
Negative	49	32	17		
Age (year)					
<60	39	29	10	0.020	0.887
≥60	29	22	7		
Tumor diameter (cm)					
<3	41	29	12	1.003	0.317
≥3	27	22	5		
Degree of histological differentiation					
Poorly differentiated	22	10	12	15.141	<0.001
Moderate to well-differentiated	46	41	5		
TNM stage					
I-II stage	35	31	4	7.085	0.008
III-IV stage	33	20	13		
Distant metastasis					
Yes	38	25	13	3.897	0.048
None	30	26	4		
Histological type					
Papillary adenocarcinoma	37	26	11	3.836	0.050
Tubular adenocarcinoma	21	18	3		
Mucinous adenocarcinoma	10	7	3		

STAT3, signal transducer and activator of transcription 3; TIPE2, tumor necrosis factor  $\alpha$  induced protein 8-like 2; RUNX1, runt-related transcription factor 1.

necrosis factor- $\alpha$  (TNF- $\alpha$ ) induces TIPE2 inhibits proliferation and tumorigenesis in breast cancer cells (7). TIPE2 suppresses breast cancer tumorigenesis, growth and metastasis possibly via regulation of the AKT and p38 signaling pathways (8). TIPE2 inhibits breast cancer

development and metastasis possibly via promoting CD8+ T and NK cell-mediated antitumor immune responses (9). This current study demonstrated that low expression of TIPE2 is an independent risk factor for the 2-year prognosis of survival in breast cancer patients. The decrease

**Table 3** Multivariate analysis of the factors affecting the 2-year prognosis and survival of breast cancer patients

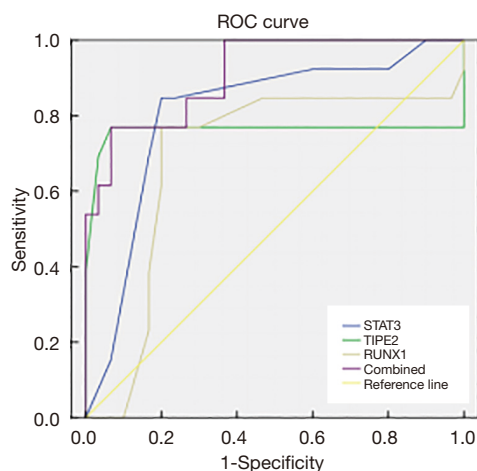
Factors	Regression coefficients	Standard error	Wald $\chi^2$	P	RR (95% CI)
STAT3 positive (control group: negative)	1.812	0.711	7.561	0.032	6.123 (1.519–24.669)
TIPE2 negative (control group: positive)	1.714	0.754	10.547	0.003	5.551 (1.266–24.333)
RUNX1 negative (control group: positive)	1.354	0.359	8.864	0.018	3.873 (1.916–7.827)
Histological differentiation: poorly differentiated (control group: moderate to well differentiated)	1.742	0.559	10.512	0.009	5.709 (1.909–17.075)
TNM stage: III–IV stage (control group: I–II stage)	1.891	0.571	8.162	0.021	6.626 (2.164–20.291)
Distant metastasis (control group: none)	1.678	0.462	11.285	0.001	5.355 (2.165–13.244)

RR, relative risk; CI, confidence interval; STAT3, signal transducer and activator of transcription 3; TIPE2, tumor necrosis factor  $\alpha$  induced protein 8-like 2; RUNX1, runt-related transcription factor 1.

**Table 4** The predictive value of STAT3, TIPE2, and RUNX1, and the combined detection of all three proteins in the 2-year prognostic survival of breast cancer patients

Predictor	Optimal threshold	Sensitivity	Specificity	ROC area under the curve	95% CI
STAT3	25.79	0.889	0.828	0.806	0.658–0.955
TIPE2	26.09	0.873	0.791	0.760	0.533–0.987
RUNX1	26.14	0.825	0.784	0.688	0.494–0.883
Combined	26.33	0.898	0.859	0.910	0.000–1.000
Predictive index model	1.564	0.756	0.780	0.895	0.734–0.994

STAT3, signal transducer and activator of transcription 3; TIPE2, tumor necrosis factor  $\alpha$  induced protein 8-like 2; RUNX1, runt-related transcription factor 1; ROC, receiver operating characteristic; CI, confidence interval.



**Figure 3** The predictive value of STAT3, TIPE2, RUNX1 and the combined detection of the three proteins in the 2-year prognostic survival of breast cancer patients. ROC, receiver operating characteristic; STAT3, signal transducer and activator of transcription 3; TIPE2, tumor necrosis factor  $\alpha$  induced protein 8-like 2; RUNX1, runt-related transcription factor 1.

in TIPE2 protein expression can be related to the decreased infiltration ability of cancer cells, the decreased ability to break through the basement membrane, or the decreased ability of lymph node adhesion. The absence or decrease of TIPE2 expression in breast cancer tissue may play an important role in breast cancer development.

RUNX1 can either activate or inhibit related genes or signaling pathways in different solid malignant tumors, and thus it can play either a carcinogenic or tumor suppressor role. Indeed, RUNX1 has been shown to be carcinogenesis or tumor suppressive in different hematological tumors (27). Rada *et al.* (28) reported that RUNX1 had a high rate of positive expression in epithelial tumors such as ovarian cancer, and head and neck squamous cell carcinomas, and thus it functions as an oncogene. In contrast, Bustos *et al.* (29) demonstrated that RUNX1 was expressed at low levels in breast and colorectal cancer tissues, and thus may act as a tumor suppressor gene. By comparing the expression of RUNX1 in breast cancer tissues and the adjacent normal

tissues, our study found that the expression of RUNX1 in breast cancer tissues was significantly lower than that in adjacent normal tissues, further confirming the tumor suppressor role of RUNX1 in breast cancer. In addition, patients with lower expression of RUNX1 had a significantly higher prognostic probability of death at 2 years after surgery compared to patients with higher expression of RUNX1. This suggested that RUNX1 has a significant role in the prognosis of breast cancer patients. The mechanisms of RUNX1 in apoptosis and tumorigenesis are complicated, and are yet to be fully elucidated (30).

RUNX1 may repress ts-112 to prevent overactive proliferation in breast epithelial cells to augment its established roles in maintaining the mammary epithelium (31). Future follow-up studies should conduct in-depth research on the specific molecular mechanisms of RUNX1 in the apoptosis and drug resistance of breast cancer cells. This will provide novel insights for the clinical implementation of targeted therapy for breast cancer patients. The ROC curve analysis examining the 2-year prognostic survival of breast cancer patients showed that the area under the curve achieved the largest value when the predictive values of STAT3, TIPE2, and RUNX1 were combined. This suggested that the combined detection of these three genes may be an effective prognostic marker for breast cancer patients following surgery.

In summary, the expression levels of STAT3, TIPE2, RUNX1 in breast cancer tissues is significantly different from that in adjacent normal tissues, and the combined detection of STAT3, TIPE2, and RUNX1 may improve the rate of early breast cancer diagnosis and prognosis. This in turn will facilitate timely and specific treatments so as to improve the overall survival of breast cancer patients.

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## Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at <http://dx.doi.org/10.21037/gs-21-108>

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uniform disclosure form (available at <http://dx.doi.org/10.21037/gs-21-108>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Sichuan Provincial People's Hospital (East Hospital), University of Electronic Science and Technology of China (No. 20180529). All patients agreed to participate in this study and signed an informed consent form. The research complies with the requirements of the Declaration of Helsinki (as revised in 2013).

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