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Expression features of TRPS1 in invasive carcinoma of no special type of the breast and its correlation with prognosis

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Abstract: **Objective** To investigate the expression characteristics of trichorhinophalangeal syndrome type 1 (TRPS1) in invasive breast carcinoma of no special type (IBC-NST) , and to analyze its correlation with clinicopathological parameters and prognosis. **Methods** A total of 122 patients diagnosed with IBC-NST at Tangshan Gongren Hospital from January 2021 to December 2023 were included as research subjects. Among them, 61 patients had normal breast tissues adjacent to the tumor margin ⩾2 cm were collected as controls. The expression status of TRPS1 protein in 122 tumor tissues and 61 adjacent tissues was detected using the immunohistochemical EnVision two-step method. Patients were divided into high expression group (⩾ 4 points) and low expression group (⩽3 points) based on the expression score of TRPS1 in immunohistochemisty. Clinical pathological data of the patients were collected simultaneously to analyze the correlation between TRPS1 expression levels and various clinical pathological characteristics. All patients were followed up for a period of 3 years, and the independent influencing factors affecting patient prognosis were explored using a multivariable Cox proportional hazards regression model. **Results** The positive expression rate of TRPS1 in IBC-NST tissues was 89.34% (109/122), which was significantly higher than that in adjacent non-tumor tissues (14.75%, 9/61) (χ^2= 98.789, P<0.01) . High expression of TRPS1 was significantly correlated with higher histological grading (P=0.002), advanced TNM staging III (P=0.013) , lymph node metastasis (P=0.017), and triple-negative breast cancer (TNBC) subtype (P=0.030). Multivariate Cox analysis revealed that TNM staging III (HR=3.215, 95% CI: 1.642- 6.298), lymph node metastasis (HR=2.547, 95%CI: 1.358-4.813) , and high expression of TRPS1 (HR=2.332, 95%CI: 1.205-4.514) were independent risk factors for disease progression during the 3-year follow-up period. **Conclusion** TRPS1 exhibits high expression characteristics in IBC-NST tissues, and its high expression is closely related to the malignant progression of the tumor and poor prognostic outcomes. It can be served as a potential independent biomarker for assessing the prognosis of IBC-NST patients.

Keywords: Breast cancer; Invasive breast carcinoma of no special type; Trichorhinophalangeal syndrome type 1; Immunohistochemistry; Clinicopathological parameters; Prognosis

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Invasive breast carcinoma of no special type (IBC-NST) is the most common pathological type of breast cancer, accounting for 70% to 80% of all breast cancer cases [1-2]. Its high heterogeneity is manifested by substantial differences in clinical manifestations, molecular characteristics, treatment response, and patient prognosis. Although the current molecular classification system based on estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 has greatly optimized the individualized treatment strategy for breast cancer, a subset of patients, especially those with triple-negative breast cancer (TNBC), still face the dilemmas of limited treatment options, high risk of recurrence and metastasis, and poor prognosis [3]. Therefore, exploring novel breast cancer biomarkers with high sensitivity and specificity is of crucial importance for deepening the understanding of the biological behavior of breast cancer, developing new therapeutic targets, and conducting accurate prognostic assessment. The trichorhinophalangeal syndrome type 1 (*TRPS*1) gene encodes a zinc finger transcription factor belonging to the GATA family, which is named for its association with TRPS caused by gene deletion [4]. In recent years, multiple studies have found that TRPS1 plays an important role in breast cancer. TRPS1 is a highly specific marker for breast epithelial cell lines and breast cancer. Its expression level is significantly upregulated in breast cancer, and it maintains a high expression rate and specificity across all molecular subtypes including TNBC, with performance even superior to that of traditional markers such as GATA3[5-6]. TRPS1 participates in maintaining the proliferation, differentiation, and survival of breast cancer cells by regulating a variety of downstream signaling pathways, and its function involves key biological processes such as epithelial-mesenchymal transition (EMT) [7]. However, there is still a lack of systematic clinical research on the expression characteristics of TRPS1 in IBC-NST of the breast in the Chinese population, especially on its correlation with detailed clinicopathological parameters and prognosis. In this study, we detected the expression of TRPS1 in 122 cases of breast IBC-NST and adjacent non-tumor tissues using immunohistochemistry, systematically analyzed the association between its expression status and various clinicopathological parameters of patients, and further explored the potential clinical value of TRPS1 as a prognostic assessment indicator based on 3-year follow-up data, aiming to provide a new theoretical basis for the individualized diagnosis and treatment of this type of breast cancer.

1 Materials and Methods

1.1 General information

A total of 122 patients diagnosed with IBC-NST in Tangshan Gongren Hospital from January 2021 to December 2022 were enrolled in this study. Among them, adjacent normal breast tissue samples at least 2 cm away from the tumor margin were collected simultaneously from 61 patients as controls.

Inclusion criteria: (1) Postoperative pathological diagnosis of IBC-NST was confirmed; (2) No neoadjuvant chemotherapy, radiotherapy, or endocrine therapy was received before surgery; (3) Complete clinicopathological data were available; (4) Complete follow-up records were available.

Exclusion criteria: (1) Patients complicated with other malignant tumors; (2) Patients who died during surgery or within 30 days after surgery.

This study was approved by the Ethics Committee of Tangshan Gongren Hospital [Approval No. [2023] Lunshenyanlin (015)], and all patients have signed the informed consent form.

1.2 Research methods

1.2.1 Immunohistochemistry

All the 122 IBC-NST tissue specimens and 61 paired adjacent normal breast tissue specimens included in this study were fixed with 10% neutral buffered formalin and routinely embedded in paraffin. Serial sections with a thickness of 3 μm were prepared and attached to anti-drop glass slides for immunohistochemical staining. Immunohistochemical staining was performed using the Dako EnVision two-step method. The primary antibody was TRPS1 monoclonal antibody (clone number: EPR16171, Abcam, UK) with a dilution ratio of 1:200. The experimental procedures were strictly performed in accordance with the kit instructions, and positive and negative control groups were set up simultaneously. Phosphate buffered saline (PBS) was used instead of the primary antibody in the negative control group to ensure the specificity of staining results.

1.2.2 Result interpretation

The immune-positive signal of TRPS1 protein was localized in the nucleus, presenting as brown-yellow granules. Slide reading was independently performed by two senior pathologists, and assessment was conducted using a modified semi-quantitative scoring system: (1) Scoring for the proportion of positive cells: 0 point (<5%), 1 point (5%-25%), 2 points (26%-50%), 3 points (>50%); (2) Grading of staining intensity: 0 point (no staining), 1 point (weak staining), 2 points (moderate staining), 3 points (strong staining). The total score was calculated as the product of the positive cell proportion score and the staining intensity score. The specific criteria were as follows: a total score of 0-1 was defined as negative, 2-3 as weakly positive (+), 4-6 as moderately positive (++), and 7-9 as strongly positive (+++). Among them, negative and weakly positive cases were classified into the low expression group (score ≤3), while moderately positive and strongly positive cases were classified into the high expression group (score ≥4).

1.3 Clinicopathological data and follow-up

Clinicopathological parameters of the patients were comprehensively collected through the hospital electronic medical record system, including core indicators such as age, menopausal status, maximum tumor diameter, histological grade, TNM stage, lymph node metastasis status, immunohistochemical status of ER/PR/HER2, and Ki-67 proliferation index. The molecular classification was strictly carried out in accordance with the criteria of the 5th edition of WHO classification of tumours of the breast. Luminal subtype was defined as positive ER/PR and negative HER2. HER2 overexpression subtype was defined as positive HER2 and negative ER/PR; TNBC was defined as negative expression of ER, PR and HER2.

Regular postoperative follow-up was conducted via a combined mode of outpatient follow-up and telephone follow-up once every 3 months, with the follow-up cutoff date set as December 2023. The primary follow-up endpoint was disease-free survival (DFS), which was defined as the duration from the date of surgery to the date of the first disease progression event. Disease progression events included local recurrence of breast tumor, regional lymph node metastasis, distant metastasis, and all-cause death caused by breast cancer. For patients without the aforementioned events, follow-up was censored at the date of the last follow-up.

1.4 Statistical analysis

SPSS 19.0 software was used for data analysis. Categorical data were presented as cases (%), and the chi-square test was used for comparison between groups. The multivariate Cox proportional hazards regression model was applied to analyze independent factors affecting the prognosis of patients. All tests were two-sided, and a P value < 0.05 was considered statistically significant.

2 Results

2.1 Expression of TRPS1 in IBC-NST and adjacent tissues

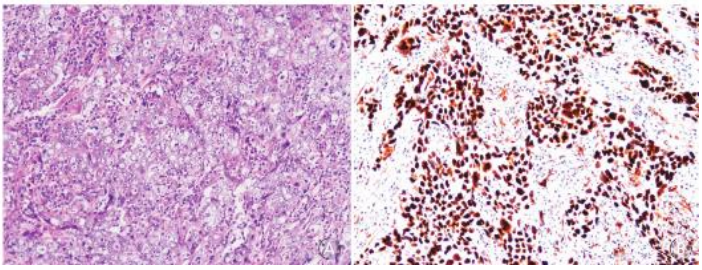
The positive staining of TRPS1 was mainly localized in the nuclei of tumor cells, presenting as brown-yellow or tan granules, and cytoplasmic staining was observed in a small number of cases (**Figure 1**). Among the 122 breast IBC-NST tissue samples, 109 cases showed positive TRPS1 expression, with an overall positive rate of 89.34%. Sixty five cases (53.28%) were classified as high expression (moderate to strong positive). In the 61 paired adjacent tissue samples, only 9 cases showed weakly positive expression, with an overall positive rate of 14.75%, and none of them exhibited moderate or strong positive staining. The overall positive rate and high expression rate of TRPS1 in IBC-NST tissues were significantly higher than those in adjacent tissues (P < 0.01), as shown in **Table 1**.

2.2 Correlation between TRPS1 expression and clinicopathological parameters

Patients were divided into the high expression group (n=65) and the low expression group (n=57) according to TRPS1 expression level. The proportions of cases with histological grade III, TNM stage III, lymph node metastasis, and TNBC subtype in the TRPS1 high expression group were significantly higher than those in the low expression group (P < 0.05), as shown in **Table 2**.

2.3 Multivariate Cox regression analysis of TRPS1 expression and patient prognosis

The median follow-up duration of the 122 enrolled cases was 36 months. During the follow-up period, a total of 35 patients experienced disease progression events, including local recurrence, regional lymph node metastasis, distant metastasis, and breast cancer-related death. Among these events, 11 cases (19.30%) occurred in the TRPS1 low expression group, and 24 cases (36.92%) occurred in the high expression group. To further evaluate whether TRPS1 serves as an independent prognostic factor for IBC-NST, variables with $P < 0.1$ in univariate analysis (including histological grade, TNM stage, lymph node metastasis status, molecular subtype, and TRPS1 expression level) and clinically widely recognized prognosis-related factors (tumor size) were jointly incorporated into the multivariate Cox proportional hazards regression model. The results showed that TNM stage III, presence of lymph node metastasis, and high TRPS1 expression were independent risk factors for disease progression in patients during the 3-year follow-up ($P < 0.05$), as shown in **Table 3**.



Note: A shows HE staining of IBC-NST (HE ×100); B shows the positive expression of TRPS1 protein detected by immunohistochemistry, which is localized in the nuclei of IBC-NST cells, presenting as brown-yellow granular staining (HE ×200).

Fig.1 Histopathological features of IBC-NST and expression of TRPS1 protein

Tab.1 Comparison of TRPS1 expression in breast NST tissue and adjacent non-tumor tissue [case(%)]

Group	Cases	Negative	Weakly positive (+)	Moderately positive (++)	Strongly positive (+++)	Total positive rate (%)	High expression rate (%)
NST tissue	122	13	44	39	26	89.34	53.28
Adjacent tissue	61	52	9	0	0	14.75	0
χ^2 value						98.789	50.403
***P* value**						<0.001	<0.001

Tab.2 Relationship between TRPS1 expression and clinicopathological parameters in patients with breast NST [case(%)]

Item		Low expression group (n=57)	High expression group (n=65)	χ^2 value	*P* value
Age (years)	<50	28（49.12）	35（53.85）	0.271	0.602
	≥50	29（50.88）	30（46.15）		
Menopausal status	No	32（56.14）	40（61.54）	0.366	0.545
	Yes	25（43.86）	25（38.46）		
Tumor size	≤2 cm	25（43.86）	23（35.38）	0.914	0.339
	>2 cm	32（56.14）	42（64.62）		
Histological grade	I-II	45（78.95）	34（52.31）	9.443	0.002
	III	12（21.05）	31（47.69）		
TNM stage	I-II	46（80.70）	39（60.00）	6.159	0.013
	III	11（19.30）	26（40.00）		
Lymph node metastasis	Absent	41（71.93）	33（50.77）	5.698	0.017
	Present	16（28.07）	32（49.23）		
ER status	Negative	14（24.56）	25（38.46）	2.698	0.100
	Positive	43（75.44）	40（61.54）		
PR status	Negative	18（31.58）	28（43.08）	1.709	0.191
	Positive	39（68.42）	37（56.92）		
HER2 status	Negative	51（89.47）	53（81.54）	1.520	0.218
	Positive	6（10.53）	12（18.46）		
Ki-67 index	<20%	22（38.60）	20（30.77）	0.824	0.364
	≥20%	35（61.40）	45（69.23）		
Molecular subtype	Luminal	43（75.44）	34（52.31）	7.039	0.030
	HER2+	6（10.53）	12（18.46）		
	TNBC	8（14.03）	19（29.23）		

Tab.3 Multivariate Cox regression analysis of factors affecting disease-free survival in patients with breast NST

Variable	*β*	*SE*	Wald χ^2	*P* value	*HR*（95%*CI*）
Tumor size (> 2 cm)	0.421	0.312	1.823	0.177	1.523(0.827-2.805)
Histological grade (III)	0.502	0.329	2.329	0.127	1.652(0.867-3.148)
TNM stage (stage III)	1.168	0.342	11.662	0.001	3.215(1.642-6.298)
Lymph node metastasis (present)	0.935	0.325	8.275	0.004	2.547(1.358-4.813)
Molecular subtype (TNBC)	0.467	0.381	1.503	0.220	1.595(0.756-3.365)
TRPS1(high expression)	0.847	0.338	6.284	0.012	2.332(1.205-4.514)

3 Discussion

3.1 Expression characteristics of TRPS1 as a novel biomarker for breast cancer

The results of this study showed that the positive rate of TRPS1 in IBC-NST tissues was as high as 89.34%, which is highly consistent with the conclusions of several recent studies. Ai *et al.* [8] analyzed more than 9,000 breast cancer samples and found that the expression rates of TRPS1 mRNA and protein in breast cancer were both over 90%, and its specificity was superior to GATA3, especially in TNBC. Similar high expression rates were also reported in the study by Li *et al.* [9]. This study further verified this phenomenon at the protein level. Its nuclear localization expression pattern is consistent with its biological function as a transcription factor. The characteristic that TRPS1 is extremely low or even not expressed in adjacent normal tissues makes it show great application potential in pathological diagnosis practice, especially in the traceability identification of metastatic cancer, and it is expected to become a reliable tool for distinguishing primary breast cancer from metastatic cancer.

3.2 Association between high TRPS1 expression and tumor invasiveness

Studies have found that high expression of TRPS1 is significantly positively correlated with multiple clinicopathological indicators suggesting strong tumor invasiveness. In this study, the proportion of grade III tumors in the high TRPS1 expression group was significantly higher than that in the low expression group, suggesting that TRPS1 may be involved in the regulation of cell dedifferentiation and abnormal proliferation. Similarly, the association between high TRPS1 expression and advanced TNM stage and lymph node metastasis suggests that it may promote local invasion and metastasis of tumors. This is consistent with the results of basic research on TRPS1. Existing studies have shown that TRPS1 transcriptionally regulates a series of downstream target genes, such as the miR-221/222 cluster, and inhibits their expression, thereby relieving the inhibition of downstream signaling pathways [such as phosphatase and tensin homolog/protein kinase B (PTEN/AKT)], and ultimately promoting the proliferation, migration and invasion of tumor cells [10-12]. In addition, TRPS1 can also participate in the regulation of EMT by regulating transcription factors such as zinc finger E-box binding homeobox 2 (ZEB2), which is an important mechanism for tumor cells to acquire migration and invasion capabilities [13]. High TRPS1 expression is significantly correlated with the TNBC subtype. TNBC has become a difficult point in breast cancer treatment due to the lack of therapeutic targets, strong invasiveness and poor prognosis. In this study, nearly 30% of the cases with high TRPS1 expression were TNBC, and among TNBC patients, the proportion of high TRPS1 expression was also as high as 70.37%. This finding has dual significance. In terms of diagnosis, the high sensitivity and specificity of TRPS1 make it a powerful tool for auxiliary diagnosis and differential diagnosis of TNBC, making up for the deficiency of GATA3 expression loss in some TNBC [14-15].

3.3 Value of TRPS1 as an independent prognostic factor

Prognostic evaluation is an important part of the clinical management of breast cancer. In this study, through multivariate Cox regression analysis, after excluding the interference of traditional strong prognostic factors such as TNM stage and lymph node status, it was found that high TRPS1 expression was still an independent risk factor affecting the 3-year disease progression of IBC-NST patients. It is suggested that among patients with similar clinicopathological characteristics, the risk of disease recurrence or metastasis in patients with high TRPS1 expression is more than 2.3 times that of patients with low expression. The mechanism may lie in the persistence of the core oncogenic function of TRPS1. By promoting proliferation, invasion and EMT, TRPS1 may affect tumor stem cell characteristics or treatment resistance, ultimately leading to a higher risk of recurrence and metastasis [16-17]. This study provides clinical evidence from the Chinese population for the prognostic value of TRPS1, which is mutually confirmed by the conclusion reported by Ai *et al.* [8] that high TRPS1 expression is associated with shorter overall survival and disease-free survival. Therefore, in clinical practice, for breast cancer with high TRPS1 expression, especially those with early stage and no lymph node metastasis, follow-up should be strengthened, and adjuvant therapy should be actively applied to improve the survival of patients.

3.4 Limitations and prospects of the study

This study has the following limitations: First, this study is a single-center retrospective cohort study with a small sample size, and there is a risk of selection bias; second, the follow-up duration is only 3 years, and the impact of TRPS1 on long-term survival has not been evaluated; finally, only correlation analysis was carried out at the protein expression level, and the specific molecular mechanism of TRPS1 regulating breast cancer progression has not been deeply explored. In the future, multicenter large-sample prospective studies can be carried out to verify its prognostic value, and the follow-up time can be extended to evaluate its significance for long-term survival.

In summary, this study confirmed that the novel biomarker TRPS1 is highly expressed in IBC-NST tissues, and its expression level is closely related to adverse clinicopathological features such as histological grade, TNM stage, lymph node metastasis and TNBC subtype, and TRPS1 can be used to predict the prognosis of breast cancer.

Conflict of interest None

Reference

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·乳腺癌专题·论著·

TRPS1 在乳腺非特殊型浸润性癌中的表达特征及其与预后的相关性

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摘要：目的　探讨毛发鼻指(趾)综合征 1 型(TRPS1)在非特殊型乳腺浸润性癌(IBC-NST)中的表达特征，分析其与临床病理参数及预后的相关性。**方法**　纳入唐山市工人医院 2021 年 1 月至 2022 年 12 月确诊的 IBC-NST 患者 122 例作为研究对象，其中 61 例患者同时收集距肿瘤边缘≥2 cm 的癌旁正常乳腺组织作为对照。通过免疫组化 EnVision 二步法检测 122 例肿瘤组织及 61 例癌旁组织 TRPS1 蛋白的表达情况，依据免疫组化 TRPS1 表达评分将患者分为高表达组(≥4 分)与低表达组(≤3 分)。收集患者的临床病理学资料，分析 TRPS1 表达水平与各项临床病理特征之间的关系。对所有患者进行为期 3 年的随访，运用多因素 Cox 比例风险回归模型分析影响患者预后的独立因素。**结果**　TRPS1 在乳腺 NST 组织中的阳性表达率为 89.34%(109/122)，显著高于癌旁组织的 14.75%(9/61)(χ^2=98.789，P<0.01)。TRPS1 高表达组 65 例，低表达组 57 例。TRPS1 高表达与较高的组织学分级(P=0.002)、TNM 分期Ⅲ期(P=0.013)、淋巴结转移(P=0.017)以及三阴性乳腺癌(TNBC)亚型(P=0.030)显著相关。多因素 Cox 回归分析显示，TNM 分期Ⅲ期(HR=3.215，95%CI：1.642~6.298)、存在淋巴结转移(HR=2.547，95%CI：1.358~4.813)和 TRPS1 高表达(HR=2.332，95%CI：1.205~4.514)是影响患者 3 年随访期疾病进展的独立危险因素。**结论**　TRPS1 在 IBC-NST 组织中呈高表达，其高表达与肿瘤的恶性发展进程以及不良的预后结局密切相关，可作为评估 IBC-NST 患者预后的潜在独立预测标志物。

关键词：乳腺癌；非特殊型浸润性癌；毛发鼻指(趾)综合征 1 型；免疫组织化学；临床病理参数；预后

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Abstract: Objective　To investigate the expression characteristics of trichorhinophalangeal syndrome type 1 (TRPS1) in invasive breast carcinoma of no special type (IBC-NST), and to analyze its correlation with clinicopathological parameters and prognosis. **Methods**　A total of 122 patients diagnosed with IBC-NST at Tangshan Workers' Hospital from January 2021 to December 2022 were included as research subjects. Among them, 61 patients had normal breast tissues adjacent to the tumor margin ≥2 cm were collected as controls. The expression status of TRPS1 protein in 122 tumor tissues and 61 adjacent tissues was detected using the immunohistochemical EnVision two-step method. Patients were divided into high expression group (≥4 points) and low expression group (≤3 points) based on the expression score of TRPS1 in immunohistochemisty. Clinical pathological data of the patients were collected simultaneously to analyze the

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correlation between TRPS1 expression levels and various clinical pathological characteristics. All patients were followed up for a period of 3 years, and the independent influencing factors affecting patient prognosis were explored using a multivariable Cox proportional hazards regression model. **Results** The positive expression rate of TRPS1 in IBC-NST tissues was 89.34% (109/122), which was significantly higher than that in adjacent non-tumor tissues (14.75%, 9/61) (χ^2=98.789, P<0.01). High expression of TRPS1 was significantly correlated with higher histological grading (P=0.002), advanced TNM staging Ⅲ (P=0.013), lymph node metastasis (P=0.017), and triple-negative breast cancer (TNBC) subtype (P=0.030). Multivariate Cox analysis revealed that TNM staging Ⅲ (HR=3.215, 95%CI: 1.642-6.298), lymph node metastasis (HR=2.547, 95%CI: 1.358-4.813), and high expression of TRPS1 (HR=2.332, 95%CI: 1.205-4.514) were independent risk factors for disease progression during the 3-year follow-up period. **Conclusion** TRPS1 exhibits high expression characteristics in IBC-NST tissues, and its high expression is closely related to the malignant progression of the tumor and poor prognostic outcomes. It can be served as a potential independent biomarker for assessing the prognosis of IBC-NST patients.

Keywords: Breast cancer; Invasive breast carcinoma of no special type; Trichorhinophalangeal syndrome type 1; Immunohistochemistry; Clinicopathological parameters; Prognosis

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乳腺浸润性癌非特殊型(invasive breast carcinoma of no special type, IBC-NST)是乳腺癌最常见的病理类型,占所有乳腺癌的70%~80%[1-2]。其高度异质性表现为在临床表现、分子特征、治疗反应及患者预后等方面存在巨大差异。尽管当前基于雌激素受体(estrogen receptor, ER)、孕激素受体(progesterone receptor, PR)、人表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)及Ki-67的分子分型系统,极大地优化了乳腺癌的个体化治疗策略,但仍有一部分患者,特别是三阴性乳腺癌(triple-negative breast cancer, TNBC)患者,面临治疗手段有限、易复发转移和预后差的困境[3]。因此,探寻新的、高敏感性与特异性的乳腺癌标志物,对于深化乳腺癌生物学行为认知、开发新的治疗靶点及精准预后评估具有至关重要的意义。毛发鼻指(趾)综合征1型(trichorhinophalangeal syndrome type 1, *TRPS*1)基因编码一种GATA家族的锌指转录因子,因其缺失可引起TRPS而得名[4]。近年来,多项研究发现TRPS1在乳腺癌中扮演着重要角色。TRPS1是乳腺上皮细胞系和乳腺癌的一个高度特异性标志物,其表达水平在乳腺癌中显著上调,且在包括TNBC在内的各分子亚型中均保持较高的表达率和特异性,其性能甚至优于传统的标志物如GATA3[5-6]。TRPS1通过调控多种下游信号通路,参与维持乳腺癌细胞的增殖、分化和生存,其功能涉及上皮-间质转化(epithelial-mesenchymal transition, EMT)等关键生物学过程[7]。然而,目前针对TRPS1在中国人群乳腺IBC-NST中的表达特征,特别是其与详细临床病理参数和预后关系的系统性临床研究尚不充分。本研究采用免疫组化技术,检测TRPS1在122例乳腺IBC-NST及癌旁组织中的表达,系统分析其表达状况与患者各项临床病理参数之间的关联,并进一步通过3年随访数据,探讨TRPS1作为预后评估指标的潜在临床价值,以期为该型乳腺癌的个体化诊疗提供新的理论依据。

1 资料与方法

1.1 一般资料 选取2021年1月至2022年12月于唐山市工人医院确诊的IBC-NST患者122例,其中61例患者同时收集距肿瘤边缘≥2 cm的癌旁正常乳腺组织作为对照。纳入标准:(1)术后病理明确诊断为IBC-NST;(2)未在术前接受过新辅助化疗、放射治疗或内分泌治疗;(3)具有完整的临床病理学资料;(4)具有完整的随访记录。排除标准:(1)合并其他恶性肿瘤;(2)术中或术后30 d内死亡。本研究经唐山市工人医院伦理委员会审批通过[编号:〔2023〕伦审研临第(015)号],患者均已签署知情同意书。

1.2 *研究方法*

1.2.1 免疫组化 本研究纳入的122例IBC-NST组织标本及61例配对的癌旁正常乳腺组织标本,所有组织样本均使用10%中性缓冲福尔马林进行固定,常规石蜡包埋。制备3 μm厚连续切片,贴附于防脱载玻片上,用于免疫组化染色。免疫组化染色采用Dako EnVision二步法检测,一抗为TRPS1单克隆抗体(克隆号:EPR16171, Abcam公司),稀释比例为1∶200。实验操作过程严格依照试剂盒说明书执行,并同步设立

阳性和阴性对照组。阴性对照采用PBS缓冲液替代一抗，以确保染色结果的特异性。

1.2.2　结果判读　TRPS1蛋白免疫阳性信号定位于细胞核，呈棕黄色颗粒。由两位资深病理医师独立完成阅片，采用改良半定量评分体系进行评估。(1) 阳性细胞占比评分：0分(<5%)、1分(5%~25%)、2分(26%~50%)、3分(>50%)。(2) 染色强度分级：0分(无着色)、1分(弱着色)、2分(中等着色)、3分(强着色)。总评分计算为阳性细胞占比评分与染色强度评分的乘积，具体判定标准如下：0~1分为阴性，2~3分为弱阳性(+)，4~6分判定为中度阳性(++)，7~9分为强阳性(+++)。其中阴性及弱阳性为低表达组(≤3分)，中度阳性及强阳性为高表达组(≥4分)。

1.3　临床病理资料与随访　通过医院电子病历系统全面收集患者的临床病理参数，包括年龄、绝经状态、肿瘤最大径、组织学分级、TNM分期、淋巴结转移情况、ER/PR/HER2免疫组化状态及Ki-67增殖指数等核心指标。分子分型严格参照第5版《WHO乳腺肿瘤分类》标准进行划分：Luminal型定义为ER/PR阳性且HER2阴性；HER2过表达型定义为HER2阳性且ER/PR阴性；TNBC则要求ER、PR、HER2三者均为阴性。

术后采用门诊随访结合电话随访的复合模式开展定期追踪，每3个月1次，随访时间截至2025年12月。随访内容主要为无病生存期(disease-free survival，DFS)，DFS定义为从患者手术日期至首次出现疾病进展事件的日期，疾病进展事件包括乳腺肿瘤局部复发、区域淋巴结转移、远处转移、因乳腺癌导致的全因死亡，无上述事件者随访至末次随访日期。

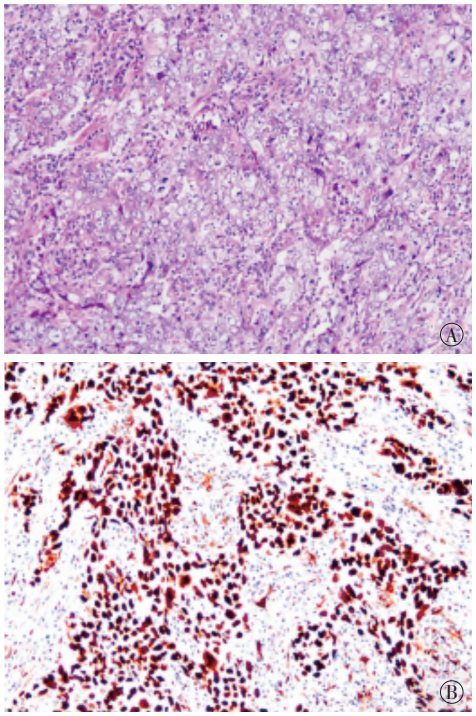
1.4　统计学方法　采用SPSS 19.0软件进行数据分析。计数资料以例(%)表示，比较采用χ^2检验。采用多因素Cox比例风险回归模型分析影响患者预后的独立因素。所有检验均为双侧检验，P<0.05为差异有统计学意义。

2　结　果

2.1　TRPS1在IBC-NST及癌旁组织中的表达　TRPS1阳性染色主要定位于肿瘤细胞核，呈棕黄色或棕褐色颗粒，少数病例可见胞质着色(图1)。122例乳腺IBC-NST组织中，TRPS1阳性表达109例，总阳性率为89.34%；其中，高表达(中-强阳性)65例，占53.28%。在61例配对癌旁组织中，仅9例显示弱阳性表达，总阳性率为14.75%，且无一例达到中或强阳性表达。IBC-NST组织中TRPS1的总阳性率和高表达率均显著高于癌旁组织(P<0.01)。见表1。

2.2　TRPS1表达与临床病理参数的关系　根据TRPS1表达水平将患者分为高表达组(65例)和低表达组(57例)。TRPS1高表达与组织学分级Ⅲ级、TNM分期Ⅲ期、淋巴结转移以及TNBC亚型比例显著高于低表达组(P<0.05)。见表2。

2.3　TRPS1表达与患者预后的多因素Cox回归分析　122例病例中位随访时间为36个月。在随访期内，总计35例患者发生疾病进展(包括局部复发区域



注：A为IBC-NST HE染色(×100)；B为免疫组化TRPS1蛋白阳性表达定位于IBC-NST细胞的细胞核，呈棕黄色颗粒状染色(×200)。

图1　IBC-NST组织病理学特征及TRPS1蛋白表达

Fig.1　Histopathological features of IBC-NST and expression of TRPS1 protein

表1　TRPS1在IBC-NST组织与癌旁组织中的表达比较　(例)

Tab.1　Comparison of TRPS1 expression in IBC-NST tissue and adjacent non-tumor tissue　(case)

组别	例数	阴性	弱阳性(+)	中度阳性(++)	强阳性(+++)	总阳性率(%)	高表达率(%)
IBC-NST组织	122	13	44	39	26	89.34	53.28
癌旁组织	61	52	9	0	0	14.75	0
χ^2值						98.789	50.403
P值						<0.001	<0.001

淋巴结转移、远处转移及乳腺癌相关死亡）。其中TRPS1低表达组出现11例(19.30%)，高表达组出现24例(36.92%)。为进一步评估TRPS1是否作为IBC-NST预后的独立影响因素，本研究将单因素分析中P<0.1的变量（包括组织学分级、TNM分期、淋巴结转移状态、分子分型及TRPS1表达水平）以及临床广泛认可的预后相关因素（肿瘤大小）共同纳入多因素Cox比例风险回归模型。结果显示，TNM分期为Ⅲ期、存在淋巴结转移及TRPS1高表达是患者3年随访中疾病进展的独立危险因素（P<0.05）。见表3。

表2 TRPS1表达与IBC-NST患者临床病理参数的关系 [例(%)]

Tab.2 Relationship between TRPS1 expression and clinicopathological parameters in patients with IBC-NST [case(%)]

项目		低表达组（n=57）	高表达组（n=65）	χ^2值	P值
年龄	<50岁	28(49.12)	35(53.85)	0.271	0.602
	≥50岁	29(50.88)	30(46.15)		
绝经状态	否	32(56.14)	40(61.54)	0.366	0.545
	是	25(43.86)	25(38.46)		
肿瘤直径	≤2 cm	25(43.86)	23(35.38)	0.914	0.339
	>2 cm	32(56.14)	42(64.62)		
组织学分级	Ⅰ~Ⅱ级	45(78.95)	34(52.31)	9.443	0.002
	Ⅲ级	12(21.05)	31(47.69)		
TNM分期	Ⅰ~Ⅱ期	46(80.70)	39(60.00)	6.159	0.013
	Ⅲ期	11(19.30)	26(40.00)		
淋巴结转移	无	41(71.93)	33(50.77)	5.698	0.017
	有	16(28.07)	32(49.23)		
ER状态	阴性	14(24.56)	25(38.46)	2.698	0.100
	阳性	43(75.44)	40(61.54)		
PR状态	阴性	18(31.58)	28(43.08)	1.709	0.191
	阳性	39(68.42)	37(56.92)		
HER2状态	阴性	51(89.47)	53(81.54)	1.520	0.218
	阳性	6(10.53)	12(18.46)		
Ki-67指数	<20%	22(38.60)	20(30.77)	0.824	0.364
	≥20%	35(61.40)	45(69.23)		
分子分型	Luminal	43(75.44)	34(52.31)		
	HER2+	6(10.53)	12(18.46)	7.039	0.030
	TNBC	8(14.03)	19(29.23)		

表3 影响IBC-NST患者疾病进展的多因素Cox回归分析

Tab.3 Multivariate Cox regression analysis of factors affecting disease progression of patients with IBC-NST

变量	β值	SE	Wald χ^2	P值	HR(95%CI)
肿瘤直径(>2 cm)	0.421	0.312	1.823	0.177	1.523(0.827~2.805)
组织学分级(Ⅲ级)	0.502	0.329	2.329	0.127	1.652(0.867~3.148)
TNM分期(Ⅲ期)	1.168	0.342	11.662	0.001	3.215(1.642~6.298)
淋巴结转移(有)	0.935	0.325	8.275	0.004	2.547(1.358~4.813)
分子分型(TNBC)	0.467	0.381	1.503	0.220	1.595(0.756~3.365)
TRPS1(高表达)	0.847	0.338	6.284	0.012	2.332(1.205~4.514)

3 讨 论

3.1 TRPS1作为乳腺癌新型标志物的表达特征 本研究结果显示，TRPS1在IBC-NST组织中的阳性率高达89.34%，这与近期多项研究结论高度一致。Ai等[8]对超过9 000例乳腺癌样本的分析发现，TRPS1 mRNA和蛋白在乳腺癌中的表达率均超过90%，且其特异性优于GATA3，尤其在TNBC中优势明显。李菲等[9]的研究也报道了类似的高表达率。本研究在蛋白水平上进一步验证了这一现象。其核定位的表达模式与其作为转录因子的生物学功能相符。TRPS1在癌旁正常组织中极低甚至不表达的特性，使其在病理诊断实践中，特别是在转移癌溯源鉴定中，展现出巨大的应用潜力，有望成为鉴别乳腺原发癌与转移癌的可靠工具。

3.2 TRPS1高表达与肿瘤侵袭性的关联 研究发现TRPS1的高表达与多项提示肿瘤侵袭性强的临床病理指标显著正相关。本研究中，TRPS1高表达组中Ⅲ级肿瘤的比例显著高于低表达组，提示TRPS1可能参与了细胞去分化和异常增殖的调控。同样，TRPS1高表达与晚期TNM分期和淋巴结转移的关联，提示其可能促进了肿瘤的局部浸润和转移。这与TRPS1的基础研究结果一致。已有研究表明，TRPS1通过转录调控一系列下游靶基因，如miR-221/222簇，抑制其表达，从而解除对下游信号通路[如磷酸酶与张力蛋白同源物/蛋白激酶B（phosphatase and tensin homolog/protein kinase B，PTEN/AKT）]的抑制，最终促进肿瘤细胞的增殖、迁移和侵袭[10-12]。此外，TRPS1还可借由调控E盒结合锌指蛋白2（zinc finger E-box binding homeobox 2，ZEB2）等转录因子，参与EMT的调控，该过程是肿瘤细胞获得迁移与侵袭能力的重要机制[13]。TRPS1高表达与TNBC亚型显著相关。TNBC因缺乏治疗靶点、侵袭性强、预后差而成为乳腺癌治疗的难点。本研究中，近30%的TRPS1高表达病例为TNBC，且在TNBC患者内部，TRPS1高表达比例也高达70.37%。这一发现具有双重意义。在诊断上，TRPS1的高敏感性和特异性使其成为辅助诊断TNBC和鉴别诊断的有力工具，弥补了GATA3在部分TNBC中表达缺失的不足[14-15]。

3.3 TRPS1作为独立预后因素的价值 预后评估是乳腺癌临床管理的重要组成部分。本研究通过多因素Cox回归分析，在排除了TNM分期、淋巴结状态等传统强预后因素的干扰后，发现TRPS1高表达仍然是影响IBC-NST患者3年随访期间疾病进展的独立

危险因素。提示在临床病理特征相似的患者中，TRPS1高表达者其疾病复发或转移的风险是低表达者的2.3倍以上。其机制可能在于TRPS1核心促癌功能的持续性。TRPS1通过促进增殖、侵袭、EMT，可能影响肿瘤干细胞特性或治疗抵抗，最终导致了更高的复发转移风险[16-17]。本研究为TRPS1的预后价值提供了来自中国人群的临床证据，与Ai等[8]报道的TRPS1高表达与较短的总生存期和无病生存期相关的结论相互印证。因此，在临床中，对TRPS1高表达乳腺癌，尤其是早期、无淋巴结转移者，应加强随访，积极辅助治疗以改善患者的生存。

3.4 *研究的局限性与展望* 本研究存在以下局限性：首先，本研究为单中心回顾性队列研究，样本量小，存在选择偏倚风险；其次，随访时长仅为3年，未能对TRPS1在长期生存方面的影响进行评估；最后，仅在蛋白表达层面开展了相关性分析，尚未深入探究其调控乳腺癌进展的具体分子作用机制。未来可开展多中心大样本前瞻性研究以验证其预后价值；延长随访时间以评估其对长期生存的意义。

综上所述，本研究证实了新型标志物TRPS1在IBC-NST组织中高表达，其表达水平与组织学分级、TNM分期、淋巴结转移及TNBC亚型等不良临床病理特征密切相关，且TRPS1可用来预测乳腺癌预后。

利益冲突 无

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