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TRPS1 Expression in Triple-Negative Breast Cancer and Its Association with the Efficacy of Neoadjuvant Chemotherapy

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Abstract

Background. Triple-negative breast cancer (TNBC) is characterized by pronounced biological heterogeneity and variable sensitivity to neoadjuvant chemotherapy, underscoring the need for additional diagnostic and predictive biomarkers. TRPS1, a GATA family transcription factor, has been identified as a highly sensitive marker of mammary differentiation; however, its clinical relevance in TNBC remains insufficiently explored.

Methods and Results. The aim of this study was to evaluate TRPS1 expression in TNBC and to assess its association with clinicopathological features, stromal tumor-infiltrating lymphocytes, and the efficacy of neoadjuvant chemotherapy. This single-center retrospective study included 54 patients with invasive TNBC treated with neoadjuvant chemotherapy. TRPS1 expression was assessed by immunohistochemistry using an H-score-based approach. Stromal tumor-infiltrating lymphocytes were evaluated on hematoxylin and eosin-stained tumor slides. Response to neoadjuvant chemotherapy was assessed by the rate of pathological complete response and the Residual Cancer Burden classification. High TRPS1 expression was detected in 53.7% of cases and was associated with a significantly higher pathological complete response rate (51.7% vs. 20.0%, *P*=0.016), a more favorable distribution of Residual Cancer Burden categories, and higher levels of stromal tumor-infiltrating lymphocytes. Overall, TRPS1 expression in TNBC was associated with improved response to neoadjuvant chemotherapy.

Conclusions. TRPS1 expression in TNBC is associated with enhanced sensitivity to neoadjuvant chemotherapy and may be considered not only a diagnostic marker of mammary differentiation but also a potential predictive marker of treatment response. (**International Journal of Biomedicine. 2026;16(1):53-58.**)

Keywords: TRPS1 • triple-negative breast cancer • neoadjuvant chemotherapy • pathological complete response • residual cancer burden

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Abbreviations

IHC, immunohistochemistry; **NACT,** neoadjuvant chemotherapy; **pCR,** pathological complete response; **RCB,** residual cancer burden; **sTILs,** stromal tumor-infiltrating lymphocytes; **TNBC,** triple negative breast cancer.

Introduction

Triple-negative breast cancer (TNBC) represents a clinically, morphologically, and biologically heterogeneous group of tumors characterized by the absence of estrogen and progesterone receptor expression and the lack of HER2 protein overexpression or gene amplification.[1,2] Despite a uniform immunophenotypic definition, TNBC demonstrates marked variability in morphological features, sensitivity to systemic therapy, and clinical outcomes, highlighting the ongoing need for additional diagnostic and predictive biomarkers.[3]

Neoadjuvant chemotherapy (NACT) constitutes a standard component of treatment for patients with locally advanced TNBC. Achievement of a pathological complete response (pCR) is associated with a more favorable prognosis; however, pCR rates remain limited, and the depth of response to

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therapy varies substantially even with the use of contemporary treatment regimens.[4,5]

The tumor microenvironment plays a crucial role in modulating therapeutic response. Previous studies have demonstrated that the level of stromal tumor-infiltrating lymphocytes (sTILs) represents a significant prognostic and predictive factor in TNBC.[6,7] Nevertheless, immune-related parameters alone do not fully capture the biological characteristics of tumor cells and require complementary tissue-based markers reflecting tumor differentiation status.

TRPS1 (tricho-rhino-phalangeal syndrome type 1), a GATA family transcription factor, is currently regarded as one of the most sensitive immunohistochemical markers of mammary tissue differentiation. Several studies have reported preserved TRPS1 expression in the vast majority of TNBC cases, including poorly differentiated and metaplastic variants, with higher sensitivity compared with conventional markers such as GATA3 and SOX10.[8-11] In addition to its diagnostic utility, TRPS1 is involved in the regulation of cellular differentiation and the maintenance of phenotypic stability in tumor cells.

Despite increasing interest in TRPS1 data, its clinical and predictive significance in TNBC remains limited. In particular, the association between TRPS1 expression and clinicopathological characteristics, as well as response to NACT, including the extent of pathological response, remains insufficiently investigated. Therefore, the aim of the present study was to evaluate TRPS1 expression in TNBC and to assess its diagnostic and potential predictive significance.

Methods

Study Design and Patients

A single-center retrospective study was conducted. The analysis included 54 cases of invasive breast carcinoma with a triple-negative molecular profile; all patients were treated at a single specialized oncological center (Cancer Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences).

The study material consisted of diagnostic core needle biopsy specimens obtained prior to the initiation of NACT, as well as surgical specimens of breast tumor tissue and axillary lymph nodes collected after completion of systemic treatment. All patients received a full course of NACT followed by surgical intervention, allowing for a comprehensive assessment of tumor morphology before treatment and evaluation of pathological response after therapy. NACT was administered in accordance with current clinical guidelines for the treatment of TNBC. Standard regimens including anthracycline- and taxane-based protocols were used. 36 patients (66.7%) received a sequential anthracycline-taxane regimen, while platinum-containing agents were additionally included in the treatment regimen of 18 patients (33.3%). The choice of chemotherapy regimen and treatment duration were determined based on clinical indications in accordance with the current guidelines of the Ministry of Health of the Russian Federation.

Histopathological Evaluation

Histological verification and classification of tumors were performed according to the World Health Organization Classification of Tumours of the Breast (WHO, 5th edition). Morphological evaluation of tumor core biopsy specimens included assessment of histological subtype, histological grade according to the Nottingham grading system, and the presence and extent of tumor necrosis. Triple-negative status was confirmed by immunohistochemistry (IHC) in all cases and defined as the absence of estrogen and progesterone receptor expression (<1% of tumor cells) and lack of HER2 overexpression or amplification (HER2 score 0-1+ by IHC or HER2 score 2+ with a negative *in situ* hybridization result).

Assessment of sTILs

In the study, sTILs were evaluated on hematoxylin and eosin-stained slides of diagnostic core biopsy specimens obtained prior to treatment. sTILs were assessed as the percentage of stromal area occupied by mononuclear inflammatory cells in accordance with the recommendations of the International TILs Working Group.[12] Areas of necrosis, artifacts, and intraductal tumor components were excluded from the analysis.

Immunohistochemistry

Evaluation of TRPS1 expression was performed on formalin-fixed paraffin-embedded sections of diagnostic core biopsy specimens. Staining was carried out using an automated immunohistochemistry stainer (Bond-Max, Leica Biosystems) according to the manufacturer's standard protocol. TRPS1 expression was detected using a monoclonal antibody against TRPS1 (clone QR099, Rabbit, RTU; Quartett). TRPS1 expression was assessed based on nuclear staining of tumor cells. Semi-quantitative evaluation was performed using the H-score, calculated by taking into account both the percentage of positively stained tumor cells and staining intensity. For analytical purposes, all tumor samples were stratified into two groups: tumors with high TRPS1 expression (TRPS1-high; H-score ≥150) and tumors with low or absent TRPS1 expression (TRPS1-low/negative; H-score <150).

Additionally, in a subset of cases, immunohistochemical analysis was performed using antibodies against GATA3 (clone L50-823, Rabbit, RTU; Cell Marque), SOX10 (clone EP268, Rabbit, RTU; Cell Marque), and androgen receptor (AR; clone AR441, Mouse, RTU; Cell Marque) to compare TRPS1 expression with other markers of mammary differentiation.

Assessment of Response to NACT

The efficacy of NACT was evaluated based on histopathological examination of surgical specimens of breast tumor tissue obtained after completion of systemic therapy. Pathological complete response (pCR) was defined as the absence of invasive carcinoma in the breast and regional lymph nodes (ypT0/is ypN0). In addition, quantitative assessment of residual tumor burden was performed in all cases using the Residual Cancer Burden (RCB) system, with classification of patients into RCB-0, RCB-I, RCB-II, and RCB-III categories according to the methodology proposed by Symmans et al.[13]

Statistical processing of the obtained data was performed using Statistica 10.0 (StatSoft Inc., USA). Quantitative indicators are presented as median and interquartile range (IQR). To compare quantitative variables between two independent groups, the nonparametric Mann-Whitney test was used. Qualitative indicators were compared using the

Pearson χ^2 test or Fisher's exact test (for expected values less than 5). To evaluate factors associated with achieving a complete pathomorphological response, univariate logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (95% CI). Differences were considered statistically significant at $P<0.05$.

Results

The study included 54 patients with TNBC. The median age was 52 years (interquartile range [IQR], 45-61 years). At the initiation of NACT, most patients presented with locally advanced disease: tumors classified as cT2 or higher were observed in 72.2% of cases, and metastatic involvement of regional lymph nodes was detected in 57.4%.

From a morphological standpoint, invasive carcinoma of no special type (NST) predominated, accounting for 85.2% of cases, whereas metaplastic carcinomas accounted for 14.8%. High histological grade (Nottingham grade 3) was identified in 75.9% of patients. The median sTIL level was 30% (IQR, 15-45%). Detailed clinicopathological characteristics of the study cohort are summarized in Table 1. pCR to NACT was achieved in 37.0% of cases (n=20). According to the RCB classification, patients with complete response (RCB-0) accounted for 37.0%, RCB-I for 16.7%, whereas 46.3% of patients demonstrated substantial residual tumor burden (RCB-II and RCB-III) (Table 1).

Table 1.
Clinicopathological characteristics of patients with TNBC (n = 54).

Parameter	Value, n (%)
Menopausal status	
Premenopausal	29 (53.7)
Postmenopausal	25 (46.3)
cT ≥2	39 (72.2)
cN+	31 (57.4)
Histological type of breast tumor	
Invasive carcinoma of no special type (NST)	46 (85.2)
Metaplastic carcinoma	8 (14.8)
Histological grade (Nottingham)	
Garde 1	-
Grade 2	13 (24.1)
Grade 3	41 (75.9)
Distribution of cases according to Residual Cancer Burden (RCB)	
RCB-0	20 (37.0)
RCB-I	9 (16.7)
RCB-II	17 (31.5)
RCB-III	8 (14.8)
pCR	20 (37.0)

TRPS1 Expression and Clinicopathological Associations

Immunohistochemical analysis revealed TRPS1 expression in 87.0% of cases (n=47/54). In most tumors, TRPS1 showed diffuse nuclear staining with moderate to high intensity. Based on semi-quantitative evaluation using the H-score, all cases were stratified into two groups: tumors with high TRPS1 expression (TRPS1-high; H-score ≥150) and tumors with low or absent TRPS1 expression (TRPS1-low/negative; H-score <150).

The TRPS1-high group comprised 29 patients (53.7%), whereas 25 patients (46.3%) demonstrated low or absent TRPS1 expression. Notably, TRPS1 expression was preserved in a subset of tumors lacking immunoreactivity for other markers of mammary differentiation, including GATA3 and SOX10, underscoring its additional diagnostic value.

Analysis of associations between TRPS1 expression and morphological parameters revealed several significant findings. Tumors with high TRPS1 expression were significantly less likely to exhibit high histological grade (Grade 3) compared with TRPS1-low/negative tumors. Similarly, metaplastic breast carcinoma variants were significantly less frequent in the TRPS1-high group, indicating an association between reduced TRPS1 expression and morphologically less differentiated tumor phenotypes.

Association between TRPS1 Expression and Tumor Microenvironment

sTIL levels were significantly higher in the TRPS1-high group. Median sTIL values in this group exceeded those observed in TRPS1-low/negative tumors. Representative morphological and immunohistochemical features of a tumor with high TRPS1 expression and prominent stromal lymphocytic infiltration are shown in Figure 1.

Androgen receptor expression was detected more frequently in TRPS1-high tumors; however, this association did not reach statistical significance. Detailed data on the relationships between TRPS1 expression and clinicopathological and immunohistochemical characteristics of TNBC are presented in Table 2.

TRPS1 Expression and Response to NACT

Analysis of the association between TRPS1 expression and response to NACT demonstrated that pCR occurred significantly more often in the TRPS1-high group. The pCR rate in this group was 51.7%, compared with 20.0% in the TRPS1-low/negative group (Figure 2A, Table 3).

Evaluation of RCB distribution revealed that tumors with high TRPS1 expression were significantly more likely to be classified as RCB-0 or RCB-I, reflecting absence or minimal residual tumor burden. In contrast, the RCB-II and RCB-III categories, indicative of substantial residual disease following NACT, predominated among patients in the TRPS1-low/negative group ((Figure 2B, Table 3).

Predictors of pCR

In univariate logistic regression analysis, pathological complete response was significantly associated with high TRPS1 expression and elevated sTIL levels. Inclusion of

platinum-based agents in NACT regimens was associated with a trend toward increased pCR rates; however, this association did not reach statistical significance. The results of the univariate analysis of factors associated with pCR are summarized in Table 4.

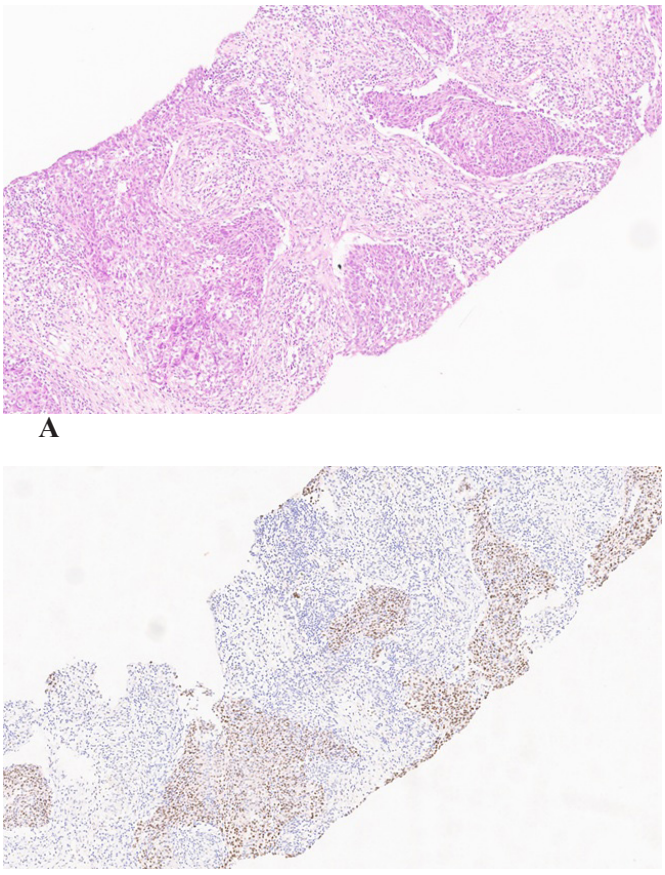

Figure 1. *Morphological and immunohistochemical features of TNBC with high TRPS1 expression.*
A - Core needle biopsy specimen showing prominent sTILs; hematoxylin and eosin staining. B - Diffuse nuclear TRPS1 expression in tumor cells; IHC staining. Original magnification ×4. Digital images were acquired using an Aperio AT2 *scanner.*

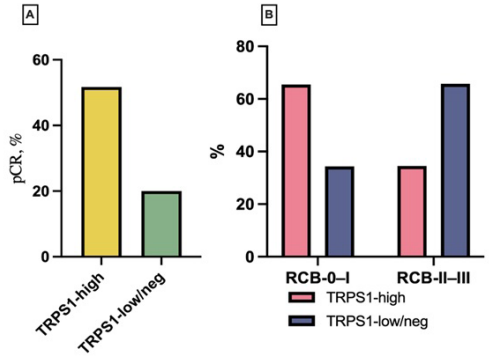

Figure 2. *Association between TRPS1 expression and the efficacy of NACT in TNBC. A - Rate of pCR in the TRPS1-high and TRPS1-low/negative groups. B - Distribution of RCB categories according to TRPS1 expression level.*

Table 2.

Association between TRPS1 expression and morphological and immunohistochemical characteristics of TNBC.

Parameter	TRPS1-high (n = 29)	TRPS1-low/negative (n = 25)	*P*-value
Histological Grade 3	19 (65.5%)	22 (88.0%)	0.054
sTILs, %, median (IQR)	35 (25-50)	20 (10-30)	0.006
Metaplastic TNBC	2 (6.9%)	6 (24.0%)	0.077

Table 3.

Association between TRPS1 expression and pathological response to NACT (pCR and RCB) in TNBC.

Parameter	TRPS1-high (n=29)	TRPS1-low/negative (n=25)	*P*-value
pCR	15 (51.7%)	5 (20.0%)	0.016
RCB-0 and RCB-I	20 (69.0%)	9 (36.0%)	0.015
RCB-II and RCB-III	9 (31.0%)	16 (64.0%)	0.015

Table 4.

Factors associated with achievement of pCR to NACT (univariate analysis).

Variable	OR	95% CI	*P*-value
TRPS1-high	4.3	1.3-14.2	0.017
sTILs (>30%)	3.9	1.2-12.7	0.021
Inclusion of platinum-based agents in NACT	2.1	0.7-6.1	0.18
Histological Grade 3	0.6	0.2-1.9	0.39

Discussion

The present study confirms the high frequency of TRPS1 expression in TNBC and underscores its significance as a diagnostic marker of mammary differentiation in the setting of loss of hormone receptor and HER2 expression. In the studied cohort, TRPS1 was detected in most cases, consistent with data from large immunohistochemical series and supporting its superior sensitivity compared with traditionally used markers such as GATA3 and SOX10. Notably, TRPS1 expression was preserved in a subset of tumors that lacked immunoreactivity for other mammary markers, underscoring its additional diagnostic value, particularly in the evaluation of biopsy specimens and metastatic tumor tissue.

Analysis of clinicopathological associations demonstrated that high TRPS1 expression was linked to less aggressive morphological features. Tumors in the TRPS1-high group showed a significantly lower frequency of metaplastic

carcinoma variants and high Nottingham histological grade, suggesting an association between reduced TRPS1 expression and loss of epithelial differentiation. These findings are consistent with current concepts regarding the role of TRPS1 in maintaining the epithelial phenotype and suppressing epithelial-mesenchymal transition. Accordingly, decreased TRPS1 expression may be regarded as a morphological indicator of biologically more aggressive, poorly differentiated TNBC.

Of particular interest is the observed association between TRPS1 expression and tumor microenvironment characteristics. In the present study, tumors with high TRPS1 expression exhibited significantly higher levels of sTILs. Given the well-established prognostic and predictive significance of sTILs in TNBC, this observation suggests that TRPS1-expressing tumors may exhibit enhanced immune reactivity, potentially contributing to improved responses to systemic therapy. At the same time, the relationship between TRPS1 expression and sTILs levels likely reflects a complex interplay between tumor cell state and the immune microenvironment rather than a simple linear dependency.

The most clinically relevant finding of this study is the association between TRPS1 expression and NACT efficacy. pCR and minimal residual tumor burden (RCB-0 and RCB-I) were observed significantly more frequently in the TRPS1-high group, whereas tumors with low or absent TRPS1 expression predominantly exhibited higher RCB categories (RCB-II and RCB-III). These results indicate a potential predictive role for TRPS1 not only in achieving pCR but also in the depth of therapeutic response.

The biological interpretation of these findings may be related to the multifaceted role of TRPS1 in regulating cell cycle control, DNA damage response, and epithelial-mesenchymal transition. Preserved TRPS1 expression may reflect a more differentiated epithelial phenotype associated with increased sensitivity to cytotoxic chemotherapy. Conversely, reduced TRPS1 expression may be accompanied by activation of cellular plasticity programs and DNA damage resistance, resulting in reduced chemotherapy efficacy and greater residual tumor burden. In this context, TRPS1 may be considered an integrative marker reflecting the combined influence of morphological, molecular, and immune tumor characteristics.

It should be noted that inclusion of platinum-based agents in NACT regimens was associated only with a trend toward increased pCR rates and did not reach statistical significance in this study. This may be attributable to the relatively limited sample size and heterogeneity of treatment regimens. Nevertheless, the observed association between TRPS1 expression and response to NACT, regardless of the specific treatment regimen, suggests that this marker may have universal predictive value.

Several limitations of the present study should be acknowledged, including its retrospective design, relatively small cohort size, and lack of molecular stratification of TNBC subtypes. In addition, TRPS1 expression was assessed in diagnostic biopsy material, which does not fully account for potential intratumoral heterogeneity. However, evaluation of pre-treatment biopsy specimens provides the greatest clinical relevance for the practical application of TRPS1 as a predictive biomarker.

In summary, the results of this study support the consideration of TRPS1 not only as a highly sensitive diagnostic marker of mammary differentiation in TNBC but also as a potential predictive factor for the efficacy of neoadjuvant chemotherapy. Further prospective studies incorporating comprehensive molecular characterization of tumors are warranted to clarify the role of TRPS1 within personalized treatment strategies for TNBC.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. It was approved by the Local Ethics Committee of the Oncology Institution (Protocol No. 13 dated 12.21, 2020). Given the retrospective nature of the study and the use of anonymized archival materials, informed consent from patients was not required.

Competing Interests

The authors declare that they have no competing interests.

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