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TRPS1 As an Immunohistochemical Biomarker in Breast Carcinoma: Clinicopathological Correlates and Molecular Subtype-Specific Expression

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Abstract

Breast carcinoma is a biologically heterogeneous malignancy showing diverse histopathological and immunophenotypic features. Immunohistochemical biomarkers complement histopathological classification of tumour. In recent times, TRPS1 (a transcriptional repressor of mammary epithelial differentiation) has been highlighted as a candidate associated to the breast lineage marker. Yet, its expression across clinicopathological parameters and surrogate molecular subtypes in different populations is still incompletely characterised. The aim of this study is to evaluate TRPS1 immunohistochemical expression in cancerous and noncancerous tissues using invasive breast carcinoma samples, as well as correlating its expression with various clinicopathological parameters and surrogate molecular subtypes among an Iraqi population. The study was performed on 50 female patients diagnosed with primary invasive carcinoma of breast. Archival formalin-fixed paraffin-embedded formalin-fixed paraffin-embedded tissue blocks were retrieved from pathology collections and stained with a rabbit monoclonal anti-TRPS1 antibody. Nuclear staining intensity and proportion of the positive tumour cells was evaluated via semi-quantitative immunoreactivity scoring system. TRPS1 expression was identified in 39/50 (78.0%) of cases, with moderate to strong nuclear staining in most instances. Expression showed some consistency between histological subtypes and tumour grades. TRPS1 expression was statistically significantly associated with surrogate molecular subtype classification ($p = 0.046$) and tended to be up-regulated in tumours classified as luminal-like compared with HER2-enriched and triple-negative groups. Associations between TRPS1 expression and age, histological type, tumour grade, or TNM components were statistically not significant. TRPS1 is commonly expressed in invasive breast carcinoma and

has a heterogeneous distribution among surrogate molecular subtypes, with the highest expression level seen in hormone receptor–positive tumours within this cohort. Nonetheless, its expression is not strongly related to grade, stage or any other major clinicopathological parameters. These results reinforce the concept that TRPS1 should be regarded as a breast-lineage–specific immunohistochemical marker rather than a prognostic determinant. It is best viewed as an adjunct to immunohistochemical panels in diagnostic settings rather than a stand-alone diagnostic test.

Keywords: Breast carcinoma; Immunohistochemistry; TRPS1; immunoreactivity.

1. Introduction

Breast carcinoma is a biologically heterogeneous disease and still one of the leading causes of mortality worldwide. Breast cancer is one of the most commonly diagnosed cancers in women, and a leading cause of cancer related mortality worldwide [1]. Breast cancer remains one of the most diagnostic and clinical challenges across many geographic regions, affecting both developed as well those nearing high-income [2], driven by varied tumour biology, stage at diagnosis & accessibility to advanced molecular tests.

Histopathological assessment is still the golden standard of breast cancer diagnosis. Nevertheless, contemporary classification relies primarily on a combination of morphology and immunohistochemical and molecular markers. Conventional markers and proliferative indices such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) expression, and Ki-67 index are used on a daily basis for guiding classification of tumours which subsequently direct clinical decision making [3–5]. Those markers are also the foundation for surrogate classification systems that reflect intrinsic molecular subtypes in routine diagnostic procedures. Breast carcinoma is turning into a two-actuality that we had mistakenly allowed as an organisation of organic various entities than only one illness. Intrinsic molecular subtypes have been defined using gene expression profiling, that is frequently reduced in clinical practice to four entities: luminal A, luminal B, HER2-enriched and triple-negative [6,7]. These surrogate classifications are of clinical benefit; however, they only partially reflect the biological complexity associated with breast cancer and overlap between categories may be seen depending on validation criteria/methodology used or availability of biomarkers.

Even with new developments in diagnostic pathology, the classification of poorly differentiated tumours or metastatic lesions and triple negative breast carcinomas still presents challenges. Standard breast-lineage immunohistochemistry markers including GATA3, mammaglobin and GCDFP-15 can demonstrate variable sensitivity in such scenarios especially when high-grade or triple-negative tumours are involved. This restriction renders the differential diagnosis from either primary breast carcinoma or metastases of non-mammary malignant neoplasms more difficult, particularly in small biopsy specimens with scant morphologic background [6].

One recent such immunohistochemical marker of breast epithelial differentiation, identified in nuclear smear preparations from invasive ductal carcinoma cases is Trichorhinophalangeal syndrome type 1 (TRPS2 also known as transcriptional repressor GATA-binding 1). TRPS1 is a transcription factor from regulatory pathways in development and epithelium which expressed mammary epithelial cells as well breast carcinomas [8,9]. Preliminary data indicate that TRPS1 may be more robustly positive across breast cancer subtypes relative to some historical markers, including in challenging diagnostic categories like triple-negative breast carcinoma [8,9]. Complementary studies have then further assessed TRPS1 expression in large cohorts of various tumour types, and noted that while its overall levels of expression are generally low, it is still consistently expressed at relatively high rates within breast carcinoma tumours [10] making it an ideal addition to diagnostic immunohistochemistry panels. Notably, distinct expression patterns have been reported in the literature [10], likely due to differences in antibody clones used for staining platforms and methods of scoring as well as selection bias with respect to tumours. Hence, its diagnostic interpretation should be accompanied by morphologic correlation and other immunohistochemical markers rather than depend on it as an isolated test. Furthermore, the biological and clinical significance of TRPS1 expression in distinct molecular or surrogate subtypes of breast carcinoma is still not well characterised. Although some studies suggest uniform expression across tumour categories, others have hinted at potential differences due to tumour phenotype or differentiation state. These discrepancies point to the imperative for replication in varied populations and practice settings.

Based on these observations, the current study aims to examine TRPS1 expression by immunohistochemistry in invasive breast carcinoma of an Iraqi cohort with correlation made between its expression and clinicopathological parameters as well as surrogate molecular subtypes. The goal is not to define diagnostic specificity or prognostic independence, but rather adding information about expression patterns in conventional clinical practice and helping it fit with established clinicopathological variables.

2. Methods

2.1 Study design

A retrospective cross-sectional analytical study was conducted in the Babylon training centre for histopathology from November 2024 to December 2025. It was designed to assess the immunohistochemical expression of TRPS1 in invasive breast carcinoma and correlate it with clinicopathologic parameters and routinely assigned molecular subtypes. The study was performed without subjecting patients to any further diagnostic/therapeutic intervention and maintaining the original clinical relevance of pathological material by taking advantage of archival formalin-fixed paraffin-embedded tissue.

2.2 Patient selection and tissue specimens

The sample consisted of 50 female patients with primary invasive breast carcinoma. Retrieval of formalin-fixed paraffin-embedded tissue blocks were retrieved from the archives of the histopathology laboratory of Al-Imam Al-Sadiq Teaching Hospital in Najaf City as well as from private histopathology laboratories in Najaf and Babylon. All cases were previously assessed for oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status as part of routine diagnostic work-up. The study was focused on women aged 18 years old or older with a diagnosis of primary invasive breast carcinoma, availability of paraffin-embedded tumour tissue, documentation of ER, PR and HER2 immunohistochemical evaluation (negative vs. positive), and sufficient clinicopathological information available for adequate analysis. All histopathological types, tumour grades and disease stages were eligible. Exclusion criteria involved male breast carcinoma, other benign breast lesions, mesenchymal breast tumours and cases with incomplete or unavailable clinicopathological data.

2.3 Histopathological review

For each case, archived haematoxylin and eosin-stained slides were reviewed to confirm the diagnosis of invasive breast carcinoma and to reassess histological type and tumour grade. Histopathological classification was performed according to the World Health Organisation classification of breast tumours. Tumour stage was assigned according to the American Joint Committee on Cancer staging system, eighth edition, using available pathological and clinical data. The clinicopathological variables recorded for analysis included patient age, histopathological type, tumour grade, molecular subtype, primary tumour category, nodal status, distant metastasis status, and overall AJCC stage.

2.4 Section preparation and haematoxylin and eosin staining

Two sections, each measuring approximately 4–5 μm in thickness, were cut from each formalin-fixed paraffin-embedded tissue block. One section was mounted for haematoxylin and eosin staining, and the other was mounted on a positively charged slide for TRPS1 immunohistochemical staining. For haematoxylin and eosin staining, tissue sections were deparaffinised in xylene following incubation at 60°C, rehydrated through descending grades of ethanol, stained with Harris haematoxylin, differentiated in acid alcohol, blued under running tap water, counterstained with eosin, dehydrated through ascending grades of alcohol, cleared in xylene, and mounted with DPX.

2.5 Immunohistochemical staining for TRPS1

TRPS1 immunohistochemistry was performed on 4 μm sections of formalin-fixed paraffin-embedded tumour tissue mounted on positively charged slides. Sections were deparaffinised by incubation at 60°C for 120 minutes, followed by immersion in two changes of xylene for 5 minutes each. Rehydration was carried out through decreasing concentrations of alcohol. Heat-induced epitope retrieval was performed using citrate buffer at pH 6.0 in a water bath at 95°C for 30 minutes. After washing in immunohistochemistry buffer, endogenous peroxidase activity was blocked using PolyDetector peroxidase blocker for 5 minutes. The sections were then incubated with rabbit monoclonal anti-TRPS1 antibody, clone EP392, for 60 minutes. The primary antibody was applied according to the manufacturer's instructions; the documented manufacturer-recommended concentration range was 1:50–1:200. After washing, PolyDetector Plus Link was applied for 15 minutes, followed by PolyDetector HRP Label for 15 minutes. Diaminobenzidine was used as chromogen, prepared by adding approximately 50 μL of DAB concentrate to 1 mL of DAB substrate. Sections were counterstained with haematoxylin for 2 minutes, dehydrated, mounted with coverslips, and examined by light microscopy.

2.6 Quality control

Positive and negative controls were included with each staining run to ensure technical validity. Ductal breast carcinoma tissue, as recommended by the antibody manufacturer, was used as the positive control. For the negative control, the staining protocol was performed in the same manner except that the TRPS1 primary antibody was omitted. Only staining runs with appropriate control performance were considered suitable for interpretation.

2.7 Assessment of TRPS1 immunohistochemical expression

TRPS1 immunoreactivity was evaluated as nuclear staining only. Cytoplasmic staining, if present, was not considered evidence of positive TRPS1 expression. Staining was assessed semi-quantitatively using both the proportion of positive tumour nuclei and staining intensity. The proportion score was graded as follows: 0, no nuclear staining; 1, nuclear staining in 1–10% of tumour cells; 2, nuclear staining in 11–50% of tumour cells; and 3, nuclear staining in 51–100% of tumour cells. Staining intensity was graded as follows: 0, absent; 1, weak; 2, moderate; and 3, strong. An immunoreactivity score was then calculated by multiplying the proportion score by the intensity score. Final TRPS1 expression categories were defined as follows: scores 0–1, negative; score 2, low positive; scores 3–4, intermediate positive; and scores 6–9, high positive. For association analyses, low, intermediate, and high positive cases were considered TRPS1-positive, whereas cases with scores 0–1 were considered TRPS1-negative.

2.8 Statistical analysis

Data were analysed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation. Categorical variables were summarised as frequencies and percentages. Associations between TRPS1 expression and clinicopathological parameters were assessed using Fisher's exact test when expected cell counts were <5, otherwise Pearson's chi-square test was applied. All tests were two-sided, and $p < 0.05$ was considered statistically significant. No multiple testing correction was applied given the exploratory nature of the study.

2.9 Ethical considerations

The current study was approved by the institutional review board of scientific council of pathology, Iraqi board for medical specialisation (Approval no: Path95, 11/12/2024). The study was carried out in accordance with relevant institutional ethical regulations and an approved study protocol and performed in accordance with the declaration of Helsinki. Patient privacy was ensured by anonymised data and secure clinical information handling.

3. Results

Data were analysed from 50 patients with invasive breast carcinoma. Continuous variables were summarised using mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Associations between TRPS1 expression and clinicopathological variables were evaluated using Fisher's exact test when expected cell counts were <5, otherwise Pearson's chi-square test was applied. A two-sided p-value < 0.05 was considered statistically significant. TRPS1 immunoreactivity was detected in 39 of 50 cases (78.0%), while 11 cases (22.0%) were negative. Most positive cases demonstrated moderate to strong nuclear staining intensity. Overall, TRPS1 expression showed a relatively consistent distribution across histological categories and tumour grades.

3.1 General clinicopathological characteristics

Mean age of the patients was 52.86 ± 11.8 years (range, 27-75 years). With 50 to be the prespecified age criterion, 34 (68.0%) patients were at least 50 years of age and 16 (32.0%) were younger than 50 years of age. Invasive ductal carcinoma of no special type (IDC-NST) predominated histopathologically, comprising 41 cases (82.0%). Three cases (6.0%) were diagnosed as Invasive lobular carcinoma, and 3 other cases (6.0%) as mucinous carcinoma, while there was one case each of metaplastic, medullary and tubular carcinomas (2.0% for each subtype).

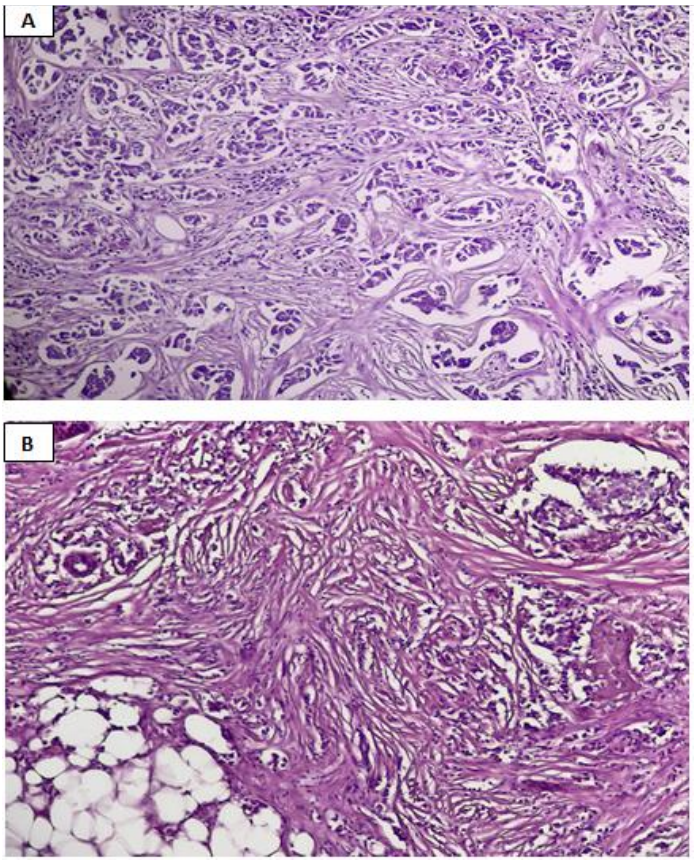


Figure 1. Histopathological morphology of invasive breast carcinoma.

Representative hematoxylin and eosin-stained sections illustrating the morphological spectrum of invasive breast carcinoma. (A) Invasive lobular carcinoma characterized by infiltrative single-file arrangements of discohesive tumor cells within a fibrotic stromal background. (B) Invasive carcinoma exhibiting irregular malignant glandular structures infiltrating a desmoplastic stroma with extension into adjacent adipose tissue. These features were used to confirm the histopathological diagnosis and assess tumor morphology prior to TRPS1 immunohistochemical evaluation.

With respect to molecular subtype, Luminal A was the most frequent category, accounting for 20 case, followed by Luminal B in 15 cases, triple-negative breast cancer in 9 cases, and HER2-enriched carcinoma in 6 cases. Thus, hormone receptor–positive tumours, represented by Luminal A and Luminal B subtypes, comprised 70% of the cohort. Tumour grading showed that most carcinomas were moderately differentiated, observed in 28 cases, followed by poorly differentiated tumours in 18 cases and well-differentiated tumours in 4 cases. According to AJCC staging, Stage II was the most frequent stage, followed by Stage III, Stage I and Stage IV in 7 patients. Regarding TNM components, T2 tumours were most common (26 cases), N0 nodal status was recorded in 17 cases, and absence of distant metastasis (M0) was documented in 43 cases, (Table 1).

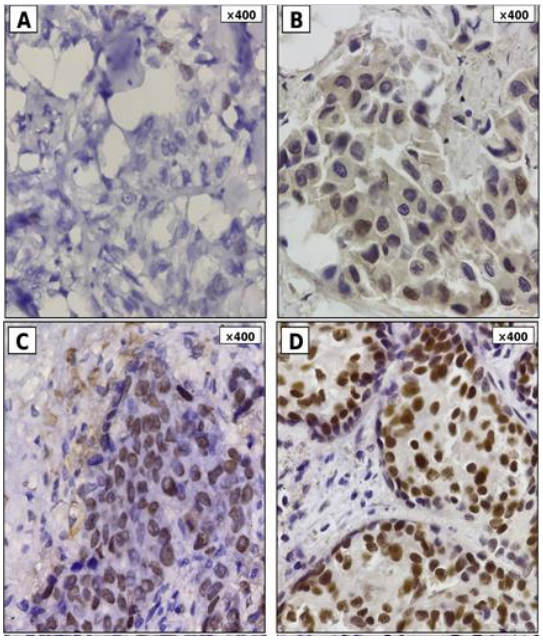
Table 1. General clinicopathological characteristics of the study cohort.

Characteristic	Category	Frequency	Percentage
Age, years	<50	16	32.0
	≥50	34	68.0
	Mean ± SD	52.86 ± 11.8	—
	Range	27–75	—
Histopathological type	IDC-NST	41	82.0
	Mucinous carcinoma	3	6.0
	Invasive lobular carcinoma	3	6.0

	Metaplastic carcinoma	1	2.0
	Medullary carcinoma	1	2.0
	Tubular carcinoma	1	2.0
Molecular subtype	Luminal A	20	40.0
	Luminal B	15	30.0
	HER2-enriched	6	12.0
	Triple-negative	9	18.0
Tumour grade	Well differentiated	4	8.0
	Moderately differentiated	28	56.0
	Poorly differentiated	18	36.0
AJCC stage	Stage I	8	16.0
	Stage II	18	36.0
	Stage III	17	34.0
	Stage IV	7	14.0
Primary tumour stage	T1	12	24.0
	T2	26	52.0
	T3	11	22.0
	T4	1	2.0
Nodal stage	N0	17	34.0
	N1	14	28.0
	N2	13	26.0
	N3	6	12.0
Distant metastasis	M0	43	86.0
	M1	7	14.0

3.2 Pattern of TRPS1 immunohistochemical expression

TRPS1 expression was evaluated as nuclear immunoreactivity within invasive tumour cells. Staining intensity varied across the cohort, ranging from complete absence of nuclear staining to low, intermediate, and strong nuclear expression. Among the 50 invasive breast carcinomas, 39 tumours were TRPS1-positive, while 11 were negative. Strong nuclear staining was the predominant pattern, present in 64.0% of all cases. This finding indicates that TRPS1 expression, when present, was usually not merely focal or weak, but frequently showed a robust nuclear immunophenotype.



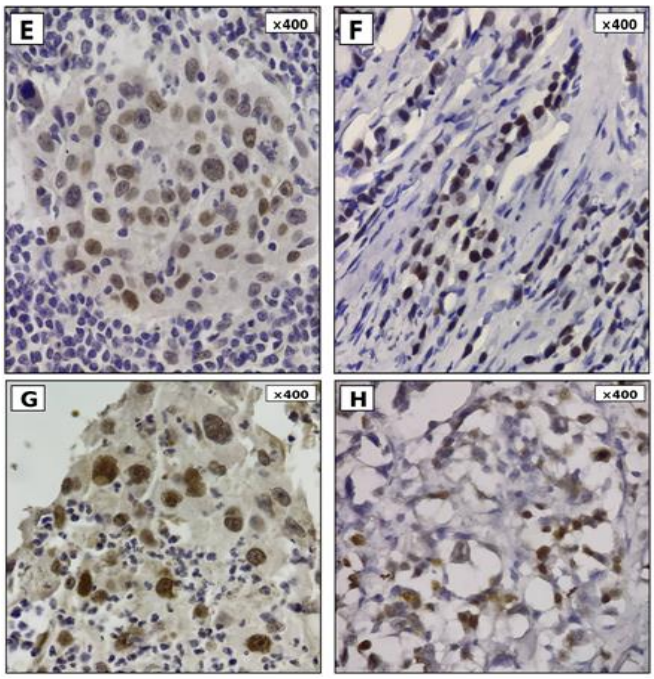


Figure 2. TRPS1 immunohistochemical nuclear expression in invasive breast carcinoma subtypes. Representative photomicrographs at ×400 magnification demonstrating variable nuclear staining intensity. (A) Invasive ductal carcinoma, no special type (IDC-NST) showing negative nuclear expression. (B) IDC-NST with low-positive nuclear immunoreactivity. (C) IDC-NST demonstrating intermediate nuclear expression. (D) IDC-NST with strong diffuse nuclear positivity. (E) Medullary carcinoma showing intermediate nuclear TRPS1 expression. (F) Invasive lobular carcinoma demonstrating strong nuclear staining. (G) Metaplastic carcinoma with strong nuclear immunoreactivity. (H) Mucinous carcinoma showing intermediate nuclear expression. All sections were stained by immunohistochemistry and counterstained with hematoxylin. Nuclear staining intensity was semi-quantitatively variable across histological subtypes.

TRPS1 immunohistochemistry demonstrates a spectrum of nuclear staining intensity in invasive breast carcinoma. Panel A shows negative TRPS1 expression, with absence of tumour-cell nuclear staining. Panel B shows low positive nuclear staining. Panel C shows intermediate nuclear expression. Panel D shows strong and diffuse nuclear TRPS1 expression. TRPS1 was interpreted as positive only when nuclear staining was present in invasive tumour cells; non-specific background or cytoplasmic staining was not used for scoring.

3.3 Association between TRPS1 expression and age

TRPS1 positivity was detected for 12 of the 16 patients aged <50 years (75.0%) in comparison with the detection rate in older patients age≥50 years (27 out of 34 patients, 79.4%) (Table 2). TRPS1 expression was not significantly associated with patient age in the cohort, since the difference between both age groups was not statistically significant (p=0.725).

Table 2. TRPS1 expression according to patient age

Parameter	Category	TRPS1-positive, n/N (%)	TRPS1-negative, n/N (%)	p value
Age, years	<50	12/16 (75.0)	4/16 (25.0)	0.725
	≥50	27/34 (79.4)	7/34 (20.6)	0.725

3.4 Association between TRPS1 expression, histopathological type, and molecular subtype

TRPS1 expression varied across surrogate immunohistochemical molecular subgroups. Among IDC-NST cases, 32 of 41 tumours (78.0%) were TRPS1-positive. All cases of invasive lobular carcinoma, metaplastic carcinoma, and medullary carcinoma showed TRPS1 positivity; however, these categories included very small sample sizes. Mucinous carcinoma showed TRPS1 positivity in 2 of 3 cases (66.7%), while the single tubular carcinoma case was negative.

No statistically robust association was observed between histological subtype and TRPS1 expression (overall p = 0.394). In contrast, a statistically significant association was observed between TRPS1 expression and surrogate molecular subtype classification (overall p = 0.046). Positivity was higher in Luminal-like B (14/15, 93.3%) and Luminal-like A (17/20, 85.0%) groups compared with HER2-enriched (3/6, 50.0%) and triple-negative groups (5/9, 55.6%). Given the small subgroup sizes, these differences should be interpreted as descriptive trends rather than definitive subtype-specific effects.

Table 3. TRPS1 expression according to histopathological type and molecular subtype

Parameter	Category	TRPS1-positive, n/N (%)	TRPS1-negative, n/N (%)	Within-category p value
Histopathological type	IDC-NST	32/41 (78.0)	9/41 (22.0)	<0.001
	Mucinous carcinoma	2/3 (66.7)	1/3 (33.3)	0.564
	Invasive lobular carcinoma	3/3 (100.0)	0/3 (0.0)	—
	Metaplastic carcinoma	1/1 (100.0)	0/1 (0.0)	—
	Medullary carcinoma	1/1 (100.0)	0/1 (0.0)	—
	Tubular carcinoma	0/1 (0.0)	1/1 (100.0)	—
Overall histopathological-type association	—	—	—	0.394
Molecular subtype	Luminal A	17/20 (85.0)	3/20 (15.0)	0.002
	Luminal B	14/15 (93.3)	1/15 (6.7)	0.001
	HER2-enriched	3/6 (50.0)	3/6 (50.0)	1.000
	Triple-negative	5/9 (55.6)	4/9 (44.4)	0.739
Overall molecular-subtype association	—	—	—	0.046

3.5 Association between TRPS1 expression and tumour grade

TRPS1 expression was observed across all tumour grades. Positivity was detected in 3 of 4 well-differentiated carcinomas (75.0%), 22 of 28 moderately differentiated carcinomas (78.6%), and 14 of 18 poorly differentiated carcinomas (77.8%). No statistically significant association was identified between tumour grade and TRPS1 expression (p = 0.987). Although minor numerical variation was observed between groups, these differences were not statistically or biologically robust.

Table 4. TRPS1 expression according to tumour grade

Parameter	Category	TRPS1-positive, n/N (%)	TRPS1-negative, n/N (%)	Within-category p value
Tumour grade	Well differentiated	3/4 (75.0)	1/4 (25.0)	0.317
	Moderately differentiated	22/28 (78.6)	6/28 (21.4)	0.002
	Poorly differentiated	14/18 (77.8)	4/18 (22.2)	0.018
Overall grade association	—	—	—	0.987

3.6 Association between TRPS1 expression and AJCC/TNM stage

TRPS1 expression was observed across all AJCC stages. Positivity was detected in 6 of 8 Stage I tumours (75.0%), 15 of 18 Stage II tumours (83.3%), 11 of 17 Stage III tumours (64.7%), and all 7 Stage IV tumours (100.0%).

However, no statistically significant association was identified between TRPS1 expression and AJCC stage (p = 0.254). Similar lack of association was observed for pathological tumour (T) stage, nodal status, and distant metastasis status. For TNM components, TRPS1 expression was present across all categories without a consistent stage-dependent pattern. Although all metastatic (M1) cases showed TRPS1 positivity, the small sample size limits interpretability of this finding. Overall, these results suggest that TRPS1 expression is not associated with tumour stage or disease progression parameters in this cohort.

Table 5. TRPS1 expression according to AJCC stage and TNM components

Parameter	Category	TRPS1-positive, n/N (%)	TRPS1-negative, n/N (%)	Within-category p value
AJCC stage	Stage I	6/8 (75.0)	2/8 (25.0)	0.157
	Stage II	15/18 (83.3)	3/18 (16.7)	0.005
	Stage III	11/17 (64.7)	6/17 (35.3)	0.225
	Stage IV	7/7 (100.0)	0/7 (0.0)	—
Overall AJCC-stage association	—	—	—	0.254
Primary tumour stage	T1	10/12 (83.3)	2/12 (16.7)	0.021
	T2	21/26 (80.8)	5/26 (19.2)	0.002
	T3	7/11 (63.6)	4/11 (36.4)	0.366
	T4	1/1 (100.0)	0/1 (0.0)	—
Overall pT-stage association	—	—	—	0.589
Nodal stage	N0	14/17 (82.4)	3/17 (17.6)	0.008
	N1	11/14 (78.6)	3/14 (21.4)	0.033
	N2	9/13 (69.2)	4/13 (30.8)	0.166
	N3	5/6 (83.3)	1/6 (16.7)	0.102
Overall nodal-stage association	—	—	—	0.832
Distant metastasis	M0	32/43 (74.4)	11/43 (25.6)	0.001
	M1	7/7 (100.0)	0/7 (0.0)	—
Overall metastatic-status association	—	—	—	0.130

4. Discussion

Breast carcinoma is a biologically diverse class of neoplasms for which immunohistochemical biomarkers are central in tumour classification, lineage typing and treatment decisions. Here, the transcription factor TRPS1 was recently identified as a nuclear breast-lineage–associated marker that may provide utility across both histological and molecular subtypes. In this study, we analysed the expression of TRPS1 in a cohort of 50 invasive breast carcinomas and correlated its expression with clinicopathological parameters as well surrogate immunohistochemical molecular subtypes.

Performing this study revealed 78% positive expression for TRPS1 with strong nuclear staining being the majority. This finding is consistent with the expected localisation of TRPS1 as a transcriptional regulator and validates in principle the immunohistochemical staining method. The positivity rate we observed is consistent with studies of TRPS1 in invasive breast carcinomas, including those that are triple-negative and special histological subtypes [14–16]. Nevertheless, variable expression rates reported between studies are likely a reflection of antibody clone selection/scoring thresholds/tissue processing conditions/cohort composition [17–19]. The association between TRPS1 expression and surrogate molecular subtype classification was also statistically significant (p = 0.046). Expression was highest in the Luminal B and luminal A groups, but lower rates were reported from HER2-enriched (aromatase-positive) subgroups and triple-negative categories. The pattern may indicate that TRPS1 expression is retained more often and at a higher level in hormone receptor–positive tumours in this population. This has been noted in earlier studies, with other larger series revealing extensive TRPS1 expression across breast cancer subtypes, including triple-negative tumours [14,16,19]. This discrepancy could arise from small sample sizes, tumour biology in specific populations and differences in

the application of immunohistochemical interpretation methods.

These studies derive their molecular subtype classification based on immunohistochemical surrogates (ER, PR and HER2 status) without analysing the Ki-67 proliferation index; the inclusion of event metaprise can confound our findings. As such, these categories should be viewed as surrogate receptor based groups rather than true gene-expression–based intrinsic subtypes. Such a limitation might affect subtype-specific associations and should be factored in when comparing results with studies that have applied more sophisticated molecular classifications.

However, the expression level of TRPS1 was not significantly associated with histological subtype. TRPS1 expression was detected in (i.e invasive ductal carcinoma of no special type, invasive lobular carcinoma and metaplastic carcinoma), being limited the number of cases amongst distinct histological variants. Thus, subtype-specific interpretations should be viewed with caution. Previous studies have reported wide expression of TRPS1 across multiple histological categories as well, supporting its general characteristic role as a lineage-associated marker instead of a histotype-specific biomarker [16-18]. With regards to tumour grade, TRPS1 expression was maintained in well and moderately differentiated carcinomas but lost or reduced in poorly differentiated tumours with no overall association. Suggesting that TRPS1 expression is largely coordinated and independent of histological differentiation and tumour grade. Therefore, TRPS1 should not be considered as an alternative marker for tumour aggressiveness or systematic histological grading.

Although previous studies have examined potential correlations with prognosis, the evidence remains inconsistent regarding TRPS1 expression being associated consistently with tumour grade or biological behavior [13,20]. In the same line, TRPS1 expression was not significantly associated with also pathological tumour stage, nodal status or overall AJCC-stage. TRPS1 positivity was noted at all stages including the advanced disease, although these findings suggest that TRPS1 may not directly relate to tumour burden or stage of disease. The TRPS1 positivity observed in advanced-stage cases appears instead of a stage-dependent biological effect and is likely explained by preserved lineage expression. Yet, the relatively small number of patients within individual AJCC categories limits interpretation of stage-specific findings. Importantly, TRPS1 was found to be expressed in metastatic cases (M1), although there were few such tumours. Although this finding might indicate retention of the TRPS1 expression in some advanced disease, we emphasise that it should not be taken as evidence for diagnostic value versus non-breast malignancies without comparative studies. To assess whether TRPS1 has utility in this diagnostic setting, larger comparative studies including metastatic cancers of unknown primary origin are needed [18,20].

For diagnostic purposes, the current data suggest that TRPS1 acts as an often-expressed breast-lineage–associated marker instead of being a sole diagnostic factor. The consistent nuclear expression in several tumour grades and stages raises the prospect of using ARID1A as an adjunctive immunohistochemical marker to characterise tumours that are difficult-to- classify. However, the lack of nonbreast tumour controls in this study prevents an evaluation of specificity; therefore, TRPS1 should not be simply regarded as a definitive breast origin marker by itself. Rather, it needs to be assessed in the context of established markers including GATA3 and SOX10 along with morphological and clinical correlation [6,22].

The association of TRPS1 expression with breast carcinoma is based on its function as an epithelial differentiation regulator and transcription factor in mammary tissue. Previous studies have indicated that TRPS1 maintains epithelial lineage traits and therefore may be generally expressed in many breast carcinoma subtypes [12]. However, its precise role in tumour progression has not been completely unraveled and existing data does not support a direct involvement as predictive marker of aggressive behavior or clinical outcome yet.

There are a number of limitations in the current study to be aware while interpreting the results. The sample size is modest, especially within individual histological and molecular subtypes limiting statistical power and the robustness of subgroup analyses. Furthermore, the lack of Ki-67 evaluation limits the accuracy of molecular subtype assignment. Additionally, the absence of a non-breast tumour control group prevents definitive conclusions about diagnostic specificity. And of course, no survival data were available to assess any prognostic relevance. Despite these limitations, this study presents regionally relevant data regarding TRPS1 expression in a cohort from Iraq and adds to the increasing literature evaluating TRPS1 as an immunohistochemical marker for diagnostic use. Our analyses support its utility as a low but stable expression breast-lineage marker that is broadly expressed in tissues, although caution should be used when interpreting results from small or heterogeneous datasets. Further studies are needed on larger multicenter cohorts with a more balanced representation of the different molecular subtypes and histological variants.

Studies including non-breast neoplasms and comparative analyses with established breast markers are required to better understand the diagnostic specificity of TRPS1. Finally, the incorporation of survival data and functional experiments could help determine whether TRPS1 has any prognostic or biologic implications aside from its current diagnostic utility [18–21].

4.1 Recommendations

Future studies, including larger, prospectively assembled cohorts with balanced representation from luminal, HER2-enriched, and triple-negative carcinomas and special histologic subtypes should be multicentre. TRPS1 must be harmonised across laboratories through standardisation of antibody clone and staining platform as well as scoring threshold and reporting terminology. TRPS1 studies should be compared with well-characterised breast markers, especially GATA3, SOX10, mammaglobin, GCDFP-15 and FOXC1 in limited specimens, metastases, cytology specimens and diagnostically problematic tumours. Additional studies should also investigate matched primary and metastatic breast carcinomas to assess whether loss of TRPS1 expression occurs during progression or following exposure to systemic therapy. TRPS1 requires further survival-based analyses adjusted for age, tumour size, nodal status, grade, ER/PR/HER2 status, Ki-67 and treatment modality to determine if it possesses independent prognostic value. Conversely, further functional studies at the molecular level will shed light on how TRPS1 integrates with hormone receptor signalling, epithelial–mesenchymal plasticity, chromatin regulation and lineage maintenance.

4.5 Strengths and Limitations

This study has several strengths. It primarily addresses a clinically very relevant diagnostic dilemma: the demand for immunohistochemical markers that when evaluated in isolation and/or panels, accurately aid in confirming a diagnosis of breast carcinoma particularly under circumstances where subtype-dependent loss of expression renders traditional markers less reliable. Second, all cases were histologically proven invasive breast carcinomas, and studying included clinically relevant variables such as molecular subtype, histologic type, grade and TNM/AJCC stage. Third, the criteria used for defining TRPS1 as positive are biologically relevant and consistent with how transcription factors are expected to localise (e.g. nuclear staining). Finally, this study provides data from an Iraqi clinical setting adding regional evidence to a literature which is otherwise still dominated by larger institutional cohorts from other population settings. Lastly, the comparison of TRPS1 expression versus molecular or clinicopathological groups creates a more nuanced diagnostic classification rather than just positive marker status. The major limitation is indeed the small sample size especially in rare histologic types and non-luminal molecular subgroups. This reduces statistical power and leaves subgroup estimates open to instability. For instance, TRPS1 expression in tubular carcinoma cannot be extrapolated from the single case of tubular carcinoma.

5. Conclusion

TRPS1 is commonly expressed in invasive breast carcinoma with variable frequency across surrogate molecular subtypes and was more frequently expressed in hormone receptor–positive tumours from this cohort. However, it has no significant association with tumour grade, stage or other clinicopathological parameters, supporting its role as a lineage-associated biomarker rather than a prognostic indicator. Its diagnostic value remains best applied as part of a broader immunohistochemical panel rather than as a standalone marker

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Ethics Statement:

The research is exclusively based on published literature; hence, ethical approval is not required.

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