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Immunohistochemical Expression of SOX10 in Triple-Negative Breast Carcinoma and its Clinicopathological Significance

Chinnadevi.B.S[1], Natarajan Suresh[2], Ajitha R[3]

[1]Postgraduate,Department of Pathology, Sree Balaji Medical college and hospital.

Email ID: chinnaa27.s@gmail.com / Orcid: 0009-0001-8595-1563

[2]MDPathology,Professor, Department of Pathology, Sree Balaji Medical college and hospital

Email ID: natarajansuresh@bharathuniv.ac.in / Orcid : 0000-0003-4966-5559

[3]MD Pathology, Assistant Professor, Department of Pathology, Sree Balaji Medical college and hospital

Email ID: ajitha.pathology@bharathuniv.ac.in / Orcid-0000-0002-5852-665X

ABSTRACT

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype lacking estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. SOX10, a neural crest transcription factor, is implicated in TNBC pathogenesis, particularly basal-like subtypes. This study evaluated SOX10 expression in TNBC and its association with clinicopathological parameters.

Methods: A cross-sectional study was conducted on 40 formalin-fixed paraffin-embedded (FFPE) TNBC tissue blocks (August 2023–March 2025). SOX10 immunohistochemistry (IHC) was performed using a rabbit monoclonal antibody (EP268). Staining was considered positive if >1% of tumor nuclei showed immunoreactivity and graded as patchy (1–10%), focal (11–70%), or diffuse (>70%). Associations with age, laterality, histologic subtype, grade, stage, and lymphovascular invasion (LVI) were analyzed using Chi-square/Fisher's exact tests (SPSS v28.0; $p<0.05$ significant).

Results: SOX10 expression was observed in 18/40 cases (45%). Expression significantly correlated with higher histologic grade ($p<0.001$): 50% of Grade 3 tumors were positive vs. 5.6% of Grade 1. Diffuse staining increased with grade ($p=0.01$). SOX10 positivity was also associated with advanced pathological T stage (T2-T4b; $p<0.001$). No significant associations were found with age, laterality, quadrant, histologic subtype, nodal status, AJCC stage, or LVI ($p>0.05$). The predominant subtype was invasive carcinoma of no special type (IBC-NST; 87.5%).

Conclusion: SOX10 is expressed in nearly half of TNBCs and is significantly associated with high-grade and advanced T-stage disease, suggesting a role in tumor aggressiveness. It may serve as a valuable biomarker for risk stratification and a potential therapeutic target in TNBC.

Keywords: *SOX10, Triple-Negative Breast Cancer, Immunohistochemistry, Biomarker, Basal-like, Prognosis.*

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1. INTRODUCTION

Breast carcinoma remains the most prevalent malignancy among women worldwide and represents a major global health challenge due to its rising incidence and mortality, particularly in developing countries. Among its molecular subtypes, triple-negative breast cancer (TNBC) accounts for approximately 10–20% of all breast carcinomas and is defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. TNBC is characterized by aggressive biological behaviour, histological heterogeneity, higher rates of recurrence and visceral metastasis, and poorer overall prognosis compared with other breast cancer subtypes. Moreover, TNBC disproportionately affects younger women and certain ethnic groups, such as African American and Hispanic women, underscoring its clinical and epidemiological significance.

Conventional diagnostic and prognostic evaluation of breast carcinoma relies heavily on immunohistochemistry (IHC) for the determination of ER, PR, HER2, and proliferation markers such as Ki-67. While these markers are valuable for treatment planning in luminal and HER2-positive subtypes, their utility is limited in TNBC, which lacks defined therapeutic

targets and presents diagnostic challenges, especially in metastatic settings. Commonly applied breast lineage markers, including gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin (MGB), and GATA-binding protein 3 (GATA3), exhibit reduced sensitivity in TNBC. Importantly, biomarker expression may also be lost during metastatic progression, further complicating the precise determination of tumor origin. Thus, identification of additional sensitive and specific IHC markers for TNBC remains an area of pressing clinical need.

In recent years, the SRY-related HMG-box 10 (SOX10) transcription factor has emerged as a promising candidate biomarker in this context. SOX10 plays a pivotal role in neural crest differentiation and regulates crucial signalling pathways such as Wnt/β-catenin, influencing progenitor cell activity and epithelial-to-mesenchymal transition. Initially recognized for its diagnostic utility in melanocytic and Schwann cell tumors, SOX10 expression has since been reported in several epithelial malignancies, including breast carcinomas. Importantly, SOX10 positivity is enriched in the basal-like and unclassified molecular subsets of TNBC, with reported expression frequencies ranging from 33% to 74%. Compared with other breast markers, SOX10 demonstrates superior sensitivity and stronger staining in TNBC, and maintains higher concordance between primary and metastatic tumors. Preliminary studies suggest that SOX10 expression may correlate with clinicopathological features and survival outcomes, raising the possibility of its utility as a prognostic biomarker in TNBC. However, large-scale studies integrating SOX10 with molecular and clinical datasets remain limited, and its biological implications in TNBC progression are still not fully elucidated.

A more comprehensive understanding of SOX10 expression in TNBC may provide valuable prognostic insights. The present study aimed to evaluate SOX10 immunohistochemical expression in TNBC and investigate its association with clinicopathological parameters to determine its potential clinical significance.

2. MATERIALS AND METHODS

This cross-sectional study was conducted in the Central Laboratory, Department of Pathology, Sree Balaji Medical College and Hospital, Chennai, between August 2023 and March 2025, after obtaining approval from the Institutional Ethics Committee. A total of 40 formalin-fixed, paraffin-embedded (FFPE) tissue blocks of immunohistochemistry (IHC)-confirmed triple-negative breast cancer (TNBC) cases, including tru-cut biopsies and resection specimens, were included. Cases with benign lesions, non-representative tissue, or inadequate material were excluded. Clinicopathological variables assessed included age, laterality, quadrant, specimen type, histologic subtype, histologic grade (Nottingham system), pathological T and N stage (AJCC 8th edition), AJCC stage, lymphovascular invasion (LVI), and SOX10 expression. For IHC, 3-µm tissue sections were subjected to antigen retrieval using Tris-EDTA buffer (pH 9) in a pressure cooker. SOX10 staining was performed using a rabbit monoclonal antibody (Clone EP268; IVD, nuclear localization), with detection by the PolyExcel HRP/DAB system. Melanoma tissue was used as positive control. Nuclear staining in more than 1% of tumor cells was regarded as positive for SOX10 and further graded as patchy (1–10%), focal (11–70%), or diffuse (>70%). Data were analyzed using SPSS version 28.0. Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were described as proportions. Associations between SOX10 expression (positive vs. negative) and clinicopathological parameters were evaluated using Chi-square or Fisher's exact test, with a p-value of <0.05 considered statistically significant.

Results

A total of 40 cases of invasive breast carcinoma were analysed. The mean patient age was 46.43 ± 9.24 years, with a peak incidence in the 41–50-year age group (42.5%). Tumors occurred more frequently in the right breast (60%) than the left (40%). The upper quadrants were the most common location (67.5%), followed by the lower quadrants (25%) and central region (7.5%). The specimens included resection specimens (65%) and trucut biopsies (35%).

Histopathology:

The predominant histological subtype was invasive breast carcinoma of no special type (IBC-NST) (87.5%). Less common subtypes included mucinous carcinoma (5%), adenoid cystic carcinoma (5%), and invasive micropapillary carcinoma (2.5%). Tumor grading revealed 17.5% Grade 1, 60% Grade 2, and 22.5% Grade 3 carcinomas.

Pathological staging (n=26 resections):

Primary tumor stage distribution was T1 (11.5%), T2 (53.8%), T3 (15.4%), T4 (3.8%), and T4b (15.4%). Nodal stage distribution was N0 (50%), N1 (27%), N2 (7.6%), and N3 (15.4%). Based on AJCC staging, 4% of cases were Stage I, 54% Stage II, and 42% Stage III. Lymphovascular invasion (LVI) was present in 52.5% of tumors.

SOX10 expression:

Overall, SOX10 was positive in 18 cases (45%) and negative in 22 cases (55%). Among SOX10-positive tumors, staining patterns included patchy (38.9%), focal (33.3%), and diffuse (27.8%) (*figure 1*).

Clinicopathologic associations:

SOX10 expression showed a statistically significant correlation with histological grade ($p<0.001$). Positivity was observed in 5.6% of Grade 1, 44.4% of Grade 2, and 50% of Grade 3 tumors. Increasing staining intensity and distribution were also significantly associated with higher tumor grade ($p=0.01$). A similar strong association was found between SOX10 expression and pT stage ($p<0.001$); while no T1 tumors demonstrated positivity, SOX10 expression was observed in T2 (30.8%), T3 (30.8%), T4 (7.7%), and T4b (30.8%) tumors. No significant associations were observed between SOX10 expression and age, laterality, quadrant, histologic subtype, nodal stage, AJCC stage, or LVI. (*Table 1*)

Table 1: Comparison of clinicopathological and histological features with SOX10 IHC expression

Sl.No	Variable		SOX10 Negative	SOX10 Positive	Chi-Square Value	P Value
1.	Age	30-40	5(22.7%)	5(27.8%)	2.637	0.487
		41-50	10(45.5%)	7(38.9%)		
		51-60	7(31.8%)	4(22.2%)		
		>60	0(0)	2(11.1%)		
2.	Laterality	Left	9(40.9%)	7(38.9%)	0.017	0.578
		Right	13(59.1%)	11(61.1%)		
3.	Quadrant	Central	1(4.5%)	2(11.1%)	3.578	0.178
		Lower	8(36.4%)	2(11.1%)		
		Upper	13(59.1%)	14(77.8%)		
4.	Histologic Subtype	ADCC	0	2(11.1%)	4.082	0.162
		IBC NST	19(86.4%)	16(88.9%)		
		Invasive Micropapillary Carcinoma	1(4.5%)	0		
		Mucinous Carcinoma	2(9.1%)	0		
5.	Grade	1	6(27.3%)	1(5.6%)	15.48	***<0.001**
		2	16(72.7%)	8(44.4%)		
		3	0	9(50%)		
6.	pT Stage (n=26)	T1	3(23.1%)	0	13.439	***<0.001**
		T2	10(76.9%)	4(30.8%)		
		T3	0	4(30.8%)		
		T4	0	1(7.7%)		
		T4b	0	4(30.8%)		
7.	pN Stage (n=26)	N0	6(46.2%)	7(53.8%)	5.257	0.146
		N1	2(15.4%)	5(38.5%)		
		N2	1(7.7%)	1(7.7%)		
		N3	4(30.7%)	0		
8.	Lympho	Absent	12(54.5%)	7(38.9%)	0.978	0.252

	Vascular Invasion (n=26)	Present	10(45.5%)	11(61.1%)		
9.	AJCC (n=26)	I	1(7.7%)	0	2.020	0.301
		II	8(61.5%)	6(46.2%)		
		III	4(30.8%)	7(53.8%)		

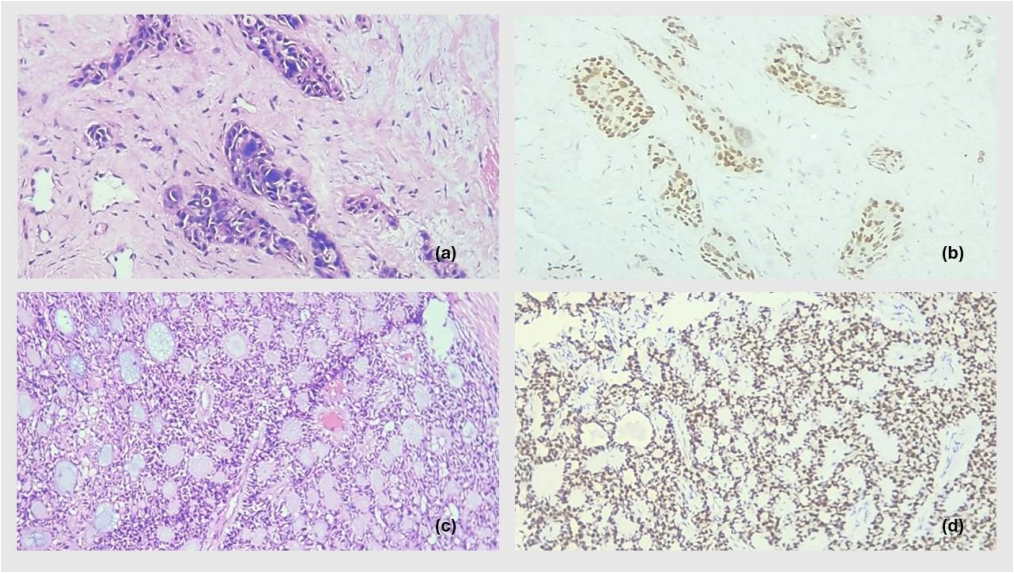

Figure 1 (a) Invasive Breast Carcinoma NST (H&E, X100); (b) Invasive Breast Carcinoma- NST Showing Positive Nuclear Stain for SOX10 (IHC, X100) (c) Adenoid Cystic Carcinoma of Breast (ADCC) (H&E, X100); (d) Adenoid Cystic Carcinoma of Breast Showing Positive Nuclear Stain for SOX10 (IHC, X100)

3. DISCUSSION

SOX10 expression in TNBC has emerged as an important diagnostic and prognostic marker with significant clinical implications. In our study, SOX10 positivity was observed in 45% of TNBC cases, consistent with reported rates ranging from 25% to 87.5% in the literature. Variability in expression frequencies across studies likely arises from differences in patient cohorts, antibody clones, staining procedures, and scoring criteria. Nonetheless, the consistent expression of SOX10 in TNBC highlights its value as a reliable immunohistochemical marker of this aggressive subtype.

A key finding across multiple studies, including ours, is the strong association between SOX10 expression and higher histological tumor grade. We demonstrated that 50% of Grade 3 tumors were SOX10 positive, compared to only 5.6% of Grade 1 tumors ($p < 0.001$). This aligns with findings by Ali et al., who also reported a strong correlation between SOX10 expression and Grade III invasive ductal carcinoma. However, relationships between SOX10 and other clinicopathological parameters exhibit heterogeneity across studies (*Table 2*). For instance, Kriegsmann et al. reported an inverse association between SOX10 positivity and tumor size, with more SOX10-positive cases in pT1 tumors, contrary to our findings and those of Syed Ahmed et al., who observed increased expression in larger tumors. These discrepancies suggest that the association of SOX10 with tumor progression may be influenced by population-specific or methodological variables requiring further investigation.

At the molecular level, Kriegsmann et al. showed that SOX10-positive TNBC often features a higher frequency of TP53 mutations, and fewer PIK3CA pathway alterations compared to SOX10-negative cases, indicating distinct molecular pathways that may affect treatment responses and prognosis.

The diagnostic utility of SOX10 is especially significant in metastatic contexts. Eric Statz et al. found that, although SOX10 sensitivity in primary TNBC is limited, it performs comparably to GATA3 in detecting TNBC metastases. Importantly, either CK7, GATA3, or SOX10 positivity was observed in all TNBC metastases, emphasizing the complementary role of these markers in diagnostic panels. SOX10 is particularly valuable in GATA3-negative TNBC metastases, where combined use enhances sensitivity for identifying mammary origin.

Several studies including those by Nelson et al. and Harbhajanka et al. demonstrate that SOX10 expression is largely

confined to basal-like TNBC, supporting its role as a basal-like/myoepithelial differentiation marker. It is frequently positive in basal-like and unclassified TNBC, with an inverse correlation to androgen receptor expression, aiding in subtype distinction. Rammal et al. also reported that SOX10 is strongly expressed in basal-like and certain salivary gland–type breast carcinomas and can help differentiate breast tumors from gynaecologic primaries. Linfang Jin et al. further highlighted SOX10 superior sensitivity and specificity over classical breast markers for primary and metastatic TNBC, reinforcing its diagnostic robustness.

Our study corroborates these findings by demonstrating SOX10 positivity in 45% of primary invasive breast carcinomas with significant associations to higher histologic grade and advanced pathological T stage, but no significant relation to nodal status or lymphovascular invasion. Collectively, these studies establish SOX10 as a dual-purpose biomarker with diagnostic and prognostic relevance in TNBC, reinforcing the rationale for its incorporation alongside GATA3 and other lineage markers in routine pathology practice.

Despite these advances, challenges remain for clinical translation. Standardization of SOX10 testing, including antibody selection, staining protocols, and scoring criteria, is needed to ensure reproducibility. Additional large-scale prospective studies are required to define definitive positivity cutoffs and validate SOX10's prognostic and predictive roles, particularly in treatment stratification.

Table 2: Association of SOX10 Expression with Clinicopathological Parameters in Various Studies

Parameter	Present Study	Ali et al.	Jin et al.	Rammal et al.	Eric Statz et al.
High Grade	Significant ($p<0.001$)	Significant ($p=0.00006$)	77.8% in high-grade	Significant association	Not reported
T Stage	Significant ($p<0.001$)	Not reported	Not reported	Inverse association	Not reported
Nodal Status	Not significant ($p=0.146$)	Not significant	Increased expression	Not reported	Not reported
Lymphovascular Invasion (LVI)	Not significant ($p=0.252$)	Not reported	Not reported	Not reported	Not reported
Marker Stability in Metastasis	Not assessed	Not assessed	Not assessed	Not assessed	GATA3 and mammaglobin lost in brain metastases

4. CONCLUSION

SOX10 is expressed in 45% of TNBCs and demonstrates a significant association with high histological grade and advanced pathological T stage, indicating its potential role in tumor aggressiveness. It serves as a useful immunohistochemical marker in the diagnostic workup of TNBC. The association with aggressive features warrants further investigation into SOX10 as a therapeutic target and its potential prognostic significance in larger, multicentre studies incorporating molecular subtyping and clinical outcomes.

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