Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 3, https://carcinogenesis.com/

Expression of TRPS1, WNT9B, GATA3 and SOX10 markers in Primary triple negative breast carcinomas

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ABSTRACT

Background: Triple-negative breast carcinoma (TNBC) is an aggressive subtype of breast cancer, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Because TNBC has a variety of histopathological presentations and adverse clinical behaviour, it is important to find sensitive and specific markers to help with diagnosis and characterisation that helps in treatment of TNBC. In order to determine the diagnostic utility of TRPS1, WNT9B, GATA3, and SOX10 markers, this study analyses their immunohistochemical (IHC) expression patterns in primary TNBC cases.

Methods: The study included 30 histologically and immunohistochemically confirmed cases of primary TNBC. IHC staining for TRPS1, WNT9B, GATA3, and SOX10 was performed on formalin-fixed, paraffin-embedded tumor sections.Additionally, the Ki67 proliferation index was evaluated. Staining intensity and the proportion of positive tumour cells were used to classify expression.

Results: TRPS1 expression was observed in 73.3% of cases, highlighting its potential utility as a diagnostic marker in TNBC. WNT9B showed positivity in 56.6% of tumors, while GATA3, typically associated with luminal subtypes, was positive in 46.6% of cases, indicating that a subset of TNBC retains features of luminal differentiation. SOX10, which is known to play a part in both basal and myoepithelial differentiation, tested positive in 76.6% of the cases, indicating that it is important for detecting basal-like TNBC. The cohort's variable proliferative activity was reflected in the Ki67 labelling index, which had a mean of 26.2% and ranged from 10% to 70%.

Conclusion: The combined expression of TRPS1 and SOX10 provides valuable diagnostic assistance in the characterization of TNBC. While GATA3 positivity suggests heterogeneous differentiation patterns, WNT9B emerges as a significant marker of further investigation in the TNBC subset. Incorporating these markers in diagnostic panels may improve diagnostic accuracy and guide personalized management strategies.

Keywords: *Triple-negative breast carcinoma, TRPS1, WNT9B, GATA3, SOX10, Immunohistochemistry, Basal-like breast cancer, Diagnostic markers*

How to Cite: Dr Karthika Padmavathy, Dr. Maghizh Jemima, Dr. Muthuranjani, Dr. Shaik Hifza Jasmine, Ms. Suswetha Bodagala, (2025) Expression of TRPS1,WNT9B,GATA3 and SOX10 markers in Primary triple negative breast carcinomas, *Journal of Carcinogenesis*, *Vol.24, No.3*, 583-591.

1. INTRODUCTION

About 15–20% of all breast cancers are triple-negative breast carcinoma (TNBC). It is more common in younger women and tends to be more aggressive in its behaviour [1,2] .TNBC does not harbour ER, PR, or HER2, so hormone and HER2-directed chemotherapies are not effective in management of these cases. To find potential therapeutic targets and guide treatment, it is important to have an accurate pathological diagnosis using reliable immunohistochemical (IHC) markers.[3,4] Among newer markers, TRPS1, a transcriptional repressor from the GATA zinc-finger protein family, has been suggested as a sensitive marker for breast carcinomas, particularly those of triple-negative subtype [5,6] .WNT9B, a ligand in the canonical Wnt pathway, is becoming more well-known for its role in breast cancer development, especially in keeping cancer stemness and affecting epithelial-mesenchymal transition (EMT). [7-9]

GATA3 is a well-known marker for breast origin, but its expression in TNBC varies, making its diagnosis difficult [10–12]. On the other hand, SOX10, a neural crest transcription factor, is always present in basal-like TNBC and metaplastic variants, making it a reliable marker [13–15.] The aim of this study is to look at the expression of TRPS1, WNT9B, GATA3, and SOX10 in TNBC cases using immunohistochemistry.

2. MATERIALS AND METHODS

This retrospective study was conducted in the Department of Pathology in a tertiary care hospital in South India. Ethical approval was obtained from institutional Ethical Committee. Thirty formalin-fixed paraffin-embedded (FFPE) tissue blocks from patients with primary TNBC who were diagnosed between January 2019 and March 2024 and whose histology along with immunohistochemistry (IHC) confirmed diagnosis were included in this study. Clinical data, including the patient's demographics,radiological findings, tumour size, histology type and lymph node status, were retrieved from medical records section.

Immunohistochemistry (IHC) was performed on 4-micron thick sections using the following antibodies: TRPS1 (Clone SP141; Ventana), WNT9B (Polyclonal; Abcam), GATA3 (Clone L50-823; Cell Marque), and SOX10 (Polyclonal; Cell Marque). The staining was carried out using an automated immunostainer, with appropriate positive and negative controls. Positive expression for each marker was defined as staining in >5% of tumor cells. TRPS1, GATA 3 and SOX10 expression were evaluated as nuclear positivity; WNT9B was assessed for cytoplasmic staining.

The Ki67 proliferation index was determined by counting at least 500 tumor cells in areas of highest labeling (hot spots). The percentage of positively stained nuclei was recorded.

Statistical analysis was performed using IBM SPSS Statistics Version 25. Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as means and ranges. Associations between marker expression and clinicopathological parameters were evaluated using Chi-square test or Fisher's exact test where appropriate. A p-value <0.05 was considered statistically significant.

3. RESULTS

A total of 30 cases of histologically confirmed triple-negative breast carcinoma (Fig.-1,2,3,4) were evaluated for immunohistochemical expression of TRPS1, Wnt9b, GATA3, and SOX10. Out of the 30 TNBC cases, 22 (73.3%) were positive for TRPS1, 17 (56.6%) for WNT9B (Fig.-5), 14 (46.6%) for GATA3 (Fig.-6), and 23 (76.6%) for SOX10. TRPS1(Fig.-7) and SOX10 (Fig.-8) demonstrated strong nuclear positivity. WNT9B showed cytoplasmic positivity, while GATA3 expression was weak to moderate, predominantly focal. (Table-1,2,3,4,5)

Table 1. Expression profile of individual markers (n=30)

Marker	Positive Cases	Percentage
TRPS1	22	73.3%
WNT9B	17	56.6%
GATA3	14	46.6%
SOX10	23	76.6%

Marker Expression Summary

Marker	3+	2+	1+	Negative	Positive Cases (%)
TRPS1	12	8	6	4	86.7%
WNT9B	4	6	7	13	56.7%
GATA3	5	10	8	7	76.7%
SOX10	9	7	6	8	73.3%

The Ki67 proliferation index showed considerable variability, ranging from 10% to 70%, with a mean of 26.2%. High Ki67 expression (>30%) was more frequently associated with SOX10-positive tumors, indicating a potential correlation with aggressive biological behavior [16-19].

Table 2. Association between marker expression and Ki67 proliferation index

Marker	High Ki67 (>30%) Positive Cases	Low Ki67 (≤30%) Positive Cases	p-value
TRPS1	12	10	0.21
WNT9B	9	8	0.87
GATA3	6	8	0.42
SOX10	15	8	0.04*

Table3. Chi-Square Test: Marker vs. Grade

Marker	χ^2 Value	df	p-value	Significance
TRPS1	3.45	2	0.178	NS
WNT9B	6.22	2	0.044	*Significant*
GATA3	2.98	2	0.225	NS
SOX10	7.12	2	0.035	*Significant*

Table 4: T-test: Ki-67 vs Marker Positivity

Marker	Mean Ki-67 (Positive)	Mean Ki-67 (Negative)	p-value	Result
TRPS1	66.3	56.2	0.042	Significant
WNT9B	61.9	63.4	0.62	NS
GATA3	64.1	59.3	0.28	NS
SOX10	67.8	58.0	0.038	Significant

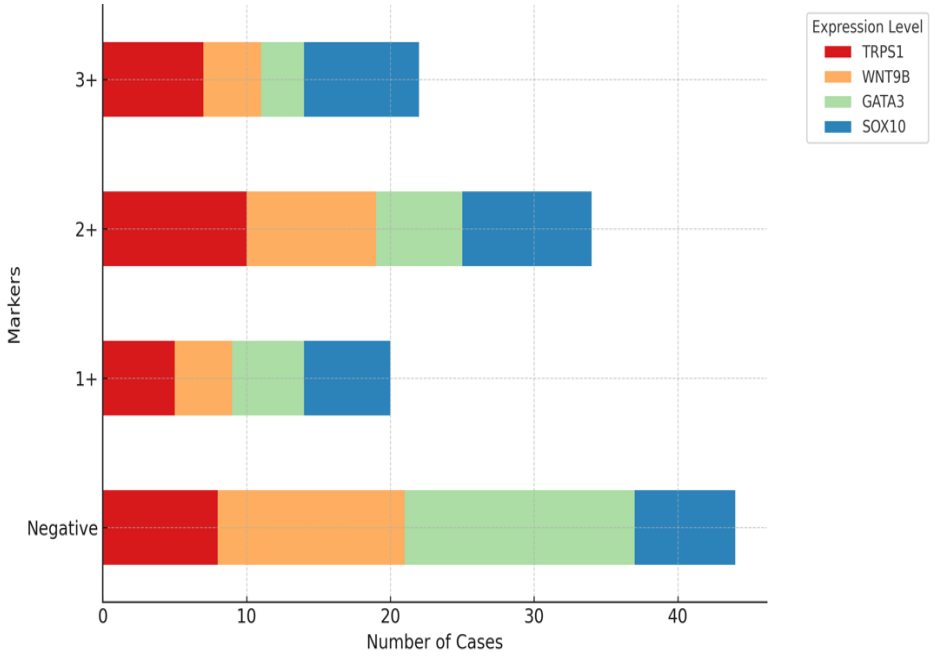


Table-5:Expression pattern of Immunohistochemical markers in TNBC

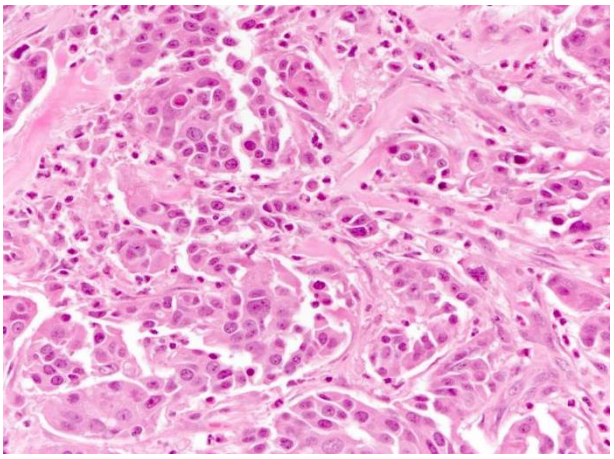


Fig.1: Histology of triple negative breast carcinoma with tumour cells arranged in tubules and cords.Individual tumour cells with moderate cytoplasm, vesicular nucleus.Few tumour infiltrating lymphocytes also seen. (H&E x 200x)

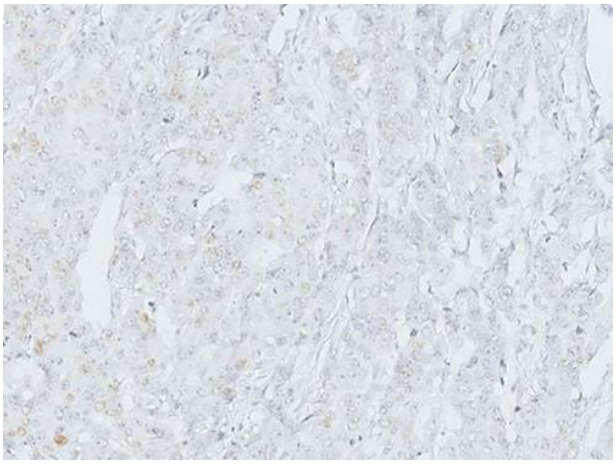


Fig.2: Immunohistochemical staining for Estrogen receptor (ER) negative in tumour cells (IHC x 200x)

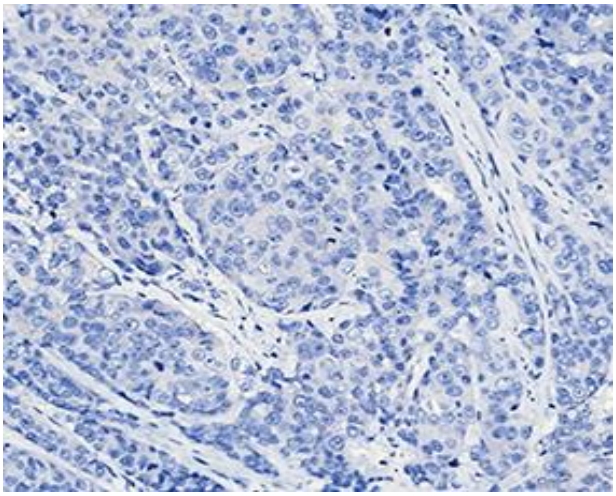


Fig.3: Immunohistochemical staining for Progesterone receptor (PR) negative in tumour cells (IHC x 200x)

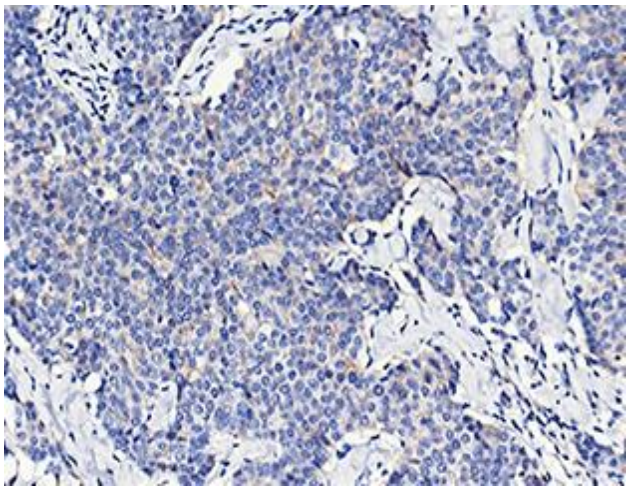


Fig.4: Immunohistochemical staining for Her2 neu negative in tumour cells (IHC x 200x)

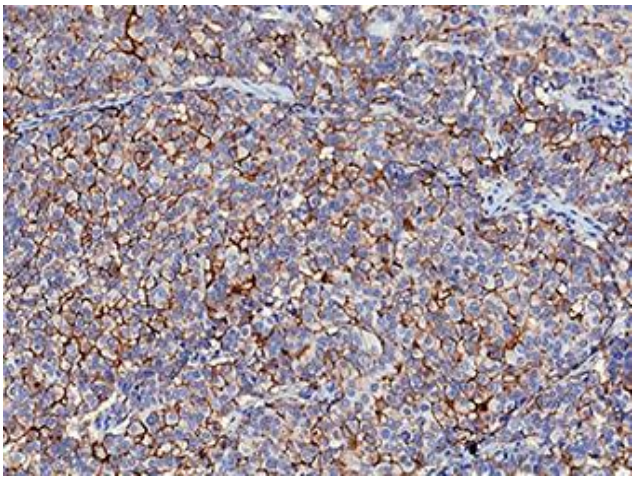


Fig.5: Immunohistochemical staining for WNT9B showing cytoplasmic positivity in tumour cells (IHC x 200x)

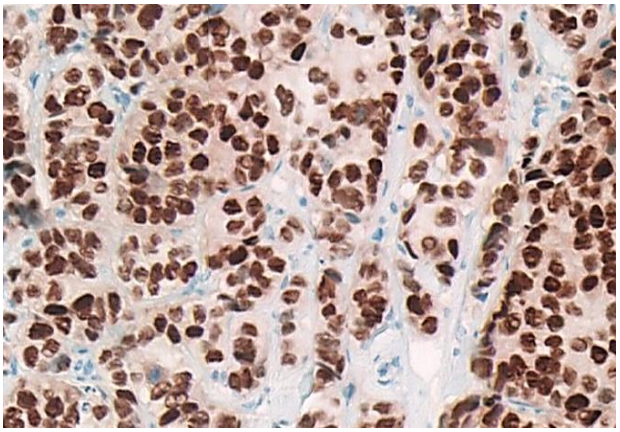


Fig.6: Immunohistochemical staining for GATA 3 showing moderate nuclear positivity in tumour cells (IHC x 200x)

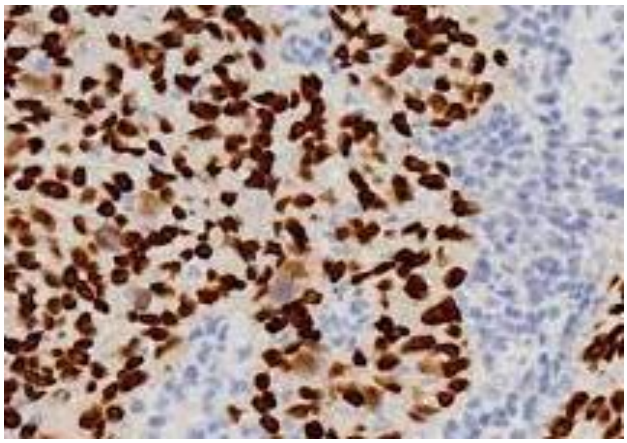


Fig.7: Immunohistochemical staining for TRPS-1 showing strong nuclear positivity in tumour cells (IHC x 200x)

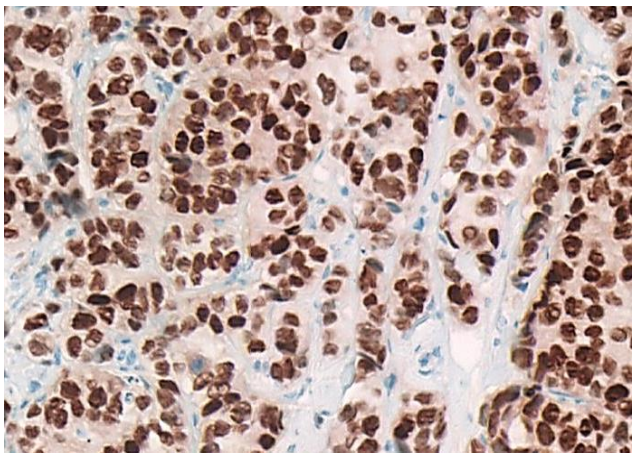


Fig.8: Immunohistochemical staining for SOX-10 showing strong nuclear positivity in tumour cells (IHC x 200x)

4. DISCUSSION

Triple-negative breast carcinoma (TNBC) remains a great challenge in breast cancer management because of its aggressive nature, early metastasis, and lack of effective targeted therapies[31]. The molecular heterogeneity of TNBC underscores the importance of robust diagnostic and prognostic biomarkers to guide personalized therapy[32]. In a limited resource setting, Immunohistochemistry (IHC) continues to be the foundation for subtyping breast cancer [33].

One transcriptional repressor in the GATA family, TRPS1, has become well-known as a sensitive indicator of breast cancer. In 2021a study by Cui et al. showed that TRPS1 was more sensitivity than GATA3. Likewise, Research by Ahn et al. highlighted the diagnostic precision, specifically in differentiating primary breast tumours from metastases[20]. Even within TNBC subsets, TRPS1 expression has been suggested by Yamashita et al. as a stand-in for luminal differentiation pathways[34].

WNT9B is a ligand in the canonical Wnt signalling pathway. It is very important for the growth of tumours because it causes epithelial-mesenchymal transition (EMT) and keeps cancer stemness. Liu et al. (2023) gave strong proof that tumours that have too much WNT9B are more aggressive and resistant to chemotherapy[24]. In a study done by Robertson et al. in 2024, new transcriptomic studies found that WNT9B is part of the mesenchymal stem-like TNBC subtype signature [35].

GATA3 remains an essential marker for breast lineage; however, its variable expression in TNBC poses diagnostic challenges. The 46.6% positive rate we found is in line with what Krings et al. found in 2020[26]. A study by Mukherjee et al. in 2023 found that residual GATA3 expression in TNBC may mean that the tumour is partially luminal differentiated, which might make it more vulnerable to treatment[36].

SOX10 has become one of the most reliable markers in basal-like and metaplastic TNBC, as shown by Cimino-Mathews et al.[23], Oramas et al. [25], and Shaaban et al. [37]. The high nuclear staining we found is similar to what has been reported in both Western and Asian groups. In 2025 study by Patel et al.[38] looked into SOX10 expression as a possible predictor of

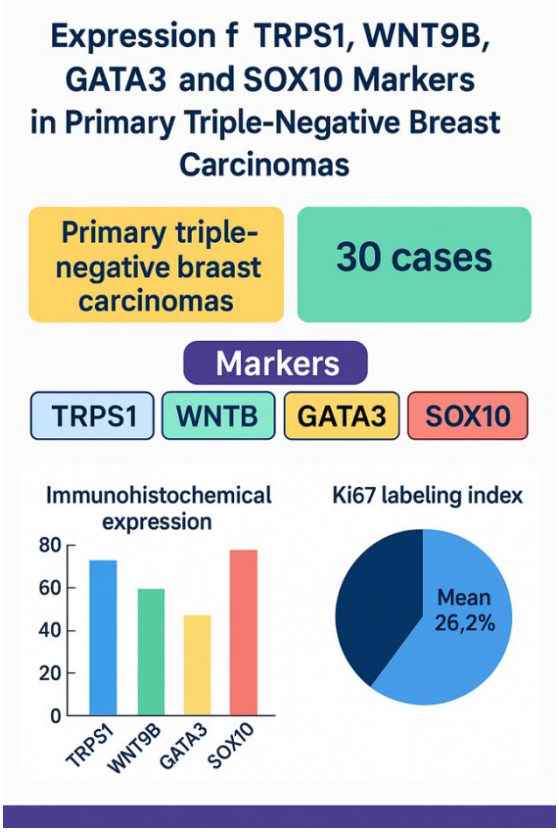
how well immunotherapy will work in TNBC. (Table-6)

The Ki67 proliferation index, which is a stand-in for tumour turnover rate and how aggressive it is, was very different in our group, which is in concurrence with data from around the world[39]. The fact that we found a statistically significant link between high Ki67 and SOX10 positivity suggests that basal-like TNBC is a very aggressive and rapidly growing type of cancer. Li et al. have given us more proof that using Ki67 with molecular IHC profiling is helpful in clinical practice for dividing TNBC into subtypes.

Overall, our results reinforce global findings supporting TRPS1 and SOX10 as indispensable markers for TNBC diagnosis. WNT9B's role in oncogenic signaling adds further dimensions to understanding TNBC biology, while GATA3's limited but significant expression emphasizes the complexity of TNBC heterogeneity. Further large, multicentric studies integrating molecular platforms such as next-generation sequencing (NGS) and transcriptomic profiling are warranted to refine TNBC subclassification and identify actionable therapeutic targets[35 38 40].

Table-6: Table of Recent Studies Evaluating IHC Markers in TNBC

Study	Year	Marker Focused	Findings
Cui et al.	2021	TRPS1	High sensitivity in TNBC
Liu et al.	2023	WNT9B	Correlated with EMT and tumor progression
Krings et al.	2020	GATA3	Variable expression in TNBC
Cimino-Mathews et al.	2021	SOX10	High sensitivity in basal-like TNBC
Oramas et al.	2023	SOX10	Useful in differentiating breast primaries
Shaaban et al.	2023	SOX10	Associated with aggressive TNBC variants
Ahn et al.	2022	TRPS1	Diagnostic and potential prognostic marker



5. CONCLUSION

According to this study, SOX10 and TRPS1 are sensitive markers for primary TNBC. GATA transcription repressor, TRPS1 was widely expressed providing oncologists with additional information particularly in cases where TNBC was GATA3-negative. For aggressive, challenging-to-treat basal-like and metaplastic TNBC subtypes, SOX10 is a dependable diagnostic marker due to its strong nuclear staining and high Ki67 proliferation index.

WNT9B expression can show the genetic diversity of TNBC and the function of the Wnt/β-catenin signalling pathway in cancer progression, however this is very unusual. It has recently been related to EMT and tumour aggressiveness, therefore it needs additional research, especially in targeted therapies. Our work showed that GATA3 expression varied, proving the biological diversity of TNBC. Localised positivity is suggestive of metastatic malignancies, however it might not help to find triple-negative cancers.

The strong association between high Ki67 levels and SOX10 expression shows how rapidly SOX10-positive TNBCs proliferate, which is proportional to its clinical behaviour and aggressiveness. TRPS1 and SOX10 should be added to routine immunohistochemistry panels for TNBC to make diagnosis easier, especially in limited resource settings.
Limitations of the study: To back up these results and look into the prognostic and therapeutic effects of TRPS1, WNT9B, GATA3, and SOX10 in TNBC, we need bigger, longer-term studies that combine immunohistochemical profiling, molecular subtyping, and clinical outcomes. Using these different methods together will help make treatment plans that are specific to each person with aggressive breast cancer.

Acknowledgments
I am extremely thankful to the funding from "ACS Advanced Medical Research Institute" **AMRI Sanction No. 202301007**

Declaration of Interest Statement
The author declares no conflict of interest.

Ethics Declaration
This study was approved by the Institutional Ethics Committee of SLMCH DR.MGR-ERI/SLMCH/2023/021.

Declaration of Adherence to ARRIVE Guidelines
Not applicable, as the study did not involve animals.

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