



Original Article

The Association between Molecular Subtypes of Breast Cancer and its Clinical and Histopathological Prognostic Factors in Southern India population

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ABSTRACT

Breast cancer is a biologically diverse disease. Immunohistochemical (IHC) profiling using estrogen receptor (ER), progesterone receptor (PR), HER2, and cytokeratin 5/6 (CK5/6) allows for molecular classification, aiding prognosis and treatment planning.

Objectives:

To evaluate the expression of ER, PR, HER2, and CK5/6 in infiltrative breast carcinomas among South Indian patients and classify them into molecular subtypes.

Methods:

We conducted a retrospective immunohistochemical analysis of 103 invasive breast carcinoma cases. Tumors were classified into five molecular subtypes (luminal A, luminal B, HER2-enriched, basal-like, and unclassified) based on their expression profiles.

Results:

The most common subtype was Luminal A (42.3%), followed by triple-negative (28.2%), Luminal B (21.1%), and HER2-enriched (8.4%). ER and PR were positive in 55.1% and 46.8% of cases, respectively; HER2 was positive in 26.9% of cases; and CK5/6 was positive in 21.8% of cases. Significant associations were found between molecular subtypes and tumor size, grade, and lymph node status ($p < 0.05$). Luminal A tumors were smaller, lower grade, and had less nodal involvement. In contrast, HER2-enriched and triple-negative subtypes were associated with larger, high-grade, and more node-positive tumors. Among triple-negative cancers, basal-like tumors showed significantly higher lymph node positivity ($p = 0.003$).

Conclusion:

Luminal A is the most prevalent molecular subtype; however, a substantial proportion of aggressive triple-negative and HER2-enriched tumors have been observed. Basal-like tumors in the triple-negative group were notably more aggressive. These findings support routine IHC subtyping to inform treatment decisions and highlight the need for subtype-specific management.

Keywords: Breast cancer, molecular subtype, ER, PR, HER2, CK5/6, triple-negative, basal-like, immunohistochemistry.

INTRODUCTION:

Breast cancer (BC) is the most commonly diagnosed cancer among women worldwide and remains a major public health challenge [1,2]. Asia accounts for 44% of global breast cancer-related deaths and 39% of all new annual cases [3]. In India, breast cancer accounts for approximately 25% of all female malignancies [4,5]. The age-adjusted incidence and mortality rates were 25.8 and 12.7 per 100,000 women, respectively, as reported in 2017 [4]. The highest incidence rates have been recorded in Delhi (41.0), Chennai (37.9), Bangalore (34.4), and Thiruvananthapuram (33.7) per 100,000 women [4].

Invasive breast carcinoma encompasses a heterogeneous group of tumors with varying clinical, radiological, histopathological, and molecular characteristics. Classification into molecular subtypes plays a critical role in guiding therapy and predicting prognosis. Key prognostic and predictive markers include axillary lymph node status, hormone receptor expression (ER and PR), HER2/neu overexpression, and tumor size [6,7]. Immunohistochemical (IHC) analysis of ER, PR, HER2, Ki-67, and CK5/6 remains the standard approach for molecular subtyping and clinical decision-making [8–10].

The St. Gallen Consensus (2011) categorizes breast cancer into four main molecular subtypes based on IHC: Luminal A (ER+/PR+/HER2-/low Ki-67), Luminal B (ER+/PR+/HER2- or HER2+/high Ki-67), HER2-enriched (ER-/PR-/HER2+), and triple-negative breast cancer (TNBC; ER-/PR-/HER2-) [8]. The basal-like phenotype, a subset of TNBC, is characterized by the expression of basal cytokeratins such as CK5/6 [10]. Despite their clinical importance, few studies from India have examined the association between molecular subtypes and histopathological parameters, such as tumor grade and lymph node involvement, using a comprehensive panel of IHC markers.

Aim and objectives:

This study aimed to assess the expression profiles of immunohistochemical markers, including Ki-67, TP53, HER2/neu, estrogen receptor (ER), and progesterone receptor (PR), in breast carcinoma. This study also evaluated the association between these molecular markers and clinicopathological parameters, such as tumor grade, lymph node status, and histological type.

Materials and Methods

Study Design and Setting

This was a hospital-based cross-sectional study conducted in the Department of Surgical Oncology and Department of Pathology at a tertiary care teaching hospital in South India over a period of 24 months (January 2023 – December 2024).

Sample Size Calculation

The sample size was calculated using Epi Info™ version 7.2. Assuming a prevalence of triple-negative breast cancer (TNBC) among Indian patients with breast cancer of 30% [11], with a 95% confidence level, 8% absolute precision, and 10% non-response rate, the required sample size was calculated as 156 patients.

Study Participants

A total of 156 female patients with histo-pathologically confirmed invasive breast carcinoma were enrolled in the study. All patients underwent modified radical mastectomy and Breast Conservative surgeries (wide local excision with axillary clearance.)

Inclusion Criteria

- Female patients aged ≥ 18 years.
- Histopathologically confirmed **invasive breast carcinoma**.
- Availability of complete clinicopathological and immunohistochemical data (ER, PR, HER2, Ki-67, and CK5/6).
- Patients who underwent surgical treatment with adequate tissue available for analysis were included.

Exclusion Criteria

- Carcinoma in situ.
- Recurrent breast cancer
- Core needle or incisional biopsy.
- Sarcomas, phyllodes tumors, benign lesions, and metastatic breast tumors were also included.
- Patients with incomplete histopathological or immunohistochemical (IHC) records.

Data Collection and Variables

Clinicopathological data, including age, menopausal status, tumor size, histological subtype, tumor grade, lymph node status, and TNM staging, were retrieved from departmental medical records. Immunohistochemistry (IHC) data, including the expression of **estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki-67 proliferation index, and cytokeratin 5/6 (CK5/6)**, were obtained from the pathology reports.

Histopathological and Immunohistochemical Procedure

Surgically excised breast specimens were fixed in 10% neutral-buffered formalin for 12–18 h. Gross examination included assessment of tumor size, quadrant involvement, and the presence of multifocality. The axillary lymph nodes were meticulously dissected, counted and sectioned.

Tumor grading was performed using the **Modified Bloom-Richardson (MBR) grading system** based on tubule formation, nuclear pleomorphism, and mitotic count. The grading was categorized as Grade I, II, or III.

Immunohistochemical evaluation was performed on formalin-fixed paraffin-embedded sections.

- **ER and PR** positivity were defined as $\geq 10\%$ tumor nuclei staining.
- **HER2** was considered positive when the IHC score was 3+ or when fluorescence in situ hybridization (FISH) showed gene amplification [12].
- **Ki-67** was considered low if $< 14\%$ and high if $\geq 14\%$.
- **CK5/6** expression was used to differentiate basal-like TNBC from non-basal-type TNBC.

Molecular Subtyping

Breast cancer molecular subtypes were determined based on the criteria proposed in the St. Gallen 2011 consensus and refined by Onitilo et al. [8,13]. The classification included:

- **Luminal A:** ER-positive, HER2-negative, and either PR-positive or negative, with Ki-67 less than 14%.
- **Luminal B (HER2-negative):** ER-positive and HER2-negative with either a high Ki-67 index ($\geq 14\%$) or low PR expression.
- **Luminal B (HER2-positive):** ER-positive and HER2-positive, irrespective of PR or Ki-67 expression.
- **HER2-enriched:** ER-negative, PR-negative, and HER2-positive.
- **Triple-negative (basal-like):** Negative for ER, PR, and HER2, but positive for CK5/6.
- **Triple-negative (non-basal-like):** Negative for ER, PR, HER2, and CK5/6.

All classifications and scores were independently reviewed by two senior pathologists to minimize observer bias.

Statistical Analysis

Statistical Analysis Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as the mean, standard deviation (SD), frequencies, and percentages, were used to summarize the clinicopathological and molecular characteristics of the study participants. Associations between the molecular subtypes of breast cancer (Luminal A, Luminal B, HER2- enriched, and Triple-Negative) and clinicopathological parameters, such as age, menopausal status, tumor size, histological grade, lymph node involvement, and Ki-67 index, were assessed using the chi-square test or Fisher's exact test, where appropriate. Statistical significance was set at $P < 0.05$.

Results

Table 1a. Demographic and Clinical Characteristics of the Study Population (N = 156)

Parameter	Distribution n (%)
Age (Mean $\pm$ SD)	51.3 $\pm$ 10.65
Menopausal Status	
Pre-Menopausal	57 (36.5%)
Post-Menopausal	99 (63.5%)
Parity	
Nulliparous	11 (7.0%)
Multiparous	145 (93.0%)
Tumor Size	
≤ 2 cm	18 (11.5%)
$> 2 - \leq 5$ cm	78 (50.0%)
> 5 cm	60 (38.5%)
Lymph Node Status	
Positive	67 (42.9%)
Negative	89 (57.1%)
Clinical Stage	
Stage I	16 (10.3%)
Stage II	89 (57.1%)
Stage III	51 (32.6%)

The study population (N = 156) had a mean age of 51.3 years (SD = 10.65), with the majority being postmenopausal (63.5%). Most of the patients were multiparous (93%). Tumors larger than 2 cm were observed in 88.5% of the cases. Lymph node involvement was observed in 42.9% of the patients. Clinically, Stage II disease was the most common (57.1%), followed by Stage III (32.6%) (Table 1a).

Table 1b. Histological and Immuno histochemical Features of the Study Population

Parameter	Distribution n (%)
Histological Type	
Invasive Ductal Carcinoma (NOS)	128 (82.1%)
Papillary Type	3 (1.9%)
Cribriform Type	4 (2.6%)
Mucinous Type	7 (4.5%)
Tubular Type	2 (1.3%)
Medullary Type	4 (2.6%)
Metaplastic Type	2 (1.3%)
Mixed Type	7 (4.5%)
Histological Grade	
Grade I	43 (27.6%)
Grade II	80 (51.3%)
Grade III	33 (21.1%)
Estrogen Receptor (ER) Status	
Positive	86 (55.1%)
Negative	70 (44.9%)
Progesterone Receptor (PgR) Status	
Positive	73 (46.8%)
Negative	83 (53.2%)
HER2 Expression	
Negative	95 (60.9%)
Borderline (Equivocal)	19 (12.2%)
Positive	42 (26.9%)
Ki-67 Expression	
< 14%	77 (49.4%)
> 14%	79 (50.6%)
CK5/6 Expression	
Positive	34 (21.8%)
Negative	122 (78.2%)

Histologically, invasive ductal carcinoma of no special type (NOS) was the predominant type (82.1%). Over half of the cases were Grade II (51.3%). Estrogen receptor positivity was observed in 55.1% of patients, and progesterone receptor positivity was observed in 46.8% of patients. HER2 was positive in 26.9% of the cases. Ki-67 expression was high (>14%) in 50.6% of the population, while CK5/6 was positive in 21.8% of the cases (Table 1b).

Table 2. Distribution of Molecular Subtypes in relation to Clinicopathological Parameters

Parameter	Category	Luminal A	Luminal B	HER2-Enriched	Triple Negative	p-value
Age (years)	20–30	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	0.749
	31–40	10 (17.5)	6 (19.4)	6 (27.3)	5 (10.9)	
	41–50	18 (31.6)	8 (25.8)	6 (27.3)	17 (36.9)	
	51–60	16 (28.1)	12 (38.7)	9 (40.9)	15 (32.6)	
	>60	13 (22.8)	4 (12.9)	1 (4.5)	9 (19.6)	
Tumor size	≤2 cm	11 (19.3)	3 (9.7)	1 (4.5)	3 (6.5)	0.015*
	>2–5 cm	32 (56.1)	16 (51.6)	6 (27.3)	24 (52.2)	
	>5 cm	14 (24.6)	12 (38.7)	15 (68.2)	19 (41.3)	
Tumor grade	Grade 1	31 (54.4)	10 (32.3)	1 (4.5)	1 (2.1)	0.001*
	Grade 2	24 (42.1)	16 (51.6)	13 (59.1)	27 (58.7)	
	Grade 3	2 (3.5)	5 (16.1)	8 (36.4)	18 (39.1)	
Lymph node status	Negative	45 (78.9)	8 (25.8)	14 (63.6)	22 (47.8)	0.001*

≤3 nodes	6 (10.5)	12 (38.7)	3 (13.6)	18 (39.1)
>3 nodes	6 (10.5)	11 (35.5)	5 (22.7)	6 (13.0)

Note: HER2-enriched = HER2-positive, ER-/PR-; triple-negative includes both basal-like and non-basal subtypes; n (%); *p*-values calculated using chi-square test; significance level set at *p* < .05.

Significant associations were found between molecular subtypes and tumor size, grade, and lymph node status (*p* < .05). HER2-enriched and triple-negative tumors were more likely to present with larger tumor sizes and higher grades, whereas Luminal A tumors were predominantly low-grade with negative lymph nodes. No significant difference was observed with age distribution across subtypes

Table 3. Clinicopathological Features Among Triple Negative Breast Cancer Patients

Parameter	Category	Basal-like	Non-Basal-like	p-value
Age (years)	20–30	0 (0.0)	0 (0.0)	0 .634
	31–40	2 (4.3)	3 (6.5)	
	41–50	6 (13.0)	11 (23.9)	
	51–60	6 (13.0)	9 (19.6)	
	>60	6 (13.0)	3 (6.5)	
Tumor size	≤2 cm	1 (2.1)	2 (4.3)	0 .571
	>2–5 cm	9 (19.6)	15 (32.6)	
	>5 cm	10 (21.7)	9 (19.6)	
Tumor grade	Grade 1	0 (0.0)	1 (2.1)	0 .819
	Grade 2	13 (28.3)	14 (30.4)	
	Grade 3	7 (15.2)	11 (23.9)	
Lymph node status	Negative	4 (8.7)	18 (39.1)	0 .003*
	≤3 nodes	11 (23.9)	7 (15.2)	
	>3 nodes	5 (10.9)	1 (2.2)	

Note: Values are frequencies, with percentages in parentheses. Basal-like and non-basal-like subtypes are classified within triple-negative breast cancer; *p*-values were calculated using the Chi-square test; significance was set at *p* < .05.

Among patients with triple-negative breast cancer, the basal-like and non-basal-like subtypes did not differ significantly in terms of age, tumor size, or tumor grade. However, a statistically significant difference was observed in lymph node status (*p* = .003), with basal-like tumors being more frequently associated with nodal involvement (Table 3).

Discussion

The present study provides a detailed clinicopathological and molecular profile of breast cancer in a cohort of Indian women, offering valuable insights into the epidemiological and biological behavior of the disease in a low- to middle-income country setting. The mean age at diagnosis was 51.3 years, which is notably younger than the median age observed in many high-income countries. In the UK, for instance, the incidence of breast cancer typically peaks between 50 and 59 and 65–70 years [14]. This younger age at onset aligns with previous studies from India, Pakistan, and other South Asian countries, which consistently reported mean diagnostic ages between 46 and 49 years [15–18]. This shift toward earlier onset in the South Asian context may reflect a combination of genetic, environmental, reproductive, and lifestyle factors, including earlier menarche, delayed first childbirth, and increased urbanization.

From a reproductive and hormonal standpoint, 63.5% of the women in this group were postmenopausal and 93% were multiparous. These findings challenge the protective association between parity and breastfeeding duration or hormone use, which is commonly observed in Western countries. While high parity is traditionally linked to a reduced breast cancer risk, the magnitude and direction of this association may be modulated by age at first childbirth, breastfeeding duration, and exposure to exogenous hormones, all of which require further exploration in the Indian context.

A key concern is the advanced stage of the disease. Tumor sizes >2 cm were observed in 88.5% of cases, with 38.5% of patients harboring lesions >5 cm, indicating delayed detection. These figures are particularly concerning when juxtaposed with those of Western and other developing country cohorts. For instance, Adedayo et al. from Nigeria reported that only 4.7% of their cohort presented with tumors >5 cm. [25]. This late presentation pattern may be attributed to a combination of low breast cancer awareness, stigma, lack of screening programs, and inadequate access to health care, especially in rural and underserved populations.

Histologically, invasive ductal carcinoma (IDC) accounted for 82.1% of cases, reinforcing its predominance in both global and regional datasets [19–24]. Grade II tumors were the most common (51.3%), consistent with prior studies from India,

and may suggest an intermediate tumor biology in this population. However, a considerable proportion of high-grade (Grade III) tumors further underscores the aggressive nature of the disease presentation.

Globally, Western populations report higher frequencies of hormone receptor (HR)-positive tumors. For instance, in the SEER database (USA), ER-positive tumors account for over 70% of breast cancers, with Luminal A comprising nearly 60% of cases [26]. Similarly, a UK study by Blows et al. found Luminal A tumors in 59.5% and triple-negative breast cancer (TNBC) in only 13.1% of cases [27]. In contrast, our study reports a lower ER positivity rate (55.1%) and a higher TNBC prevalence (28.2%), corroborating the findings of another Indian study by Badwe et al., who reported TNBC rates ranging between 25% and 32% [28].

Furthermore, the relatively lower HER2-enriched subtype in this study (8.4%) is consistent with data from AlAbayah et al. in Saudi Arabia, where HER2 positivity was also low, suggesting regional variability in HER2 overexpression [25]. Meanwhile, Munjal et al. from North India reported a 26% HER2 positivity rate, indicating intra-national heterogeneity likely due to referral bias, institutional differences, and technical variability in IHC protocols [29,30].

Progesterone receptor (PR) positivity was observed in 46.8% of patients. These rates are slightly lower than those reported by Sofi et al. in Kashmir (66.3% ER-positive, 63.4% PR-positive) [24] but remain comparable to other Asian studies [29,30]. This variability likely reflects geographic and ethnic heterogeneity, as well as differences in laboratory techniques and cutoff criteria. HER2 positivity, observed in 26.9% of patients, has important therapeutic implications given the availability of targeted anti-HER2 therapies such as trastuzumab, although access and affordability may remain barriers in low-resource settings.

The proliferation index marker Ki-67 was elevated (>14%) in 50.6% of patients, indicating a substantial proportion of biologically aggressive tumors. High Ki-67 levels are associated with poor prognosis, higher recurrence rates, and reduced survival, particularly in hormone receptor-negative BC subtypes. Similar Ki-67 expression patterns have been reported in other Indian cohorts, confirming the biological aggressiveness observed in this demographic group [14,16,20,21]. Additionally, CK5/6, a cytokeratin marker typically expressed in basal-like tumors, was positive in 21.8% of patients. This finding highlights the significant burden of basal-like and triple-negative breast cancer (TNBC) phenotypes, which are known for their aggressive clinical behavior and limited targeted treatment options [17,18,23,30].

One of the key contributions of this study is the molecular subtyping of breast cancer and its association with clinicopathological variables. Luminal A tumors, generally characterized by ER/PR positivity, HER2 negativity, and low Ki-67, were associated with favorable features such as lower histological grade, smaller tumor size, and negative nodal status, consistent with their typically indolent course and good prognosis [14,19,21]. In contrast, HER2-enriched and triple-negative subtypes were more frequently associated with larger tumor size (>5 cm), higher histological grade (Grade III), and greater axillary lymph node involvement, reinforcing their established links with adverse outcomes [16,22,24,29].

Within the triple-negative group, further stratification into basal-like and non-basal-like subtypes (based on CK5/6 expression) revealed that basal-like tumors had significantly higher lymph node involvement than their non-basal counterparts, despite no significant differences in tumor size or grade. This observation aligns with the literature, suggesting that basal-like TNBCs exhibit a highly invasive phenotype and early metastatic potential and are often unresponsive to conventional hormone- or HER2-targeted therapies [17,23,30]. Studies have also shown that these tumors are enriched with cancer stem-like cells and demonstrate intrinsic chemoresistance, factors that contribute to their poor clinical outcomes.

Collectively, these findings highlight the marked heterogeneity of breast cancer in Indian women, characterized by a high prevalence of aggressive molecular subtypes, delayed clinical presentation, and limited protective and reproductive outcomes. These findings highlight the need for regionally adapted breast cancer strategies, enhanced molecular profiling, and broader access to targeted therapy. The growing body of Indian and South Asian literature—including findings from Devadass et al., Priyathersini et al., Raju et al., Nawaz et al., and Kumar et al.—reinforces the urgent need for culturally tailored awareness strategies, improved access to early diagnostic tools, and equitable access to molecular testing and targeted therapies [14–24].

Limitations:

Additionally, the absence of follow-up data limited our ability to correlate biomarker expression with clinical outcomes. Future prospective studies with larger cohorts and survival analyses are warranted to validate these findings.

Declaration:

Conflicts of interests: The authors declare no conflicts of interest.

Author contribution: All authors have contributed in the manuscript.

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Conclusion:

This study highlights the distinct expression patterns of ER, PR, HER2, Ki-67, and CK5/6 in infiltrative breast carcinomas, with estrogen receptor positivity in over half of the cases and a substantial proportion showing HER2 amplification and high Ki-67 levels, indicating an aggressive tumor biology. Triple-negative and basal-like subtypes were also notably prevalent, underscoring the importance of routine molecular subtyping in guiding personalized treatment. These findings are representative of a high-referral population from multiple adjoining districts in a semi-urban region of South India, making them particularly relevant for regional cancer care strategies. However, the absence of follow-up and survival data limits prognostic correlations; hence, future prospective studies with outcome analyses are recommended to validate and build upon these observations.

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