https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 28(1) (January 2025); 102-113
Research Article

Molecular Phenotypes of Ductal Carcinoma of The Breast And Its Association With Histopathological Prognostic Markers

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Abstract
Background: Globally, breast carcinoma is a major cause of cancer-associated deaths among women, which is significantly impacting India. Compared to women in developed countries, Indian women often present with breast cancer (BC) at younger ages and with more aggressive forms. This study focused to determine the prevalence of different molecular phenotypes and their associations with histological prognostic markers in infiltrating ductal carcinoma-no special type (IDC-NST) in an Indian population.
Materials and methods: An analytical cross-sectional study was conducted on 351 BC patients at a tertiary care hospital. Immunohistochemistry was used to identify molecular phenotypes: triple-negative breast cancer (TNBC), HER2-enriched, luminal-A, and luminal-B. Clinical and histopathological data, including age, multifocality status, lymph node status, BR grade, tumor volume, pathological stage, microvessel density (MVD), and proliferation index (Ki-67), were assessed for associations with molecular phenotypes.
Results: The most common molecular phenotype was TNBC, while luminal-B was second most. Significant differences were observed in tumor grade, tumor volume, tumor stage, percentage of positive lymph nodes, MVD, and Ki-67 score among the molecular phenotypes. The luminal A subgroup had significantly lower tumor volumes and Ki-67 scores, while the HER2-enriched subtype had increased lymph node positivity.
Conclusion: This study highlights the distinct prevalence and prognostic features of molecular subtypes of IDC-NST in an Indian cohort. These findings underscore the importance of molecular profiling in guiding treatment strategies and improving prognostic assessments for BC patients in India.

Key words: Breast cancer, molecular phenotypes, prognostic markers, IDC-NST

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Received: 30/11/2024 Accepted:13/12/2024

DOI: https://doi.org/10.53555/AJBR.v28i1.5264

1. Introduction

Breast carcinoma is a leading cause of cancer-associated death among women globally, with India experiencing a significant burden [1]. Despite higher incidence rates in developed nations, mortality is higher in developing countries, including India [1, 2], where women are diagnosed a decade earlier than in their Western counterparts [3, 4]. This earlier onset predominantly affects premenopausal women and often presents more aggressively, with larger tumors and advanced-stage diagnoses [5-7]. Younger women with breast cancer (BC) tend to have poorer prognoses despite early diagnosis and intensive treatment. The complexity of this disease, with diverse clinical, pathological, and molecular features, necessitates a nuanced approach to prognosis and treatment [5-7].

Globally, the incidence rate of BC is increasing, with more than 2.1 million new cases annually, and this number is projected to reach 3.2 million by 2030. This increase necessitates proactive healthcare measures [8-10], especially in regions such as India, where BC is the second most common cancer among women. Understanding regional variations in incidence and mortality is crucial for effective healthcare planning, targeted screening programs, awareness campaigns, and optimized resource allocation [11-13].

Histologically, breast tumors are primarily ductal (80%) or lobular (10-15%), with the disease progressing from ductal hyperproliferation to invasive carcinoma and metastasis [14, 15]. BC is classified into four different molecular phenotypes based on immunohistochemistry (IHC) profiles in accordance with the expression of the human epidermal growth factor receptor-2 (HER2), and hormonal receptor that is progesterone receptor (PR), and estrogen receptor (ER) [16, 17].

The majority of BCs are luminal tumors, categorized into subtypes with varying prognoses, which include luminal-A, which has the best prognosis, lowest recurrence rates, and highest survival among the various molecular subtypes of BC [18, 19]; luminal-B, which is often found in younger women and is associated with p53 mutations and a poor prognosis [20]; HER2-enriched characterized by high recurrence and a poor prognosis with a low survival rate and can be treated by targeted therapy; and triple-negative breast cancer (TNBC), which is more aggressive and linked to BRCA1 mutations and a poor prognosis [21].

The Ki-67 antigen is an important biomarker for estimating cell proliferation, assessed through immunohistochemical techniques [22]. Ki-67 is crucial for assessing disease prognosis, resistance to endocrine therapy or chemotherapy, and residual risk in patients undergoing routine treatments. Additionally, Ki-67 is used to evaluate treatment efficacy, particularly in patients undergoing neoadjuvant endocrine therapy [23]. The most aggressive and short-lived molecular phenotypes of breast cancer include HER2-enriched and TNBC subtypes. Compared to those without lymphocytic infiltration, TNBC patients with TILs (tumor-infiltrating lymphocytes) typically have better prognoses and survival rates, despite their favorable response to chemotherapy [24-27]. Thus, even breast cancer tumors of the similar histological features or type may show different prognoses and responses to treatment. Consequently, molecular characterization has become essential for tailoring targeted therapies and optimizing treatment outcomes.

Identifying biomarkers such as ER, PR, and HER2 is critical for diagnosis, management, staging, and treatment. These markers not only help identify high-risk phenotypes but also guide clinicians in selecting effective therapeutic strategies [28, 29].

Given the diverse behavior of BC lesions and their variable response to therapy, this study focused to assess the distribution of various molecular subtypes of BC and their association with other histological prognostic markers of infiltrating ductal carcinoma of the breast-no special type (IDC-NST).

2. Materials and methods

The Pathology Department of a tertiary care hospital and medical college in Delhi is the site of the current analytical cross-sectional study. The Institutional Ethics Committee approved the study (No. IEC/NDMC/2022/109, dated 17.06.2022). The study was conducted in accordance with the Declaration of Helsinki. Every participant provided written informed consent.

A total of 351 BC patients of IDC-NST participated in this study. The inclusion criteria were women who were diagnosed with IDC-NST and who presented to the hospital between June 2022 and April 2024. The exclusion criteria included male patients, those with incomplete tumor samples that is needle biopsy, those who did not provide written consent, and also those who underwent surgery post-neoadjuvant therapy. Clinical details such as age, sex, tumor volume, multifocality, number of isolated lymph nodes (LNs), and detailed histopathological features, including type, pathological tumor stage, Nottingham modified Bloom Richardson grade (BR grade), proliferation index, and microvessel density (MVD), were recorded. IHC was performed using monoclonal antibodies (BioGenex, CA, USA) for ER, PR, HER2, and Ki-67 to identify molecular phenotypes. Microvessel density (MVD) was assessed using the hot-spot method on CD34-stained tumor sections.

Formalin-fixed paraffin-embedded (FFPE) tissue blocks were subjected to IHC staining technique using an optimized procedure. After being cut to a thickness of 4 μm, sections of FFPE tissue were dewaxed, and rehydrated with water. For HER2, PR, ER, Ki-67, and CD34, heat-induced antigen retrieval was done in Tris-EDTA buffer (pH 9.0, Merck, India) by using a domestic pressure cooker. The sections were washed with phosphate-buffered saline solution (PBS, pH 7.2–7.4)

after being treated for 10 minutes with a peroxidase-blocking solution that is 1% hydrogen peroxide.

Followed by two PBS wash, specific ready-to-use mouse primary monoclonal antibodies against HER2, PR, ER, Ki-67, and CD34 (catalog no. AM297-5, AN471-5ME M AN710-5ME, and AN711-5ME, BioGenex) were then added to the slides and incubated in moist chamber for an hour at room temperature. The slides were then kept for overnight at 4-6°C. Following two PBS wash, the sections were incubated at 22-24° C for 30 minute with polymer HRP, a secondary antibody (Catalog No. HK595-50KN, BioGenex), and then stained for 5 minutes with DAB chromogen-substrate solution (Catalog No. HK124-025KN, BioGenex). After 30 seconds of counterstaining with hematoxylin (Merck, India), the slides were mounted with DPX. The IHC-stained tissue sections were examined by a skilled pathologist using a compound light microscope (Olympus, India).

All patients were classified into four distinct molecular phenotypes: TNBC, characterized by the absence of hormonal receptor (ER, PR), and HER2; HER2-enriched, defined by the presence of HER2 receptor only with no expression of hormonal receptors; Luminal A, identified by the presence of either or both hormonal receptors, with HER2 expression being variable and Ki-67 positivity <14%; and Luminal B, defined by the presence of either or both hormonal receptors, with variable HER2 expression but Ki-67 positivity >14%.

Statistical analysis was conducted using Python (version 3.0) with Jupyter (version 5.0) as the integrated development environment. Differences in age, multifocality, BR grade, tumor volume, percentage of LN positivity, MVD index, and Ki-67 score among different molecular phenotypes were assessed using the Kruskal-Wallis and Chi-square test. Dunn's post hoc test was used if the Kruskal-Wallis test revealed significance. A p-value of less than 0.05 was considered as statistical significant.

3. Results

3.1. Molecular phenotypes

In this study, among all the patients with the IDC-NST, the most common molecular phenotype was TNBC (140/351 patients), accounting for 39.9% of the patients, followed by luminal-B (97/351 patients, 27.6%), luminal-A (62/351 patients, 17.7%) and HER2-enriched subtypes (52/351 patients, 14.8%; Table 1).

Table 1. Distribution and analysis of histopathological prognostic markers with molecular phenotypes of breast cancer.

Prognostic markers	**Luminal-A, *n* (%) 52 cases (17.7)**	**Luminal-B, *n* (%) 97 cases (27.6)**	**HER2-enriched, *n* (%) 52 cases (14.8)**	**TNBC, *n* (%) 140 cases (39.9)**	**p-value (Kruskal-Wallis test)**
Age Median (range), years	44.5 (30-78)	44 (20-70)	46 (29-70)	46.5 (25-72)	0.324
Tumor volume Median (range), cm^3	18.2 (1.8-112.5)	63.6 (4.0-224.0)	25.4 (0.6-120)	56.3 (1.15-440.0)	**< 0.001**[a]
PLN Median (range), %	17.2 (0-100)	15.7 (0-100)	37 (0-100)	14.2 (0-100)	**< 0.001**[b]
MVD Median (range), microvessels/hpf	13.0 (5-35)	18.0 (7-100)	14.0 (3-60)	14.7 (4-35)	**< 0.001**[c]
Ki-67 Median (range), %	7 (2-80)	35 (15-85)	25 (5-80)	35 (5-85)	**< 0.001**[d]

[a]Result of pairwise analysis by *Dunn's* test: Luminal-A vs B, **p < 0.001**; HER2-enriched vs Luminal-A, p < 0.158; TNBC vs Luminal-A, **p < 0.001**; HER2-enriched vs Luminal-B, **p < 0.001**; TNBC vs Luminal-B, **p < 0.001**; TNBC vs HER2-enriched, **p = 0.002**.

[b]Result of pairwise analysis by *Dunn's* test: Luminal-A vs B, p = 0.494; HER2-enriched vs Luminal-A, **p < 0.001**; TNBC vs Luminal-A, p = 0.453; HER2-enriched vs Luminal-B, **p < 0.001**; TNBC vs Luminal-B, p = 0.815; TNBC vs HER2-enriched, **p < 0.001**.

[c]Result of pairwise analysis by *Dunn's* test: Luminal-A vs B, **p < 0.001**; HER2-enriched vs Luminal-A, p = 0.718; TNBC vs Luminal-A, p = 0.265; HER2-enriched vs Luminal-B, **p = 0.008**; TNBC vs Luminal-B, **p = 0.011**; TNBC vs HER2-enriched, p = 0.718.

[d]Result of pairwise analysis by *Dunn's* test: Luminal-A vs B, **p < 0.001**; HER2-enriched vs Luminal-A, **p < 0.001**; TNBC vs Luminal-A, **p < 0.001**; HER2-enriched vs Luminal-B, **p = 0.035**; TNBC vs Luminal-B, p = 0.685; TNBC vs HER2-enriched, **p = 0.039**.

p-values (<0.05) in bold font in legend and the table shows statistically significant differences.

3.2. Comparison of molecular phenotypes with other prognostic markers.

3.2.1. Age

The average age of patients with the luminal-A molecular subtype was 47.8 years (SD ± 13.7 years), with a median age of 44.5 years (range 30-78 years). The average age of patients with the luminal-B subtype was 44.6 ± 10.5 years, the median age was 44 years (range 20-70 years). In the HER2-enriched subgroup, the mean age of the patients was 46.2 ± 11.4 years, and the median age was 46 years, with an age ranging from 29 to 70 years. For patients with the TNBC subtype, the mean age was 47.1 ± 10.5 years with the median age of 46.5 years (range 25-72 years). The difference in patients age among all the molecular phenotypes of BC patients was statistically insignificant (Kruskal-Wallis test, p = 0.324) in the present study (Table 1).

3.2.2. Multifocality

In the present study, the multifocality of tumors was also assessed among the four molecular phenotypes of BC, and we found that the most of the lesions were single lesions (unifocal tumor) and present in luminal-A (59/62 patients, 95.2%), luminal-B (96/97 patients, 99%), HER2-enriched (47/52 patients, 90.4%) and in TNBC (136/140 patients, 97.1%). The difference in the multifocality of tumors among all molecular phenotypes of BC was not statistically significant (p = 0.056, chi-square test; Table 2).

Table 2. Distribution and analysis of histopathological prognostic markers with molecular phenotypes of breast cancer.

Prognostic markers	Total cases *N* = 351	Luminal A, *n* (%) 52 cases (17.7)	Luminal B, *n* (%) 97 cases (27.6)	HER2-enriched, *n* (%) 52 cases (14.8)	TNBC, *n* (%) 140 cases (39.9)	p-value Chi-square test
Multifocal	*n* = 13	3 (4.8)	1 (1)	5 (9.6)	4 (2.9)	0.056
BR grade-I	*n* = 51	23 (37.1)	10 (10.3)	1 (1.9)	17 (12.1)	< **0.001**[a]
BR grade-II	*n* = 144	22 (35.5)	45 (46.4)	21 (40.4)	56 (40)	
BR grade-III	*n* = 156	17 (32.7)	42 (43.3)	30 (57.7)	67 (47.9)	
Stage-I	*n* = 29	2 (3.2)	2 (2.1)	0 (0)	25 (17.9)	< **0.001**[b]
Stage-II	*n* = 243	49 (79)	87 (89.7)	13 (25)	94 (67.1)	
Stage-III	*n* = 78	10 (16.1)	8 (8.2)	39 (75)	21 (15)	
Stage-IV	*n* = 1	1 (1.6)	0 (0)	0 (0)	0 (0)	

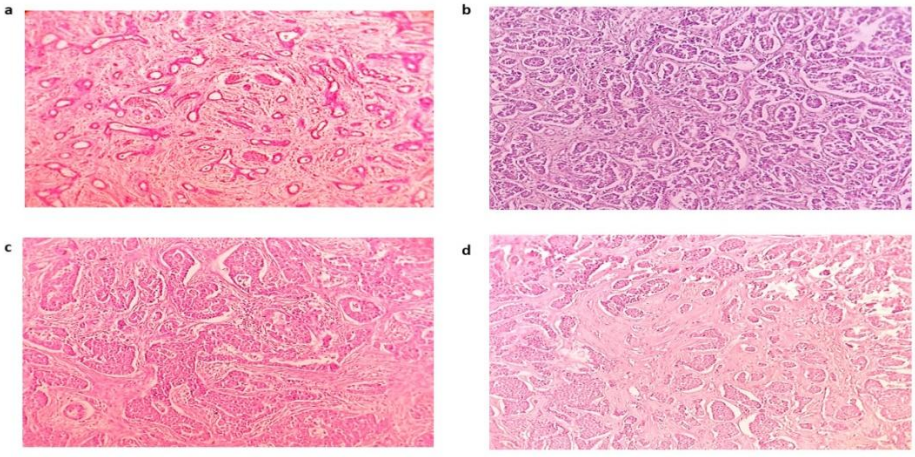
[a]Pairwise *Chi-square* test: Luminal A vs B, **p < 0.001**; HER2-enriched vs Luminal A, **p < 0.001**; TNBC vs Luminal A, **p < 0.001**; HER2-enriched vs Luminal B, p = 0.084; TNBC vs Luminal B, p = 0.613; TNBC vs HER2-enriched, p = 0.084.

[b]Pairwise *Chi-square* test: Luminal A vs B, p = 0.249; HER2-enriched vs Luminal A, **p < 0.001**; TNBC vs Luminal A, **p = 0.020**; HER2-enriched vs Luminal B, **p < 0.001**; TNBC vs Luminal B, **p < 0.001**; TNBC vs HER2-enriched, **p < 0.001**.

p-values (<0.05) in bold font in legend and the table shows statistically significant differences.

3.2.3. BR grade

On assessing the BR grade in different molecular subtypes of BC, the most common BR grade in luminal-A was Grade-I, which was found in 23/62 cases (37.1%) of tumors, followed by Grade-II (22/62 cases, 35.5%) and Grade-III (17/62 cases, 32.7%). In the luminal-B subgroup, the most common BR grade was Grade-II (45/97 patients, 46.4%), followed by Grade-III (42/97 patients, 43.3%) and Grade-I (10/97 patients, 10.3%). In the HER2-enriched subtype, the most common BR grade was Grade-III (30/52 patients, 57.7%), followed by Grade-II (21/52 patients, 40.4%) and Grade-I (1/52 patients, 1.9%). However, in the TNBC subtype, the most common BR grade was Grade-III (67/140 patients, 47.9%), followed by Grade-II (56/140 patients, 40.4%) and Grade-I (17/140 patients, 12.1%; Figure 1).



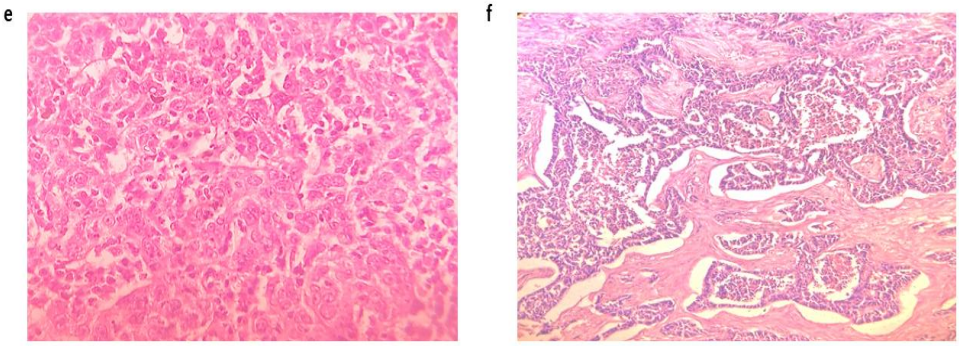


Figure 1: Two cases of ductal carcinoma breast NOS type, **(a), (b).** modified BR Grade-I (H&E, 10x). **(c), (d).** modified BR Grade-II (H&E, 10x). **€, (f).** modified BR Grade-III (H&E, 40x, 10x).

The differences in BR grade among the various molecular phenotypes of BC were statistically significant (Chi-square test, $p < 0.001$). Pairwise analysis of the four molecular phenotypes revealed that the differences in BR grade between the luminal-A and B; luminal-A and HER2-enriched; and TNBC and luminal-A subtypes was statistically significant (Chi-square test, all $p = 0.001$). However, the differences in BR grade between HER2-enriched and luminal-B as well as between TNBC and luminal-B subtypes were insignificant ($p = 0.084$ and $p = 0.613$, respectively; chi-square test). Moreover, the differences in BR grade between TNBC and HER2-enriched patients were also statistically insignificant ($P = 0.084$, chi-square test; Table 2).

3.2.4. Tumor volume

The mean tumor volume in the luminal-A subtype was 17.0 cm^3 (SD ± 19.3 cm^3), and the median tumor volume was 18.2 cm^3 (range 1.8-112.5 cm^3). However, the mean tumor in the luminal-B subtype was 60.0 cm^3 (SD ± 36.4 cm^3), and the median volume of tumor volume was 63.6 cm^3 (range 4.0-224.0 cm^3). The mean volume of tumor in the HER2-enriched was 24.13 cm^3 (SD ± 23.7 cm^3), and the median volume of tumor was 25.4 cm^3 (range 0.6-120 cm^3). However, the mean volume of tumor in TNBC subtype was 54.5 cm^3 (SD ± 68.4 cm^3), and the median tumor volume was 56.3 cm^3 (range 1.15-440.0 cm^3).

The differences in tumor volume among all the molecular phenotypes were statistically significant (Kruskal–Wallis test, $p < 0.001$,). According to pairwise analysis, the differences in volume of tumor between luminal-A and B subtypes and also between TNBC and luminal-A subtypes were statistically significant (Dunn's test, $p < 0.001$ for both). There were also statistically significant differences in tumor volume between the HER2-enriched and luminal-B; between TNBC and luminal-B; and between the TNBC and HER2-enriched subtypes ($p < 0.001$, $p < 0.001$, and $p = 0.002$, respectively, according to Dunn's test; Table 1). However, this difference between HER2-enriched and luminal-A patients was statistically insignificant (Dunn's test, $p = 0.159$).

3.2.5. The percentage of positive lymph nodes (PLNs) was calculated as follows:

The PLN in luminal-A was 23.3% (SD ± 20.5%) and median was 17.2% (range 0-100%). Whereas, in luminal-B it was 23.5% (SD ± 33%) and median was 15.7% (range 0-100%). PLN in HER2-enriched was 38.6% (SD ± 21.2%) and median was 37% (range 0-100%). However, PLN in TNBC was 21.7% (SD ± 23.5%) and median was 14.2% (range 0-100%).

The differences in the PLN among all molecular phenotypes were statistically significant (Kruskal-Wallis test, $p < 0.001$,) in the present study. On pairwise analysis the difference of PLN between HER2-enriched and luminal-A; HER2-enriched and luminal-B; TNBC and HER2-enriched subtypes were statistically significant (Dunn's test, all $p < 0.001$). However, this difference among rest of the groups were statistically insignificant (Dunn's test, all $p > 0.05$; Table 1).

3.2.6. Pathological tumor stage

The most common pathological tumor stage in the luminal-A subtype was Stage-II (49/62 cases, 79%), followed by Stage-III (10/62 cases, 16.1%), Stage-I (2/62 cases, 3.2%) and Stage-IV (1/62 case, 1.6%). In luminal-B subtype, the most common tumor stage was Stage-II (87/97 cases, 89.7%), followed by Stage-III (8/97 cases, 8.2%), Stage-I (2/97 cases, 2.1%) with no cases in Stage-IV. In HER2-enriched subtype, the most common tumor stage was Stage-III (39/52 cases, 75%), followed by Stage-II (13/52 cases, 25%) and there were no cases in Stage-I and IV. However, in TNBC subtype, the most common tumor stage was Stage-II (94/140 cases, 67.1%), followed by Stage-I (25/140 cases, 17.9%), Stage-III (21/140 cases, 15%) and no case in Stage-IV.

The difference in Pathological tumor stage among all molecular phenotypes of BC was statistically significant (chi-square test, $p < 0.001$; Table 2).

3.2.7. MVD index (microvessels/hpf)

The mean MVD in the luminal-A subtype was 14.7 (SD ± 7.0) microvessels/hpf, and the median was 13.0 (range 5-35) microvessels/hpf. However, the MVD in the luminal-B was 20.4 (SD ± 13.4) microvessels/hpf, and the median was 18.0 (range 7-100) microvessels/hpf. The MVD in the HER2-enriched subtype was 16.4 (SD

± 11.1) microvessels/hpf, and the median was 14.0 (range 3-60) microvessels/hpf. However, the MVD in TNBC subtype was 16.0 (SD ± 6.6) microvessels/hpf, and the median was 14.7 (range 4-35) microvessels/hpf. The differences in the MVD among all molecular phenotypes were statistically significant ($p < 0.001$, Kruskal-Wallis test) in the present study. According to pairwise analysis, the differences in the MVD between HER2-enriched and luminal-B patients and between TNBC and luminal-B subtype were statistically significant ($p = 0.008$ and $p = 0.011$, respectively; Dunn's test). Moreover, this difference was also statistically significant between luminal-A and B subtypes (Dunn's test, $p <0.001$). However, the differences in the MVD between rest of the groups were statistically insignificant (Dunn's test, all $p > 0.05$; Table 1).

3.2.8. Ki-67 score

The luminal-A subtype demonstrated a mean Ki-67 score of 8.7% (SD ± 9.6%), with a median score of 7% and a range of 2 to 80%. In the luminal-B subtype, the mean Ki-67 score was 37.5% (SD ± 17.7%), and the median was 35%, ranging from 15 to 85%. For the HER2-enriched, the mean Ki-67% score was 29.1% (SD ± 17.4%), with a median score of 25% and a range of 5 to 80%. However, in the TNBC subtype, the mean Ki-67 score was 37.9% (SD ± 21.4%), and the median score was 35%, ranging from 5 to 85%.

Statistical analysis revealed statistically significant differences in the Ki-67 score among the molecular phenotypes (Kruskal-Wallis test, $p < 0.001$). Pairwise analysis revealed that the difference in Ki-67 score were statistically significant between luminal-A and B subtypes and also between TNBC and HER2-enriched subtypes (Dunn's test, all $p < 0.001$). Moreover, a significant difference in the Ki-67 score was also observed between the HER2-enriched and luminal-B subtypes as well as between the TNBC and HER2-enriched subtypes ($p = 0.035$ and $p = 0.039$, respectively; Dunn's test). However, this difference was statistically insignificant difference in the Ki-67 score between the TNBC and luminal-B subtypes (Dunn's test, $p = 0.685$; Table 1).

4. Discussion

The breast carcinoma is a highly heterogeneous and complex disease influenced by various pathological, clinical, and biological factors that differ across population. Recognizing these factors is crucial for effective management due to their prognostic importance. This study focused to determine the prevalence of different molecular phenotypes of BC and their associations with key histopathological prognostic factors, including patient age at diagnosis, multifocality, BR grade, tumor volume, positive lymph node status, pathological tumor stage, MVD index, and Ki-67 score (tumor proliferation index).

Previous studies have demonstrated a varied prevalence of molecular phenotypes of BC among Indian women. In North India (Punjab), Somal et al. [30], observed that the most prevalent phenotype was luminal-B (41.72%), followed by TNBC (27.32%), luminal-A (15.69%) and HER2-enriched (15.26%). Whereas, in South India (Mangalore) Pareira et al. [31], found the most prevalent subtype was TNBC (34.3%), followed by luminal-B (33.4%), luminal-A (17%) and HER2-enriched (15.3%). In contrast, studies indicate that there was predominance of the luminal-A subtype of BC among Western women [32].

Additionally, Jonnada et al. [33], conducted an extensive meta-analysis and systematic review incorporating 30 different studies, which revealed that luminal-A is typically the most predominant phenotype (33%), followed by TNBC (30%), luminal-B (17%), and HER2-enriched (15%). This study also emphasized a significantly greater prevalence of TNBC subtype among the Indian subcontinental women than in white women, a trend consistent with other international studies [34-37]. This increased incidence of TNBC may partially explain the reason of higher death rate of BC patients in India, as TNBC subtype is known for its aggressive nature and limited treatment options compared to other subtypes.

In our study, TNBC (39.9%) was found to be the most prevalent subtype of BC among the population in northern India at this hospital, followed by luminal-B (27.6%), luminal-A (17.7%), and the least common being HER2-enriched subtype (14.8%).

Although, studies in various countries, Abousahmeen et al. [38], reported most of the patients were in the 36-45 year's age group (33.2%), with TNBC predominant under 55 years of age (83.3%) and luminal-A over 55 years of age (33.3%). Uyisenga et al. [39], reported the highest mean age in patients with TNBC and the lowest in patients with HER2-enriched subtypes (51.9 ± 14.7 and 47.3 ± 10.1 years, respectively). HER2-enriched was most common in the under 50 years of age group (65%), with TNBC equally distributed between the < 50 and > 50 years of age groups (50% in each), showing no significant difference in age ($p > 0.05$).

Shukla et al. [40], noted that BC was most prevalent in the premenopausal group (< 48 years, 50.9%), with luminal-A and TNBC subtypes being the most common (56.25 and 55.55%, respectively), while postmenopausal individuals (> 55 years) had higher HER2-enriched and luminal-B incidences (36.66 and 35.29%, respectively), without any significant age differences among different subtypes ($p = 0.800$).

Nguyen et al. [41], reported that most of the BC patients were over 50 years old (51.8%), with HER2-enriched and TNBC subtypes being the most common (66.7% in each). Luminal-B with HER2+ tumors were most prevalent in patients under 50 years of age (52.1%), and there was statistically insignificant association with age difference ($p = 0.260$). Jain et al. [42], reported that the lowest mean age was in the HER2-enriched (50.2%), and the highest was in the luminal-A subtype (56.8%), with significant age differences among the different subtypes ($p = 0.030$). Overall, the above-stated studies indicate that the median age of BC patients in India is younger than that in Western countries, consistent with our findings.

In Indian studies, Somal et al. [30], who reported that TNBC had the lowest mean age (50.4 Years) and that luminal-A subtype had the highest mean age (56 years). Additionally, they have demonstrated that TNBC was most prevalent under 50 years' group (52%), and luminal-A subtype was most prevalent over 50 years' group (64.7%). Furthermore, Sharma et al. [32], reported that patients with both luminal-B and TNBC subtypes had the lowest median age (45 years), while patients with luminal-A subtype had the highest (48.5 years). They have also shown that Luminal-B was most common in the younger age group (<50 years, 70%), while luminal-A was more predominant in older age group (>50 years, 42.4%), with no statistically significant difference in age. Pereira et al. [31], reported that BC was most prevalent in those older than 50 years (53%), with luminal-A was most prevalent in the younger than 50 years of age group (50.9%), while luminal-B and HER2-enriched subtypes were most prevalent in the older than 50 years of patients (54% and 54.3%, respectively).

In our study, we found that luminal-B patients had the lowest average age (44.6 ± 10.5 years) at presentation, while luminal-A subtype patients had the highest average age (47.8 ± 13.7 years) at presentation. Luminal-B subtype was most common in patients under 50 years of age, while TNBC subtype was most common in those over 50 years of age; however, there was insignificant age difference among all the molecular phenotypes of BC ($p = 0.324$).

In this study, we observed that the majority of the BC tumors were unifocal. Most of the multifocal tumors were in HER2-enriched subtype. However, the difference in multifocality was statistically insignificant among the various molecular subtypes of BC ($p = 0.056$). Pekar et al. [43], also reported maximum multifocal tumors in the HER2-enriched subtype (33.3%), while TNBC tumors were predominantly unifocal (69.2%). They also reported that patients who had multifocal tumors were at greater risk (2.75-fold) of death than those who had unifocal tumors.

In our study, most of the patients had BR grade-III (44.4%), with the fewest having Grade-I (14.5%). Luminal-A subtype of tumor was primarily Grade-I (37.1%), while luminal-B tumor were primarily Grade-II (46.4%). However, HER2-enriched and TNBC subtypes of tumors were mainly Grade-III (57.7% and 47.9%, respectively). There was a significant difference in tumor grade among the different molecular phenotypes of BC ($p < 0.001$).

Our results align with those of Shukla et al. [40], who reported mostly Grade-III tumors (41.2%) in their study with luminal-A tumor was mostly Grade-I (50%), lumina-B tumor was mostly Grade-II (61.8%), and TNBC and HER2-enriched tumors were mostly Grade-III (83.3% and 73.3%, respectively). The differences were statistically significant ($P = 0.001$). Similarly, Somal et al. [30], also observed mostly Grade-III tumors (75.8%) in their study, with all Grade-I tumors were luminal-A subtype (100%) whereas, Grade-III tumors were predominant in the HER2-enriched and TNBC subtypes (94.4% and 90.1%, respectively).

However, Abousahmeen et al. [38], reported most of the tumors were Grade-III (46.9%), with Grade-I was most prevalent in the luminal-B subtype (9.2%) and Grade-II tumor was in the luminal-A subtype (57.1%). Grade-III was the most common in TNBC subtype (67.3%), with significant differences among molecular subtypes of BC ($p = 0.008$).

In contrast, Jain et al. [42], reported that most of the patients had Grade-II tumor (38.6%), with luminal-A tumors were primarily Grade-I (73%), TNBC tumors were Grade-III (50%), and HER2-enriched tumors were Grade-II (53.7%). The differences were significant among different subtypes of BC ($p = 0.001$).

Whereas, Pereira et al. [31], reported that most of the cases were Grade-II (45%), with luminal-A tumors mostly Grade-I (33.3%), Grade-II tumors most commonly luminal-A and HER2-enriched (51% and 50%, respectively), and Grade-III (46.6%) TNBC subtype. This differences were also significant among the subtypes ($p = 0.001$).

Moreover, Nguyen et al. [41], reported that the majority of cases were Grade-II (57.7%), with luminal-A tumors were mainly Grade-I (31.9%), luminal-B with HER2+ ware in Grade-II (66.7%), and TNBC subtype of tumors were in Grade-III (63.9%). The differences were statistically significant among the different subtypes ($p = 0.001$).

In context with tumor size, we considered tumor volume (cm^3) instead of the largest dimension for the assessment of tumors and found that the lowest mean tumor volume was in the luminal-A (17.0 cm), and the highest was in the luminal-B subtype (60 cm^3), with a statistically significant difference in volume of tumor among all the molecular phenotypes ($p < 0.001$). Pairwise analysis revealed significant differences between most of the phenotypes ($p < 0.002$), except between HER2-enriched and luminal-A patients ($p = 0.159$).

Our results align with those of Sharma et al. [32], who also reported the smallest mean volume of tumor in luminal-A (14.6 cm^3) and the largest in TNBC subtype (69.4 cm^3), with significant differences among most of the subtypes ($p = 0.001$). Similarly, Jain et al. [36], reported that the smallest mean tumor size of 3.2 cm was in luminal-A, and the largest (4 cm) was in the HER2-enriched subtype, with a significant difference among the different subtypes of BC ($p = 0.030$). Somal et al. [30], observed the smallest mean tumor size in luminal-A (3.83 cm) and the largest in luminal-B with HER2+ subtype (4.67 cm), with most of the tumors being 2-5 cm (63.24%). The differences were not statistically significant ($p = 0.157$).

In contrast, Pereira et al. [31], reported that most TNBC tumors were > 5 cm (19.4%), and most luminal-A tumors were < 2 cm (33.3%), with no statistically significant difference in tumor size among different subtypes ($p = 0.119$). Abousahmeen et al. [37], reported that most tumors were 2-5 cm (59.9%), with luminal-A < 2 cm (20%) and HER2-enriched 2-5 cm (73%). Luminal-B tumors were mostly > 5 cm (27.4%), with no significant difference ($p = 0.088$).

Shukla et al. [40], reported that tumors < 2 cm in diameter were most common in luminal-A subtype

(6.25%), while 2-5 cm tumors were most common in luminal-A (75%) and luminal-B (73.52%) subtypes. The largest tumors of > 5 cm) were most commonly found in HER2-enriched (60%) and TNBC subtypes (50%), with significant differences among the different subtypes of BC ($p = 0.009$).

Most of the studies evaluated LN status by checking for tumor involvement or metastasis, recognizing it as a crucial prognostic marker. To improve accuracy, we estimated the percentage of tumor-positive LNs in each patient. Our study revealed the lowest mean percentage of tumor-positive LNs in the TNBC subtype (21.7%) and the highest in the HER2-enriched subtype (38.6%), with a significant difference between HER2-enriched subtype and the other subtypes of BC ($p < 0.001$).

Our findings align with those of Pereira et al. [31], who reported the highest proportion of LN-negative for tumor among TNBC patients (53.4%) while, the LN-negative in HER2-enriched patients (67.4%), although the difference was statistically insignificant ($p = 0.092$). Similarly, Jain et al. [40], reported that most of the LN-positive cases were luminal-B with HER2+ (73.8%), and LN-negative cases were, luminal-A (45.1%), luminal-B with HER2- (45%), and TNBC subtypes (43.6%). The difference was statistically significant among the different molecular phenotypes of BC ($p = 0.006$).

Moreover, Somal et al. [30], reported that most of the tumor-negative LNs in TNBC patients (57.44%) while, tumor-positive LNs in HER2-enriched, luminal-B with HER2+, and luminal-B with HER2-, subtypes (63.97%, 67.95%, and 70.3%, respectively). The differences were significantly different ($p < 0.001$). Nguyen et al. [40], reported that most of the patients were LN-negative (83.6%), with the highest percentage of LN-negative patients in luminal-B with HER2- and HER2-enriched subtypes (22.2% in each) and the highest percentage of LN-positivity in TNBC subtype patients (88.9%). However, no significant differences were found among various subtypes of BC ($p = 0.400$).

In contrast, Abousahmeen et al. [38], reported the highest proportion of LN-positive patients in the luminal-B subtype (68.7%), with significant differences among various subtypes ($p = 0.017$). Shukla et al. [40], reported the greatest proportion of LN-negative patients in luminal-A subtype (71.87%) and the greatest percentage of LN-positive patients in HER2-enriched subtype (46.66%), although the difference was not statistically significant among the different molecular phenotypes of BC ($p = 0.420$).

In our study, among the molecular subtypes of BC, most of the luminal-B tumors were in Stage-II (89.7%), and there were none of the cases in Stage-IV among the molecular subtypes except luminal-A which had 1.6% of cases. Additionally, HER2-enriched tumors were most commonly found in Stage-III patients (75%). The difference in tumor stage among the molecular phenotypes of BC were significant ($p < 0.001$).

Our results align with those of Pereira et al. [31], who reported that most of the patients were diagnosed with Stage-II disease (59.7%). Specifically, most of the luminal-A tumors were in Stage-I (21.6%), TNBC and HER2-enriched tumors were in Stage-II (67% and 45.7% respectively). They also reported a significant difference in stage of tumor among different molecular phenotypes of BC ($p = 0.016$).

However, Abousahmeen et al. [38], reported that most of the BC patients were diagnosed with Stage-II disease (47%). Most of the HER2-enriched tumors were in Stage-II (56.8%) and luminal-B at Stage-III (43.3%), with Stage-IV predominance in the HER2-enriched and TNBC subtypes (8.1% and 7.6%, respectively). They found no significant difference in tumor stage among the various subtypes of BC ($p = 0.619$).

In the present study, we found the lowest mean MVD in the luminal-A (14.7 microvessels/hpf) and the highest (20.4 microvessels/hpf) in the luminal-B subtype. The difference in the MVD among most of the molecular subtypes of BC was significant ($p < 0.001$). However, Goyal et al. [44], reported that the highest mean MVD was in the luminal-A (25.17 ± 7.37 microvessels/hpf), and the lowest mean MVD was in the HER2-enriched subtype (22.65 ± 7.74 microvessels/hpf). However, there was no significant difference in the MVD among the different molecular subtypes of BC ($p = 0.490$).

We found that the luminal-A had the lowest mean Ki-67 score ($8.7 \pm 9.6\%$), while the highest mean was found for the TNBC subtype ($37.9 \pm 21.4\%$), followed by the luminal-B subtype ($37.5 \pm 17.7\%$). The difference in the Ki-67 score among most of the molecular subtypes was statistically significant ($p < 0.001$). However, this difference was not significant between the luminal B and TNBC subtypes ($p = 0.685$).

Our findings are in concordance with the study performed by Jain et al. [41], in which they also reported that the lowest mean Ki-67 score was in the luminal-A (9.5%), and the highest mean Ki-67 score was in the TNBC subtype (57.1%). Additionally, they reported a statistically significant difference in the Ki-67 score among various molecular phenotypes of BC ($p = 0.001$).

We found that, the most prevalent phenotype was TNBC, followed by the luminal-B, luminal-A, and HER2-enriched among the population in the northern region of India. No significant differences in age distribution or multifocality were observed among the subtypes, indicating that these factors are not strongly influenced by molecular phenotype. Significant differences in BR grades and tumor volumes were noted, particularly between luminal-A tumors and more aggressive subtypes (luminal-B, HER2-enriched, and TNBC). This indicates a correlation between molecular phenotype and tumor aggressiveness.

A significantly greater percentage of patients with the HER2-enriched subtype were LN positive for tumor, which is a marker for poorer prognosis. Pathological tumor staging also varied significantly, with more advanced stages being predominant in the TNBC and HER2-enriched phenotypes than in the luminal type BC. MVD and Ki-67 scores, both indicators of tumor proliferation and aggressiveness, were significantly greater in the luminal-B and TNBC subtypes, correlating with their more aggressive clinical behavior. The key findings highlighted the significant variation in tumor behavior and prognosis across different subtypes, underscoring the necessity for personalized treatment

strategies. The schematic representation of these finding is illustrated in Figure 2. Finding of present study are compared with similar previous studies in Table 3.

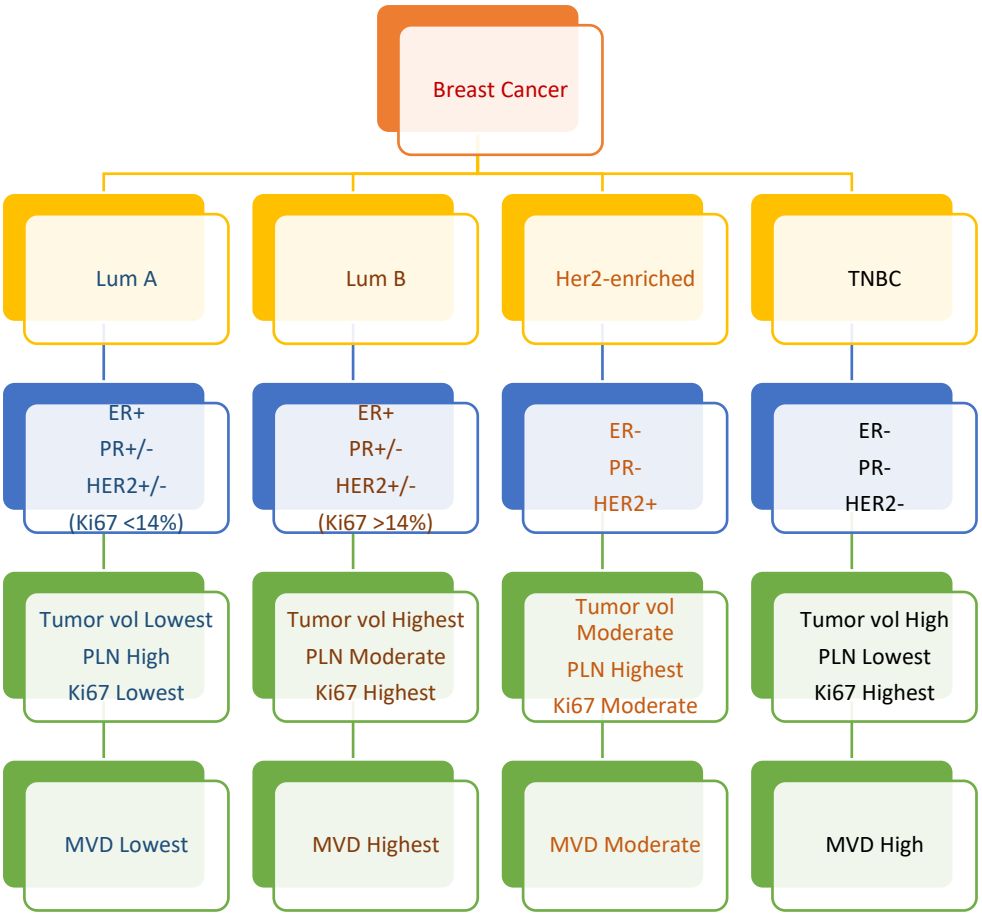


Figure 2: Salient features of various molecular phenotypes of breast cancer.

Table 3. Comparison of present study with previous similar studies.

Author's	Year	Most prevalent Molecular phenotype	Tumor size	Lymph Node positive status	MVD
Shukla et al. [40]	2018	Luminal B (29.8%)	Lowest in Luminal A	Highest in HER2-enriched	Increased in Luminal A
Jain et al. [42]	2021	Luminal B (47.2%)	Lowest in Luminal A	Highest in Luminal B	Not studied
Pareira et al. [31]	2022	TNBC (34.3%)	Lowest in Luminal A	Highest in HER2-enriched	Not studied
Somal et al. [30]	2023	Luminal B (41.7%)	Lowest in Luminal A	Highest in Luminal B	Not studied
Goyal et al. [44]	2023	TNBC (29.4%)	Not studied	Not studied	Not studied
Nguyen et al. [41]	2023	Luminal B (37.2%)	Not studied	Highest in TNBC	Not studied
Abousahmeen et al. [38]	2023	Luminal B (63.7%)	Lowest in Luminal A	Highest in Luminal B	Not studied
Sharma et al. [32]	2024	TNBC (39%)	Lowest in Luminal A	Not studied	Not studied
Present study	**2024**	**TNBC (39.9%)**	**Lowest in Luminal A**	**Highest in HER2-enriched**	**Increased in Luminal B**

The advent of molecular subtyping has revolutionized breast cancer treatment by identifying distinct biological behaviours associated with each subtype. Luminal A tumors, characterized by low proliferation and hormone receptor positivity, are associated with the most favorable prognosis and are often treated with hormonal therapy alone [45]. In contrast, Luminal B tumors, which exhibit higher proliferation and worse outcomes, are more likely to require chemotherapy in addition to hormonal therapy [46]. HER2-enriched and Basal-like

(triple-negative) tumors, representing the most aggressive subtypes, necessitate more intensive treatments, including chemotherapy and targeted therapies for HER2-positive cancers. The role of molecular subtyping in guiding treatment decisions continues to evolve, with ongoing research aiming to refine subtype-specific therapeutic strategies.

In conclusion, this study emphasizes the importance of molecular phenotyping in BC, which not only aids in understanding tumor behavior but also in tailoring individualized treatment plans. The significant variations in prognostic markers among the subtypes highlight the need for targeted therapies and robust screening programs to improve outcomes, particularly in aggressive types such as HER2-enriched and TNBC subtypes of BC. This tailored approach is crucial for the effective management and improved prognosis of BC patients in developing regions such as India.

Acknowledgment and/or disclaimers, if any

The authors would like to thank all participants who participated in this study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest declaration

The authors declare that they have no competing interests.

Ethics approval and consent to participate:

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of NDMC Medical College and Hindu Rao Hospital, Delhi (IEC/NDMC/2022/109 dated 17.06.2022). Written informed consent from patient for participation were also taken.

Authors' contributions

Conceptualization, S.S. R.C.; Formal analysis, S.R., R.C., S.K.S., P.R.; Methodology, S.S., S.K.S.; Project administration, S.S., S.K.; Supervision, S.S., S.K.; Validation, S.K.S., R.C., S.S., S.K., S.R., P.R.; Visualization, S.S., S.K.S.; Writing – original draft, S.K.S.; Writing – review & editing, S.K.S., P.R., R.C., S.R., S.S., S.K. All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

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