Original Article

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Histomolecular Trends of Breast Carcinoma: Insights from Tertiary Care Centre of Northern India

Pathology Section

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ABSTRACT

Introduction: The most prevalent cancer among women worldwide is breast cancer. This can be separated into three molecular subtypes: Luminal, HER2-enriched, and triple negative. There is significant regional variation in epidemiology profile of this malignancy in India. The present study provides insightful information about breast cancer cases from North India.

Aim: To study the distribution and patterns of histomorphology and molecular subtypes of carcinoma breast over a period of one year.

Materials and Methods: The present prospective cross sectional study conducted in a Tertiary Centre in Ludhiana, Punjab, India, over a period of 12 months (September 2022 to September 2023). All cases of Invasive Breast Carcinoma (IBC) undergoing Immunohistochemistry (IHC) testing were included in the study. A total of 15,395 biopsy and surgical specimens were received during this period, out of which 203 cases were of IBC on which IHC testing was done. Molecular subtypes were determined using expression of oestrogen and progesterone receptors, HER2/neu and Ki-67. Additional markers including CK, GATA-3, mammaglobin, CK5/6, SOX-10, p40, Vimentin, etc., were put, wherever required. Trends of molecular subtypes and histomorphology were studied. The histopathology parameters included Modified Bloom Richardson (MBR) grade, Ductal Carcinoma In Situ (DCIS) (pattern and grade), tumour necrosis, skin invasion, lymphovascular and perineural invasion, tumour margins, lymph node status, Extranodal Extension (ENE) (if any), etc. All collected data was entered into Microsoft Excel spreadsheet and anaysed using software Statistical Package for Social Sciences (SPSS) 26. Normality of continuous variables was assessed using Shapiro-Wilk test, and data was presented as mean ± Standard Deviation (SD). Fisher-exact test was utilised if any of the frequencies were <5, and the Chi-square ($\chi2$) test was used to examine the association between categorical variables.

Results: Infiltrating Duct Carcinoma (IDC), NOS formed the largest histological group 181 (89.2%) cases with majority - (115; 56.6%) belonging to MBR grade 2. Majority cases belonged to pT2 106 (68.8%) without any nodal involvement 68 (54.4%). Among the molecular subtypes, Luminal-B emerged as the most prevalent 110 (54.2%) cases, followed by Triple negative 51 (25.1%), HER2/neu enriched 28 (13.8%); and Luminal-A 14 (6.9%).

Conclusion: Looking at the deviation from the established patterns and significant heterogeneity in its pathological features and molecular characteristics, there is a need of region-specific breast cancer profiling and tailored management guidelines. This will deliver more efficient, equitable, and personalised breast cancer care to patients, while ultimately contributing to a reduction in morbidity and mortality.

Keywords: Histomorphology, Immunohistochemistry, Molecular subtypes

INTRODUCTION

In Invasive Breast Cancers (IBCs), five-year survival rates of more than 80% have been reported in many studies from the west [1]. Whereas in India, five-year survival rates calculated in population-based studies on breast cancer range from 42-48%, and hospital-based studies report five-year relative survival rate of 40-45%. Breast cancer is a diverse condition with several histomorphological and molecular subgroups that affect recurrence patterns, treatment choices, and prognosis. Triple-negative and HER2-enriched malignancies need chemotherapy and targeted therapies, while luminal tumours respond to hormonal therapy. Recurrence patterns are also determined by these histomorphological and molecular differences, with triple-negative tumours reoccurring early and luminal types exhibiting late relapse. Although IDC, NOS having molecular subtype Luminal A (accounting for 50 to 60% of all breast carcinoma cases) continues to be the most common kind worldwide, growing awareness of lobular and unique variations reveals changing patterns in the biology of breast cancer.

There has been a paradigm shift in the epidemiological fabric of breast cancer in India also, with reports of younger age at onset, changing molecular subtype patterns, and different histology and stage distribution at presentation. For tailored care and better patient outcomes, morphology and molecular classification must be correlated. It has been noted that the majority of Indian breast cancer data comes from multicentric or metropolitan research. Nevertheless, there are still few region-specific assessments available, especially for North India. In comparison to recognised national and international trends, this prospective study assesses the pathological profile of breast cancer patients in a tertiary care facility in North India, identifying differences in tumour biology and molecular subtype. This analyses the trends of histomorphological and molecular subtypes of breast carcinoma in order to provide a unique evidence foundation to inform customised awareness, screening, and management strategies for the region by gathering real-time data and emphasising epidemiological divergences.

MATERIALS AND METHODS

The present prospective observational cross-sectional study conducted in a Tertiary Care Hospital in Ludhiana, Punjab, India over the period of 12 months (September 2022 to September 2023). The study was approved by Research and Ethics Committee of the institution vide letter no. DMCH/P/2022/988-94 dated 13.09.2022.

Inclusion and Exclusion criteria: All the trucut biopsies, mastectomy and Breast Conservation Surgery (BCS)/lumpectomy specimens those were received and diagnosed as IBC on histopathology and underwent IHC testing for molecular subtyping were included in the study. All non-neoplastic lesions, non-epithelial tumours of breast and all cases of carcinoma breast in which IHC was not done were excluded.

Study Procedure

A detailed history was obtained. Detailed gross and histopathological examination was done as per College of American Pathologists (CAP) Protocol. At least two Pathologists examined each Haematoxylin and Eosin (H&E) slide, and the tumours were categorised using the most recent WHO classification of breast cancers and graded using the MBR system [2]. FFPE tissue was stained with IHC markers such as ER, PR, HER2/neu (with FISH for 2+), and Ki-67. Validated antibody clones with standardised pre-analytical conditions, on-slide positive and negative controls, and adherence to departmental standard operating procedures (SOPs) with external quality assurance involvement were used to perform IHC. According to ASCO/CAP recommendations, each case was then subclassified into Luminal-A, Luminal-B, HER2/neu enriched and TNBC subtypes. HER2/neu equivocal (2+) cases were subjected to Fluorescence In Situ Hybridisation (FISH) in Genetics Department where HER2 (ERBB2): CEP17 ratio ≥2 was considered HER2 amplification and the final molecular categorisation was done accordingly. All histological parameters were examined separately by two Pathologists who were blinded to clinical data. In case of discrepancy, opinion of third pathologist was taken. IHC evaluation was done by all the Pathologists together, and disagreements were settled by consensus.

Interpretation of IHC study: The Allred scoring system was used for ER/PR reporting which combines a proportion score (0-5) and an intensity score (0-3) to yield a total score of 0-8, with ≥3 considered positive [3,4]. HER2/neu reporting was done based on ASCO/CAP 2018 guidelines with regards to intensity, completeness and percentage of staining and was graded as 0, 1+, 2+ and 3+ accordingly [5]. Percentage of cells expressing Ki-67 was determined by counting 1000 cells/slide. A threshold of 14% was taken for helping to discriminate between cases likely to correlate with the more aggressive luminal-B molecular subtype (having Ki-67 proliferation index more than/ equal to 14%) versus the less aggressive luminal-A subtype (having Ki-67 proliferation index <14%). However, this threshold has not been validated for predicting the response to chemotherapy [6].

STATISTICAL ANALYSIS

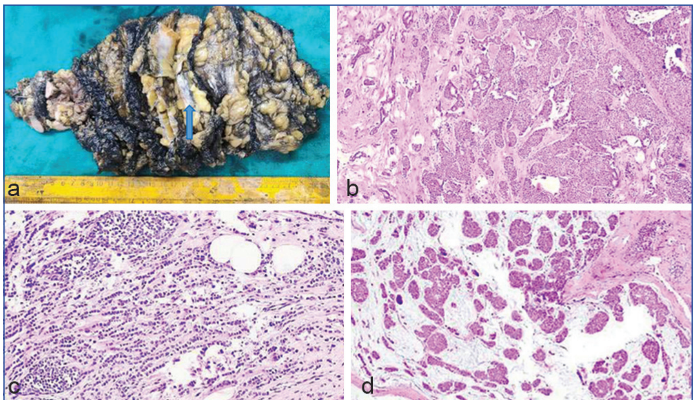
Kolmogorov Smirnov or Shapiro-Wilk tests were applied in this case to assess the normality of data. Univariate analysis was used to obtain a summary of the study individuals' attributes. The Fisher-exact test was utilised if any of the anticipated frequencies were <5 and the Chi-square (χ^2) test was performed to examine the association between categorical variables. Statistical significance was attained when the two-tailed p-value was less than 0.05. The statistical software for Microsoft Windows called SPSS 26 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) was used for all statistical computations.

RESULTS

A total of 203 cases of carcinoma breast were analysed during the duration of one year. The age of patient presentation ranged from 28 to 88 years with maximum cases occurring in individuals with age more than 50 years (131/203; 64.5% cases) with the specific age group of 51-60 years (57/203; 28.1% cases) and a mean age of 56.3+/-12.4 years. All cases were females, majority of whom were post-menopausal (153/203; 75.4%); except for one male patient (aged 50 years). All the tumours were histopathologically classified according to the World Health Organisation (WHO) classification of IBCs [Table/Fig-1,2] [2]. IDC, NOS formed the largest group with

Histopathological type	Number of cases	Percentage
IDC, NOS	181	89.2
Invasive Lobular carcinoma (ILC)	8	3.9
Mucinous carcinoma	6	3.0
Metaplastic carcinoma	3	1.4
Cribriform carcinoma	1	0.5
Mixed IDC, NOS and ILC	1	0.5
Encapsulated papillary carcinoma	1	0.5
Invasive papillary carcinoma	1	0.5
Invasive solid papillary carcinoma	1	0.5
Total	203	100.0

[Table/Fig-1]: Distribution of IBCs (n=203).



[Table/Fig-2]: a) Photograph showing mastectomy specimen with axillary lymph nodes containing grey white tumour (arrows); b) Photomicrograph of Infiltrating Duct Carcinoma (IDC), NOS showing clusters and nests of tumour cells, separated by sclerotic stroma (H&E, 40X); c) Photomicrograph of Invasive Lobular Carcinoma (ILC) showing Indian file pattern of tumour cells (H&E, 100X); d) Photomicrograph of Mucinous carcinoma showing clusters of tumour cells present in pools of extracellular mucin (H&E, 100X).

181 cases (89.2%). Histopathological variables including tumour type, grade, Ductal Carcinoma In Situ (DCIS) patterns and grades, necrosis, skin invasion, lymphovascular and perineural invasion, microcalcifications, tumour margins, lymphocytic response at the advancing margins, etc., were systematically recorded in a tabulated format for clarity [Table/Fig-3].

Variables		Number of cases (n, %)
MBR grade	Grade 1	19 (9.4)
	Grade 2	115 (56.6)
	Grade 3	69 (34.0)
Architectural patterns of DCIS	Papillary	3 (1.5)
	Micropapillary	6 (3.0)
	Solid	45 (22.2)
	Comedo	47 (23.2)
	Cribriform	27 (86.7)
Cytonuclear grade of DCIS	Low	0 (0.0)
	Intermediate	28 (13.8)
	High	23 (11.3)
Tumour necrosis	Present	53 (26.1)
	Absent	150 (73.9)
Skin invasion	Ulceration of the overlying skin	4 (2.0)
	Dermis involvement	2 (1.0)
	Epidermis involvement	0 (0.0)
	Absent	197 (97.0)
Lymphatic and/or Vascular Invasion (LVI)	Present	41 (20.2)
	Absent	162 (79.8)
Microcalcifications	Present	38 (18.7)
	Absent	165 (81.3)

Tumour margins	Infiltrating	196 (96.5)
	Pushing	6 (3.0)
	Pushing with focally infiltrating	1 (0.5)
Lymphocytic response at advancing margins	Mild	56 (27.6)
	Moderate	13 (6.4)
	Marked	7 (3.4)
	Not significant	127 (62.6)
Perineural invasion	Present	10 (4.9)
	Absent	193 (95.1)

[Table/Fig-3]: Various histological and epidemiological parameters studied and correlated afterwards.
Statistically significant associations were found between the molecular subtypes [Table/Fig-4,5] and histopathological type, MBR grade, necrosis, skin invasion, microcalcifications and ENE.

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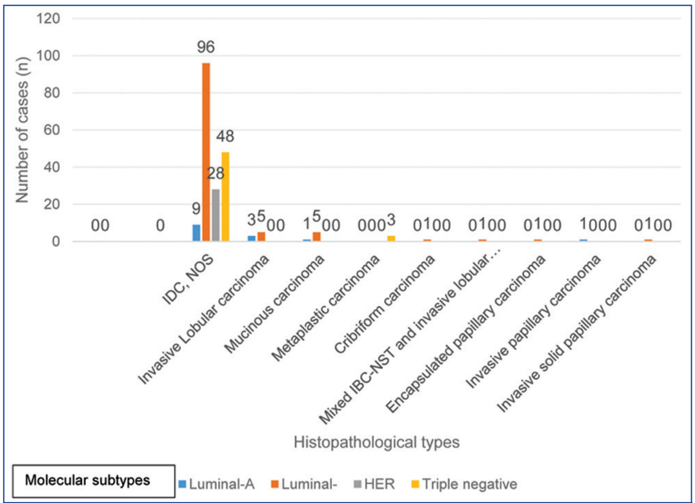
Molecular subtype	Number of cases	Percentage
Luminal-A (ER and PR-positive, HER 2/ neu-negative and Ki-67 <14%)	14	6.9
Luminal-B (HER 2/neu-positive or negative, significant proliferative activity (Ki-67≥14%) or low PR)	110	54.2
HER2/neu enriched (HER-2 overexpression/ gene amplification with absence of ER and PR)	28	13.8
Triple negative (Lack of overexpression or amplification of the HER 2/ neu gene, and negative ER and PR expression)	51	25.1
Total	203	100.0

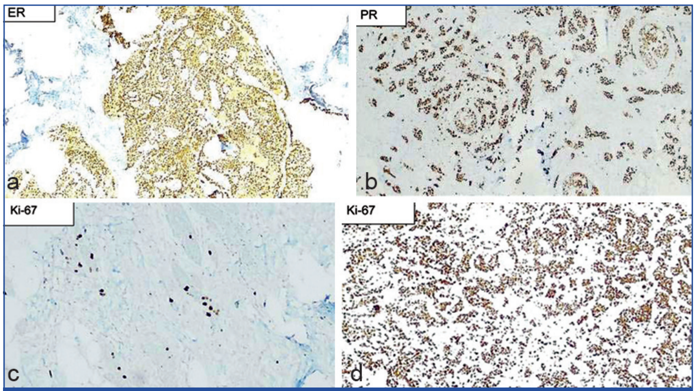
[Table/Fig-4]: Molecular subtypes of IBCs (n=203).



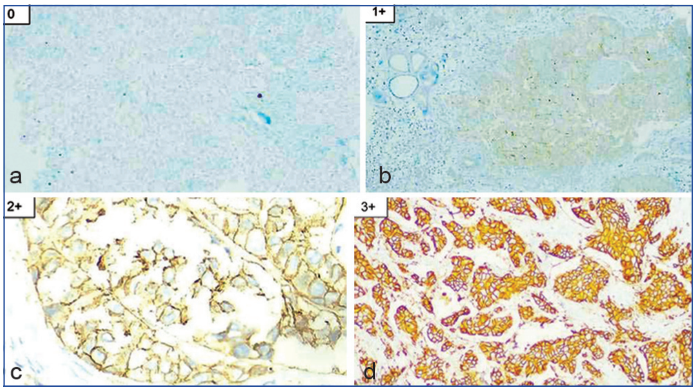
[Table/Fig-5]: Comparison of histopathological types of carcinoma breast with molecular subtypes (n=203).

In the present study, there were 14 Luminal-A cases; all of which had an Allred score of 8/8 for ER, while 10 out of 14 cases had a score of 8/8 for PR. Amongst 110 Luminal-B cases, there were 95 cases with an ER interpretation of 8/8 and 62 cases with a PR interpretation of 8/8 [Table/Fig-6]. For HER2/neu, 121 cases (59.6%) were interpreted as immunonegative (0 or 1+); while 45 cases (22.2%) were immunopositive (3+). There were 37 cases (18.2%) with equivocal (2+) interpretation; out of which 35 underwent FISH testing for final evaluation of the case, out of which six cases turned out to be positive [Table/Fig-7].

Overall, the most commonly found molecular subtype was Luminal-B with 110 (54.2%) cases followed by Triple negative with 51 cases (25.1%). HER2/neu enriched cases constituted 28 (13.8%) cases; while the least cases were found with Luminal-A molecular subtype (14; 6.9% cases). Additional markers were applied in TNBC cases and in eight out 51 TNBC cases; CK 5/6, SOX-10 and GATA-3 were



[Table/Fig-6]: a) Photomicrograph of Estrogen Receptor (ER) interpretation = 8/8 (Proportional Score+Intensity Score) (IHC, 40X); b) Photomicrograph of Progesterone Receptor (PR) interpretation = 8/8 (Proportional Score + Intensity Score) (IHC, 40X); c) Photomicrograph of Ki-67 in the highest proliferating areas = 12% (IHC, 100X); d) Photomicrograph of Ki-67 in the highest proliferating areas = 95% (IHC, 40X).



[Table/Fig-7]: a) Photomicrograph of HER 2/neu interpretation = 0 (Negative), showing no staining (IHC, 100X); b) Photomicrograph of HER 2/neu interpretation = 1+ (Negative), showing incomplete membranous staining that is faint/ barely perceptible and within >10% of the tumour cells (IHC, 100X); c) Photomicrograph of HER 2/neu interpretation = 2+ (Equivocal), showing weak and moderate complete membranous staining in >10% of the tumour cells (IHC, 400X); d) Photomicrograph of HER 2/neu interpretation = 3+ (Positive), showing complete, intense, circumferential membranous staining within >10% of the tumour cells (IHC, 100X).

positive. A combination of Synaptophysin, Chromogranin A and NSE showed immunopositivity in a single case of Mucinous carcinoma (showing Luminal-B molecular profile). E-cadherin expression was lost in all eight cases of ILC. It was also lost in most of the tumour cells in the case of mixed IDC, NOS and ILC (85% lobular), but retained in few tumour cells. In all three cases of Metaplastic carcinoma, additional markers including CK, mammaglobin, p40, Vimentin, SMA and EMA were applied. CK was positive in all three cases, mammaglobin and Vimentin were positive in 2 cases, while p40 was positive was positive in one case. None of the cases showed immunopositivity for SMA or EMA. 34βE12 and p63 were used in a single case of IDC with DCIS component.

A significant association existed between histopathological and molecular subtypes ($p<0.05$); of 181 IDC-NOS cases, 96 were Luminal-B. In patients≥60 years, Luminal-A was more likely (OR=3.494, 95% CI: 1.011-12.074, $p=0.045$), especially in non-IDC-NOS tumours (OR=5.0, $p=0.028$). Among 203 cases, 115 (56.6%) were Grade 2 (74 Luminal-B; $p<0.001$), 69 (34.0%) Grade 3, and 19 (9.4%) Grade1. Also, the tumours (mastectomy/BCS/excision/ lumpectomy specimens; but not trucut biopsies) were classified according to the pTNM classification and maximum cases belonged to T2; comprising 106/154 cases (68.8%); followed by T1 (23/154; 14.9% cases), T3 (21/154 cases; 13.6%) and T4 (4/154; 2.6%). Out of the 106 T2 cases, 59 cases belonged to molecular subtype Luminal-B. DCIS was noted in 51 (24.6%) cases (28 intermediate, 23 high-grade) and LCIS in one case; most ductal cases were Luminal-B (28 in number), followed by HER2-enriched (11 in number). Necrosis was present in 53/203 (26.1%), mainly Luminal-B (25 cases) and TNBC (17 cases) ($p<0.05$). Skin invasion occurred in six cases (4.2%) with strong subtype correlation ($p<0.001$). LVI was seen in 41

(20.2%), 21 of which were Luminal-B. Microcalcifications occurred in 38 (18.7%), most Luminal-B (26; p<0.05). Infiltrating tumour margins were found in 196/203 (96.5%), with Luminal-B being most frequent (107 cases). Lymphocytic response was observed in 76 (37.4%), mainly Luminal-B (40 cases). Perineural invasion was rare (10 cases), mostly Luminal-B (8 cases). Among axillary dissections, 68 (54.4%) were node-negative (38 Luminal-B). ENE was seen in 39/57 (19.2%) metastatic cases, significantly associated with subtypes (p<0.001); 24 were Luminal-B. Treatment-related changes were noted in two cases. The status of lymph nodes in carcinoma breast cases (wherever applicable) is shown in [Table/Fig-8].

Lymph node status	Number of cases	Percentage
N0	68	54.4
N1	16	12.8
N2	19	15.2
N3	22	17.6
Total	125	100.0

[Table/Fig-8]: Status of lymph nodes in carcinoma breast (n=125).

DISCUSSION

In the present study, of 203 cases, the age of patient presentation ranged from 28 to 88 years, with the majority of breast cancers occurring in post-menopausal females above 50 years (64.5%), particularly in the 51-60 year age group. The mean age was 56.3±12.4 years. This is older compared to earlier studies such as Bouropoulou V et al., who focused on histological features like microcalcifications, and Ahmad Z et al., who reported a younger age distribution in their mastectomy-based cohort [7,8]. Similarly, Rao C et al., and Tiwari S et al., found that the majority of patients presented in the 41-50 year age group (perimenopausal and early post-menopausal) [9,10]. Thus, the present study cohort appears slightly older at presentation. The impact of age and its correlation with molecular subtypes, however, was not statistically significant (p=0.180).

With respect to molecular subtypes, the majority of cases in our study were Luminal-B (54.7%), whereas Luminal-A was the least common (6.9%). This pattern is in partial agreement with Serrano-Gomez SJ et al., from Colombia, who also reported a higher Luminal-B rate (37.2%) with relatively fewer Luminal-A tumours (26.3%) [11]. In contrast, most Indian studies including those by Tiwari S et al., Kumar S et al., Biswal P et al., and Soni S et al., as well as international studies such as Bennis S et al., from Morocco, have consistently shown Luminal-A as the predominant subtype [10,12-15]. Regional studies from Saudi Arabia also reported Luminal-A as the most common (41.7%), followed by Luminal-B (23.4%), HER2/neu enriched (15.4%), and TNBC (19.5%). The discrepancy in Luminal subtype distribution across populations may be explained by differences in Ki-67 cut-off values used for IHC-based classification, or by underlying population-specific tumour biology.

In the present study, Triple Negative Breast Cancer (TNBC) accounted for 25.1% of cases. This aligns with Bhagat VM et al., who reported 25.9% TNBCs, and is slightly higher than the 19.9% documented by Patil VW et al., [16,17]. Other Indian studies such as Soni S et al., and Biswal P et al., found even higher TNBC prevalence at 35%, whereas Bisht M et al., reported only 9% [13,14,18]. Internationally, Thike AA et al., described TNBCs as a distinct aggressive entity with basal-like morphology, underscoring the biological heterogeneity across regions [19]. The relatively high prevalence in our cohort may be attributed to genetic predisposition (e.g., BRCA1/2 mutations) as well as lifestyle and environmental influences.

HER2/neu-enriched tumours constituted 13.8% of the present study cases. Of these, 59.6% were immunonegative (0 or 1+), 22.2% were strongly positive (3+), and 18.2% were equivocal (2+), necessitating FISH testing in 17.2% of cases. In comparison, Soni S et al., reported 21.8% positivity, 9.2% equivocal, and 69% negative cases. Mittal A and Mani NS similarly documented 30% HER2/neu-positive cases, with 17% negative and 8% equivocal, though many equivocal cases were lost to follow-up for confirmatory testing [14,20].

Histologically, 56.7% of our cases were MBR Grade 2, followed by Grade 3 (34.0%) and Grade 1 (9.4%). A statistically significant association was noted between histological grade and molecular subtype (p≤0.001), with most TNBC cases being Grade 3 tumours. This observation is consistent with the findings of Bisht M et al., and Geethamala K et al., both of whom highlighted the high-grade morphology of TNBC [18,21].

Regarding tumour size, the majority of the present study cases were T2 (68.8%), in contrast to Tiwari S et al., who observed more T3 tumours (61.4%) [10]. In Western populations, as reported by Antalio AA et al., most breast cancers presented at smaller sizes (71% were T1, <2 cm) [22]. This highlights differences in stage at presentation, likely due to variations in screening and healthcare access.

DCIS was identified in 24.6% of our cases, predominantly intermediate- or high-grade. In contrast, a large screening cohort from the Netherlands by Van Luijt PA et al., reported 50.9% high-grade, 31.4% intermediate, and 17.7% low-grade DCIS, reflecting earlier detection in screened populations [23]. Tumour necrosis was present in 26.1% of our cases, lower than the 46.2% reported by Soni S et al., [14] and 63.3% reported by Ahmad Z et al., [8]. A significant association was observed between necrosis and molecular subtype (p<0.05).

Microcalcifications were noted in 18.7% of our cases, again showing a significant correlation with molecular subtype. This was lower than the 41% incidence reported by Bouropoulou V et al., [7]. Tumour margins were predominantly infiltrative (96.6%), comparable to Thike AA et al., who reported 84% infiltrating margins in TNBC [19].

A lymphocytic response at the advancing tumour margin was observed in 37.4% of cases in our study, with varying degrees of intensity. Jayalakshmi S and Manjula AA, however, reported a higher rate of peritumoural lymphocytic infiltrates (66.7%), indicating potential prognostic significance [24]. Perineural invasion was relatively uncommon in our study (4.9%) compared to Narayan P et al., who documented 15.6% [25].

In terms of nodal status, 45.6% of the present study cases demonstrated lymph node metastasis, most commonly N3 (17.6%). This is comparable to Bhagat VM et al., Soni S et al., and Mittal A and Mani NS who reported 53.4%, 55.2%, and 58% node-positive cases, respectively [14,16,20]. Ahmad Z et al., observed most cases as N1 (27.1%) [8]. ENE was seen in 19.2% of the node-positive cases, whereas Ahmad Z et al., reported a much higher frequency (70%) [8]. Importantly, we observed a strong association between ENE and molecular subtype (p<0.001), with Luminal-B comprising the majority of ENE-positive cases.

The present study's prospective design is one of its main advantages since it made it possible to collect data on the clinical, histological, and molecular characteristics of breast cancer in a methodical and consistent manner throughout the study period. The addition of consecutive, histologically verified cases from a North Indian tertiary care facility to the scant literature from this region provides important region-specific information. Interobserver variability was decreased and methodological consistency was guaranteed through standardised histological examination and IHC profiling in accordance with departmental SOPs. The present study is notable for having a larger percentage of Luminal-B cases and a higher prevalence of TNBC. This pattern points to a propensity for more aggressive tumour biology in North Indian population, which may have consequences for treatment planning and rapid progression. This study emphasises how national and international standards may not adequately represent the local breast cancer situation.

Limitation(s)

Nonetheless, it is important to recognise some limitations. Due to regional healthcare disparities and referral bias, the results of this single-center study from a tertiary referral hospital might not be entirely generalisable to the broader population. The sample size limited statistical power for certain subgroup comparisons, and the 1-year period makes it difficult to evaluate long-term trends. Minor misclassification may have been introduced by the use of IHC surrogates for molecular subtype categorisation rather than genomic profiling. Furthermore, the absence of follow-up data makes it impossible to correlate subtypes with outcomes related to survival or recurrence.

CONCLUSION(S)

The present study reported several shifts including the shift in the predominant molecular profile with increasing prevalance of histological grade 2 Luminal-B and triple negative molecular subtypes and decreasing evidence of necrosis, LVI, microcalcifications, perineural invasion, lymph nodal metastasis and ENE. These may be the part and parcel of regional variations, different genetic predispositions and lifestyles. Urbanisation and delayed childbirth may also contribute to this. Associated factors like age distribution, genetic predisposition (e.g., BRCA mutations) can also result in these. This can even be due to the institutional bias reflecting more advanced or high-proliferation cases being referred. Variation in Ki-67 cut-off can also lead to differences in IHC interpretation. These shifts in the trends lead a need of region-specific breast cancer profiling and tailored management guidelines. This will lower over-treatment or under-treatment of the patient and will result in their improved survival outcomes.

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