Original Article

DOI: 10.7860/JCDR/2025/78110.20880

Radiology Section

Comparison of Mammography Findings of Triple Negative Breast Cancer with Non Triple Negative Breast Cancer Subtypes: A Retrospective Observational Study

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ABSTRACT

Introduction: Different molecular subtypes of breast cancer demonstrate variations in their clinical course, treatment response, and prognosis, which are defined by the expression of biological markers Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2).

Aim: To analyse the spectrum of mammography findings in different Immunohistochemical (IHC) subtypes of breast cancer and to compare the findings of Triple negative Breast Cancer (TNBC) with other non TNBC subtypes.

Materials and Methods: A retrospective observational study was conducted at the Department of Radiodiagnosis and Interventional Radiology, Dr. DY Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India, from December 2023 to March 2024. A total of 65 histopathology-proven breast cancer patients with a known IHC profile were included. Mammography findings were analysed in four major IHC subtypes, namely Luminal A (HR+, HER2-), Luminal B (HR+, HER2+), HER2-enriched (HR-, HER2+), and triple negative (HR-, HER2-). Imaging findings of TNBC were also compared with those of other non TNBC subtypes. The association between different variables was compared using the Chi-square test. For all the tests, a p-value of <0.05 (two-tailed) was considered statistically significant.

Results: The age of patients ranged from 30 to 83 years (Mean=53.7 years). The most common finding was a mass, which was present in 56 (86%) cases. Asymmetry was the least common finding, observed in 8 (12%) of cases. A total of 24 (36.9%) cases were classified as Luminal A, followed by 22 (33.8%) cases classified as TNBC. A total of 18.2% of TNBC cases demonstrated suspicious micro-calcifications, compared to 46.5% of non TNBC cases (p-value 0.031). The margins of the mass were circumscribed in 8 (40%) of TNBC cases, in comparison to other molecular subtypes (p-value 0.001).

Conclusion: The characterisation of mammography findings in various IHC subtypes aids in diagnosis and management planning.

Keywords: Breast cancer, Carcinoma, Molecular, Oncology, Screening

INTRODUCTION

Breast cancer is not only the most commonly diagnosed malignancy in women worldwide, but it is also a leading cause of cancer-related death among women [1,2]. There has been a significant increase in the frequency of breast cancer globally, with more than 2.3 million new cases diagnosed each year [3]. Early diagnosis and prompt treatment improve overall prognosis and survival rates [4]. The development of breast carcinoma results from multiple genetic alterations. The various subtypes of breast cancer, widely recognised by their signature gene expression, include luminal (Type A and B), HER2-enriched, and basal-like. Although basal-like breast cancers are often grouped with TNBC, basal-like breast cancers show high expression of p63, CK14, and CK5 compared to TNBC [5]. TNBC is a diverse group of breast cancers that do not express Oestrogen Receptors (ER), Progesterone Receptors (PR), or Human Epidermal Growth Factor Receptor 2 (HER2) [6]. These types of cancers are associated with a rapid clinical course and a higher propensity for early metastasis, leading to poorer outcomes [6,7].

Approximately 50-60% of breast carcinomas are classified as Luminal A, exhibiting ER/PR positivity, HER2 negativity, and low proliferation rates [8]. These cancers respond well to endocrine therapy and have a good prognosis. About 10-20% of breast cancers are classified as Luminal B, which express ER positivity, PR negativity, and variable HER2 expression or high proliferation rates [8,9]. These tumours respond to tamoxifen and aromatase inhibitors, but their response to chemotherapy is variable. Around 10-15% of breast cancers are HER2-enriched. They are ER and PR negative and exhibit a high proliferation rate. Histologically, they are characterised as high-grade invasive ductal carcinoma (NST) and have the worst prognosis among the subtypes [10]. These patients respond to trastuzumab (Herceptin). Triple negative tumours represent about 20% of breast cancers and are associated with high proliferation rates, TP53 mutations, and BRCA1 dysfunction. Histologically, they may present as high-grade invasive ductal carcinoma (NST), metaplastic carcinoma, or carcinoma with medullary features. They do not respond to endocrine therapy or trastuzumab (Herceptin) but appear to be sensitive to platinum-based chemotherapy and Poly-adenosine Diphosphate Ribose Polymerase (PARP) inhibitors, generally leading to poor prognosis [10]. Recently, the development of new therapeutic strategies for managing TNBC has focused on microRNAs and long non coding RNAs as targets of interest [11]. In other words, specific targeted therapies will aid in better patient management; hence, molecular subtyping is essential [12].

Different breast cancer subtypes also demonstrate variations in their mammographic appearance, with some distinct features correlating well with particular subtypes [13-15]. Therefore, determining the molecular subtype before planning any therapy is of utmost importance. With this background, the present study was conducted with the aim of comparing the imaging findings of TNBC with non TNBC subtypes.

MATERIALS AND METHODS

The present retrospective observational study was conducted in the Department of Radiodiagnosis and Interventional Radiology at Dr. DY Patil Medical College, Hospital and Research Centre, Pune,

Maharashtra, India, from December 2023 to February 2024. Data from June 2022 to May 2023 were collected retrospectively and analysed. A total of 65 histopathology-proven breast cancer patients with known IHC profiles were included in the study.

Inclusion criteria: Female patients over 18 years of age with histopathology-proven breast malignancy and available IHC findings were included in the study.

Exclusion criteria: Male patients, patients under 18 years of age, and patients for whom IHC receptor evaluation was not available were excluded from the study.

Study Procedure

Full-field digital mammography images of these patients were retrieved from the Picture Archiving and Communication System (PACS) and reviewed. The final assessment category was assigned using the mammographic lexicon according to the American College of Radiology Breast Imaging-Reporting and Data System (ACR-BIRADS) lexicon [16].

All mammography images were analysed for their breast parenchymal density pattern and lesions characteristics. Parenchymal density is categorised as follows: Category A is predominantly fatty parenchyma, Category B consists of scattered glandular and fibrous tissue, Category C is characterised by dense glandular and fibrous tissue (heterogeneously dense parenchyma), and Category D is extremely dense breast parenchyma. Every lesion was evaluated for shape, margins, microcalcifications, and associated findings. The radiological imaging findings were compared among the four major IHC subtypes, namely Luminal A (HR+, HER2-), Luminal B (HR+, HER2+), HER2-enriched (HR-, HER2+), and triple negative (HR-, HER2-). Imaging findings of TNBC were also compared with those of other non TNBC subtypes.

STATISTICAL ANALYSIS

Statistical analysis was conducted using MS Excel (Microsoft 365) and IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp. Released 2020, Armonk, NY: IBM Corp). Since the data were categorical, values were summarised using frequencies and percentages. The association between different variables was compared using the Chi-square test. For all tests, a p-value of <0.05 (two-tailed) was considered statistically significant.

RESULTS

The age range was from 30 to 83 years (mean=53.7 years). The peak age at diagnosis was between 60 and 69 years, observed in 20 (30.8%) of cases. Luminal A was the most common molecular subtype, seen in 24 (36.9%) of cases, followed by TNBC at 22 (33.8%) [Table/Fig-1].

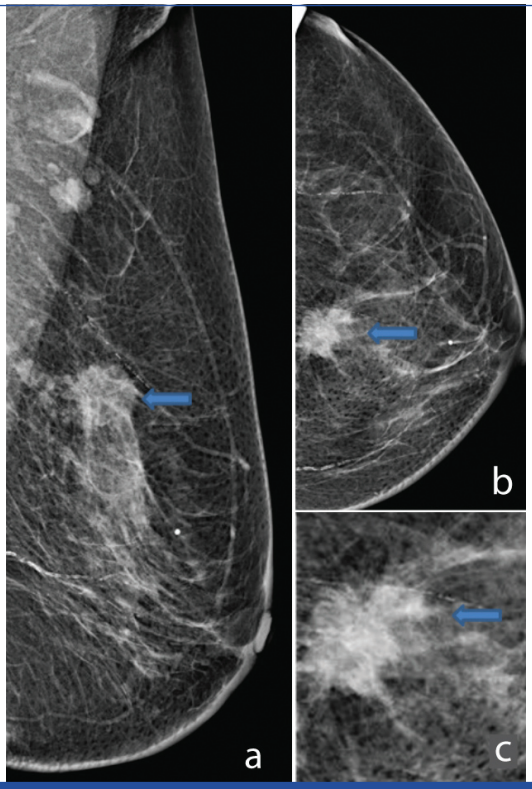
Age range (in years)	Luminal A	Luminal B	HER2 enriched	Triple negative	Total	p-value
30-39	3 (12.5%)	2 (18.2%)	0	3 (13.6%)	8 (12.3%)	
40-49	1 (4.2%)	0	0	5 (22.7%)	6 (9.2%)	
50-59	7 (29.2%)	2 (18.2%)	1 (12.5%)	9 (40.9%)	19 (29.2%)	0.020*
60-69	11 (45.8%)	2 (18.2%)	4 (50.0%)	3 (13.6%)	20 (30.8%)	
>70	2 (8.3%)	5 (45.5%)	3 (37.5%)	2 (9.1%)	12 (18.5%)	
Total	24 (36.9%)	11 (16.9%)	8 (12.3%)	22 (33.8%)	65	

[Table/Fig-1]: Distribution of patients based on age groups and cross-tabulation of age groups with frequency of molecular subtype.
Values represented are frequency (%); Test used: Chi-square test; *p-value of <0.05, statistically significant

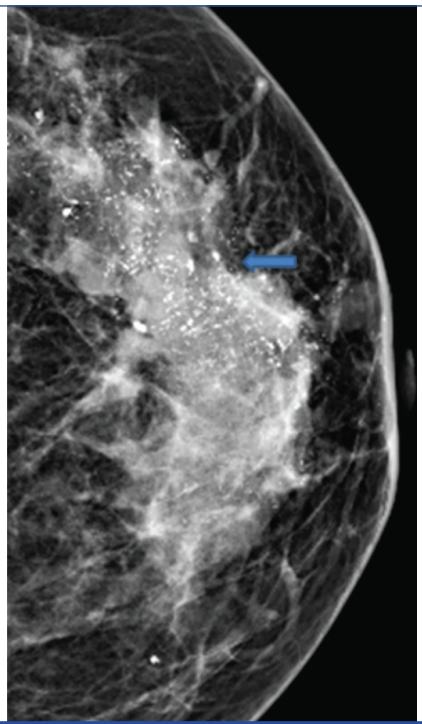
The most common finding was a mass, which was present in 56 (86%) of cases. Asymmetry was the least common finding, occurring in 8 (12%) of cases [Table/Fig-2]. The mass presented with circumscribed, indistinct, obscured, or spiculated margins [Table/Fig-3]. Mammographic evidence of suspicious calcifications correlated strongly with HER2-enriched breast cancer (75%) [Table/Fig-4,5].

Findings	n (%)
Mass	56 (86.2)
Asymmetry	8 (12.3)
Architectural distortion	38 (58.5)
Suspicious calcifications	24 (36.9)
Associated features	44 (67.7)

[Table/Fig-2]: Mammographic findings of malignant cases.



[Table/Fig-3]: Case of Invasive ductal carcinoma, Luminal A in 59-year-old female a: Mammogram Mediolateral Oblique (MLO) (a) and Cranio-caudal (CC) (b) view showing an irregular mass with spiculated margins (arrow). (c) Magnified view of the mass revealed irregular shape, spiculated margins, no microcalcification (arrow).



[Table/Fig-4]: Case of Invasive ductal carcinoma of subtype HER2 enriched in 55-year-old female. Mammogram CC views showing a heterogeneous non mass lesion in left breast demonstrating microcalcification (arrow).

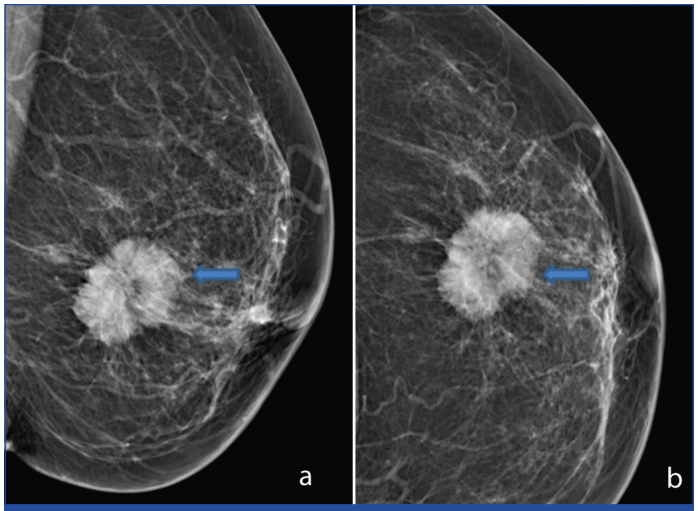
Mammography findings	Luminal A	Luminal B	HER2 enriched	Triple negative	p-value
Parenchymal density					
A	0	3 (27.3%)	0	0	0.005*
B	8 (33.3%)	3 (27.3%)	0	10 (45.5%)	
C	15 (62.5%)	5 (45.5%)	8 (100.0%)	10 (45.5%)	
D	1 (4.2%)	0	0	2 (9.1%)	
Mass					
Present	20 (83.3%)	9 (81.8%)	7 (87.5%)	20 (90.9%)	0.858
Absent	4 (16.7%)	2 (18.2%)	1 (12.5%)	2 (9.1%)	
Asymmetric density					
Present	3 (12.5%)	2 (18.2%)	1 (12.5%)	2 (9.1%)	0.905
Absent	21 (87.5%)	9 (81.8%)	7 (87.5%)	20 (90.9%)	
Architectural distortion					
Present	13 (54.2%)	7 (63.6%)	8 (100.0%)	10 (45.5%)	0.057
Absent	11 (45.8%)	4 (36.4%)	0	12 (54.5%)	
Suspicious calcifications					
Present	10 (41.7%)	4 (36.4%)	6 (75.0%)	4 (18.2%)	0.036*
Absent	14 (58.3%)	7 (63.6%)	2 (25.0%)	18 (81.8%)	
With mass	7 (29.2%)	3 (27.3%)	6 (75.0%)	4 (18.2%)	0.043*
Without mass	3 (12.5%)	1 (9.1%)	0	0	
Associated features					
Present	17 (70.8%)	8 (72.7%)	7 (87.5%)	12 (54.5%)	0.333
Absent	7 (29.2%)	3 (27.3%)	1 (12.5%)	10 (45.5%)	

[Table/Fig-5]: Distribution of mammographic findings and cross-tabulation with molecular subtypes.
Values represented are frequency (%); Test used: Chi-square test; *p-value of <0.05, statistically significant

Parenchymal density Category C was the most common, observed in 38 (58.5%) of cases, which was statistically significant (p-value <0.05). A mass was present in 90.9% of cases of triple negative and in 83.3% of Luminal A cases. Suspicious calcifications were most commonly seen in Luminal A (41.7%) and least common in triple negative cases, demonstrated only in 18.2% of cases, which was statistically significant (p-value <0.05) [Table/Fig-5].

In this study, 37 (56.9%) of the masses were classified as BI-RADS Category 5, and 28 (43.07%) of cases were categorised as BI-RADS 4. The HER2-enriched subtype had the highest incidence of BI-RADS 5 lesions (87.5%); however, this finding was not statistically significant (p=0.309).

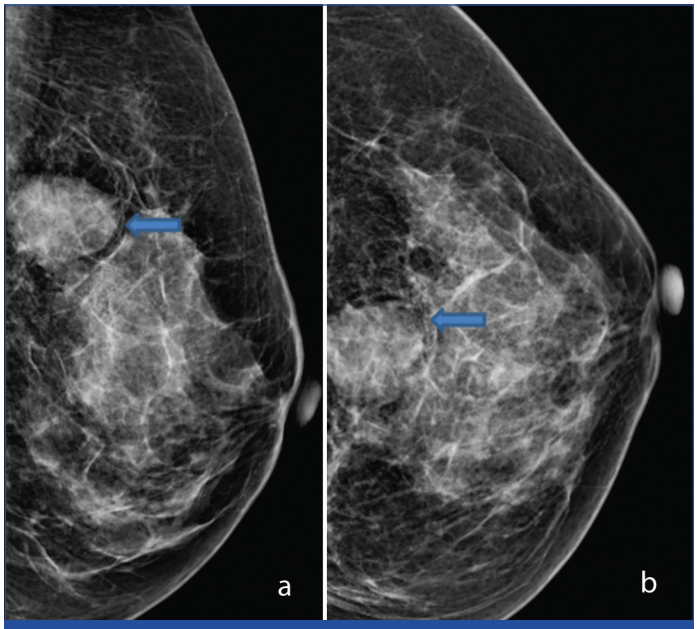
Spiculated margins were most frequently associated with the Luminal B subtype [Table/Fig-6]. The predominant mammography finding in all subtypes was a mass with an irregular shape, which was present in 53 (81.5%) of cases. Only two masses demonstrated an oval shape, while one was of a round shape [Table/Fig-7]. Circumscribed masses were more common in TNBC [Table/Fig-8].



[Table/Fig-6]: Case of Invasive ductal carcinoma, Luminal B type in 65-year-old female Mammogram (a) MLO and (b) CC view showing an irregular mass with spiculated margins (arrow) and no microcalcification.

Mass present (n=56)	Luminal A	Luminal B	Her2 enriched	Triple negative	p-value
Shape					
Round	0	0	0	1 (5.0%)	0.941
Oval	1 (5.0%)	0	0	1 (5.0%)	
Irregular	19 (95.0%)	9 (100.0%)	7 (100.0%)	18 (90.0%)	
Margin					
Circumscribed	0	0	0	8 (40.0%)	0.021
Indistinct	3 (15.0%)	0	2 (28.6%)	1 (5.0%)	
Microlobulated	5 (25.0%)	1 (11.1%)	1 (14.3%)	1 (5.0%)	
Spiculated	12 (60.0%)	8 (88.9%)	4 (57.1%)	10 (50.0%)	
Density					
Equal	2 (10.0%)	1 (11.1%)	0	2 (10.0%)	0.851
High	18 (90.0%)	8 (88.9%)	7 (100.0%)	18 (90.0%)	
Total	20 (83.3%)	9 (81.8%)	7 (87.5%)	20 (90.9%)	

[Table/Fig-7]: Mammographic findings in TNBC and cross-tabulation with other molecular subtypes.
Values represented are frequency (%); Test used: Chi-square test; *p-value of <0.05; statistically significant



[Table/Fig-8]: Case of Triple Negative Breast Cancer (TNBC) in a 50-year-old female: Mammogram (a) MLO and (b) CC view showing an oval mass with circumscribed margins (arrow), no microcalcification.

Suspicious calcifications were more frequently associated with other molecular subtypes compared to TNBC (46.5% vs. 18.2%), which was statistically significant (p-value=0.031) [Table/Fig-9]. The margins of masses were circumscribed in 8 (40%) of TNBC cases, compared to other molecular subtypes (n=0), which was statistically significant (p-value=0.001) [Table/Fig-9].

DISCUSSION

Breast cancer is the most common cancer among women globally. Ginsburg O et al., reported the peak age at diagnosis in Asian countries as 40 to 50 years [17]. In the present study, the age range was 30 to 83 years, with a median age of 53 years. The most common molecular subtype in the present study was Luminal A (36.9%), followed by TNBC (33.8%). Among participants aged 30 to 59, TNBC was the more common subtype in the present study, occurring in 51.5% of cases. A meta-analysis conducted by Jonnada PK et al., reported that the most common molecular subtype was Luminal A, followed by TNBC, Luminal B, and HER2-enriched

Findings	TNBC	Other molecular subtypes	p-value
Mass			
Present	20 (90.9%)	36 (83.7%)	0.706
Absent	2 (9.1%)	7 (16.3%)	
Asymmetric density			
Present	2 (9.1%)	6 (14.0%)	0.706
Absent	20 (90.9%)	37 (86.0%)	
Architectural distortion			
Present	10 (45.5%)	28 (65.1%)	0.184
Absent	12 (54.5%)	15 (34.9%)	
Suspicious calcifications			
Absent	18 (81.8%)	23 (53.5%)	0.031*
Present	4 (18.2%)	20 (46.5%)	
Without mass	0	4 (9.3%)	
With mass	4 (18.2%)	16 (37.2%)	
Mass present	**In cases of TNBC with mass (n=20)**	**Other molecular subtypes with mass (n=36)**	**p-value**
Shape			
Round	1 (5.0%)	0	0.435
Oval	1 (5.0%)	1 (2.8%)	
Irregular	18 (90.0%)	35 (97.2%)	
Margin			
Circumscribed	8 (40.0%)	0	0.001*
Indistinct	1 (5.0%)	5 (13.9%)	
Microlobulated	1 (5.0%)	7 (19.4%)	
Spiculated	10 (50.0%)	24 (66.7%)	
Density			
Equal	2 (10.0%)	3 (8.3%)	0.713
High	18 (90.0%)	33 (91.7%)	
Low	0	0	
Total	20 (90.9%)	36 (83.7%)	

[Table/Fig-9]: Distribution based on characterisation of mass and cross-tabulation of TNBC with other molecular subtypes.
Values represented are n (%); Test used: Chi-square test; *p-value of <0.05; statistically significant

subtypes [18]. The majority of the cases in the present study fell into BI-RADS Category 5 {37 (56.9%)}. The HER2-enriched subtype had the highest incidence of BI-RADS 5 lesions (87.5%); however, this finding was not statistically significant. The HER2 subtype of breast cancer and its significant association with higher BI-RADS categories were documented by Sohn YM et al., [19].

Variations in the imaging appearance of different molecular subtypes have been described in several studies [10,15,19]. Tamaki K et al., found that irregular mass shape and/or spiculated margins were significantly associated with Luminal A breast cancers [15]. In the present study, irregular shapes were frequently observed in all four subtypes, with spiculated margins demonstrated in 60% of Luminal A subtypes and 88% of Luminal B subtypes; however, this finding was not statistically significant. Tamaki K et al., also found oval and round mass shapes, as well as well-defined masses, to be more common in TNBC subtypes, while irregular shapes and spiculated margins were more frequently detected in Luminal A subtypes [15]. In the present study, well-defined circumscribed masses were seen in 40% of cases, which were of the TNBC subtype, while spiculated margins were detected in 60% of the Luminal A subtypes. Taneja S et al., observed a predominance of ill-defined masses, with spiculated masses being most frequent in Luminal A subtypes [20]. In the present study, the authors observed that irregular masses with spiculated margins are more common in Luminal A subtypes (60%). Calcification is an important parameter in mammography, and it can be the only imaging finding in some early breast cancers. Four cases in the present study showed suspicious calcification without a mass; three of them were of Luminal A type, and one was of Luminal B type. One case in the present study presented with suspicious micro-calcifications in a grouped distribution without any features of a mass or asymmetric density; it was diagnosed as low-grade Ductal Carcinoma In-situ (DCIS) with a Luminal A molecular subtype on histopathology. Seventy-five percent of HER2-enriched cases in the present study showed suspicious micro-calcifications. This finding was statistically significant (p<0.05) and concorded with other studies that found calcifications more commonly associated with HER2 neu overexpressing tumours [21-23]. Tamaki K et al., reported a more frequent association of architectural distortion with the Luminal A subtype [15]. Non mass asymmetric density and architectural distortion were more common in the HER2-enriched subtype in the present study, though it was not statistically significant. Associated features were seen more commonly in the HER2-enriched subtype in the present study. However, suspicious axillary lymph nodes were more frequent in Luminal A compared to other subtypes, which was not statistically significant. This differs from other studies that found that HER2-overexpressing tumours were more likely to present with nodal involvement [23]. Out of the four subtypes, Luminal A has the most favourable prognosis. HER2-enriched and TNBCs have poorer survival compared to other subtypes [24,25]. Triple negative breast cancer represents a distinct entity, as it is associated with aggressive behaviour and poorer outcomes [24]. It is also found to be a poor prognostic factor irrespective of the histological grade and tumour stage [24]. Moreover, they are commonly encountered in younger patients, less than 40 years of age, and tend to be of larger size at presentation. The reason for the delayed presentation could be partly due to their imaging appearance or missed diagnosis on imaging. On mammography, TNBC lesions usually appear as ill-defined masses, with a smaller proportion showing spiculations or architectural distortion, making their detection difficult in some cases [20].

The authors compared the mammographic findings of TNBC with cases of non TNBC subtypes. Mass was the predominant presenting feature in both categories; however, microcalcifications and architectural distortion are less common in TNBC subtypes. This finding is consistent with other studies [19,26-28]. Yang WT et al., found that TNBC lesions commonly demonstrate round, oval, or lobular shapes and indistinct margins [24]. In the present study, TNBC had an equal association with indistinct and spiculated margins, whereas microlobulated and spiculated margins were the predominant findings in non TNBC subtypes. The present study showed no statistically significant difference in mass shape, margin, and density between the TNBC and non TNBC groups. Suspicious calcifications were not a predominant feature of TNBC compared to the non TNBC group, which was statistically significant (p<0.05) in the present study. A similar finding was observed by Ko ES et al., who reported that, in mammography, TNBC usually presents as a mass or with focal asymmetry and is less associated with calcifications. The lack of calcification on mammography was attributed to TNBC progressing rapidly into the invasive stage with fewer major in-situ components or precancerous stages [29]. Despite their large size at presentation, TNBC usually demonstrates benign or indeterminate findings on mammography, such as focal asymmetry or circumscribed round or oval masses, with less frequent calcifications [26]. The relatively low frequency of calcification in TNBC has been supported by many other studies [26,27,29,30]. A meta-analysis conducted by Jonnada PK et al., reported a higher prevalence of TNBC in India than in other parts of the world. Considering the poor prognosis of TNBC, this could partly explain the higher fatality rate of breast cancer patients in India [18]. A large-scale multicenter prospective study, including other adjunct imaging modalities, is recommended to validate the results. Furthermore, an aggressive screening program and extensive research to study the association between genetic and environmental factors and the high incidence of TNBC in India is recommended.

Limitation(s)

It is a single-institution study with a small sample size. As a retrospective study design, it may be affected by selection bias;

therefore, only cases with known IHC profiles were included in the study. The present study analysed the mammographic findings in various IHC subtypes. However, the inclusion of other imaging modalities, such as ultrasonography and MRI, would yield better results.

CONCLUSION(S)

Characterisation of the mammography findings in various IHC subtypes helps in diagnosis, management, and monitoring. The present study aids in understanding the imaging findings across different subgroups and their comparison with TNBC subtypes, which further helps in predicting the prognosis of breast cancer, as well as improving diagnosis and management planning.

Acknowledgement

The authors are thankful for the support from Ms. Madhura Gandhi Statistician, CRF, DPU for the statistical calculations in the present study.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 20, 2025
- Manual Googling: Mar 07, 2025
- iThenticate Software: Mar 09, 2025 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 17, 2025**
Date of Peer Review: **Feb 13, 2025**
Date of Acceptance: **Mar 11, 2025**
Date of Publishing: **Apr 01, 2025**