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Association of Multimodality Imaging Features with Breast Cancer Molecular Subtypes

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ABSTRACT

Background and aim: Breast cancer comprises distinct molecular subtypes with different biological characteristics and treatment responses. This study evaluated the association between multimodality imaging features and immunohistochemically defined breast cancer molecular subtypes.

Material and methods: This cross-sectional observational study included 50 women with histopathologically confirmed breast cancer who underwent mammography, ultrasonography (USG), and contrast-enhanced magnetic resonance imaging (MRI) between October 2023 and December 2024. We assessed imaging features and correlated them with molecular subtypes. We evaluated associations using contingency tests and univariate logistic regression, and assessed diagnostic performance using receiver operating characteristic (ROC) analysis.

Results: The mean age was 51.56 ± 10.3 years. Luminal A was the most frequent subtype (30%), followed by Luminal B (28%). Mammographic calcifications were more frequent in HER2-enriched tumors but were not significantly associated with this subtype (OR: 3.33, 95% CI: 0.62–18.0, p=0.162). Posterior acoustic enhancement was significantly associated with TNBC (OR: 20.9, 95% CI: 10.5–415, p<0.001; AUC=0.88), as was a circumscribed margin (OR: 18.75, 95% CI: 3.46–101.6, p<0.001; AUC=0.86). Posterior acoustic shadowing was associated with Luminal A (OR: 5.33, 95% CI: 1.27–22.32, p=0.035; AUC=0.69).

Conclusions: Selected imaging features were associated with specific breast cancer molecular subtypes. Larger multicenter studies with integrated and validated predictive models are needed to confirm these findings.

1. Introduction

Breast cancer is the most frequently diagnosed malignancy and remains a leading cause of cancer-related mortality among women worldwide. It accounted for 11.6% of all newly diagnosed cancer cases and 6.9% of cancer-related deaths globally in 2022, with breast cancer representing a substantial proportion of cancers among women in India.[1–3] Breast cancer is a biologically heterogeneous disease characterized by substantial variation in histopathology, molecular characteristics, clinical behavior, prognosis, and response to treatment. Based on immunohistochemical assessment of biomarkers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, breast cancers are commonly classified into clinically relevant surrogate molecular subtypes, including Luminal A, Luminal B, HER2-positive/enriched, and triple-negative breast cancer (TNBC). These subtypes demonstrate distinct biological and therapeutic characteristics. Hormone receptor-positive tumors generally benefit from endocrine therapy, whereas HER2-positive tumors may benefit from HER2-targeted treatment.

In contrast, TNBC lacks ER, PR, and HER2 expression and is generally associated with more aggressive behavior, earlier recurrence, and poorer outcomes.[4] TNBC may also demonstrate imaging characteristics that overlap with benign breast lesions, including smooth or circumscribed margins, which can complicate imaging-based assessment. Accurate characterization of breast cancer subtype is important for prognostic assessment and treatment planning. Although molecular classification ultimately relies on pathological and immunohistochemical assessment, imaging may provide complementary information about tumor morphology and biological behavior before definitive tissue diagnosis. Mammography, ultrasonography (USG), and magnetic resonance imaging (MRI) provide different and potentially complementary perspectives on breast lesions. Mammography can characterize mass morphology and calcifications, USG can demonstrate lesion margins and posterior acoustic characteristics, and MRI can provide information regarding enhancement patterns and tumor vascularity.[5-7] Previous studies have reported associations between individual imaging

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characteristics and specific breast cancer molecular subtypes. However, many investigations have focused on a single imaging modality or evaluated selected imaging features independently. Consequently, the extent to which findings obtained from mammography, USG, and MRI are associated with immunohistochemically defined molecular subtypes remains insufficiently characterized, particularly in the Indian population.[7, 8] A systematic assessment of imaging characteristics across multiple routinely used modalities may therefore provide clinically relevant information for preoperative breast cancer characterization. Accordingly, the present study aimed to evaluate the association between selected mammographic, ultrasonographic, and MRI features and immunohistochemically defined breast cancer molecular subtypes.[9, 10] Rather than establishing a definitive non-invasive molecular classification system, the study sought to identify imaging characteristics associated with specific subtypes that could contribute to future validated predictive approaches. Previous studies have reported associations between individual imaging characteristics and specific breast cancer molecular subtypes. However, many of these studies have evaluated mammography, ultrasonography, or MRI separately or have focused on selected imaging characteristics.[11–14] Therefore, the association between findings obtained from routinely used imaging modalities and immunohistochemically defined molecular subtypes remains incompletely characterized, particularly in the Indian population. The present study was designed to evaluate selected imaging characteristics across mammography, ultrasonography, and MRI in relation to breast cancer molecular subtypes. The primary objective was to identify imaging features associated with specific molecular subtypes rather than to establish a definitive or externally validated non-invasive classification model. The findings were therefore considered exploratory and intended to provide a basis for future studies investigating integrated multimodality predictive models.

2. Material and methods

Study design and setting

After obtaining approval from the Institutional Ethics Committee (approval no. Acad/Ethical Clearance/Batch 2022/2023/47), the study was conducted between October 2023 and December 2024. The study included consecutive eligible female patients with breast masses who underwent mammography, ultrasonography, and contrast-enhanced breast MRI as part of their diagnostic evaluation. All included patients subsequently underwent histopathological and immunohistochemical assessment for definitive diagnosis and molecular subtype classification. This study was a single-center observational investigation. We recruited patients according to predefined inclusion and exclusion criteria and included only those with complete clinical, imaging, histopathological, and immunohistochemical data in the final analysis.

Sample size and patient selection

Because this observational study included consecutive eligible patients presenting during the predefined study period from October 2023 to December 2024, we did not perform a formal a priori sample size calculation. A total of 50 patients fulfilled the eligibility criteria and had complete clinical, imaging, histopathological, and immunohistochemical data. We considered the relatively small sample size, particularly within individual molecular subtype groups, when interpreting the statistical findings. The limited number of observations restricted statistical modeling and precluded the development of a robust multivariable prediction model. Accordingly, we considered the analyses exploratory and interpreted the estimated associations with appropriate caution.

Inclusion, exclusion, and potential selection bias

Female patients aged 18–80 years presenting with a breast mass and scheduled to undergo mammography, ultrasonography, and MRI for breast cancer evaluation were eligible for inclusion after obtaining informed consent. Patients with a previous history of breast cancer or previous treatment, another systemic malignancy, systemic diseases that could affect study participation, or contraindications to MRI were excluded.

Consecutive recruitment and predefined eligibility criteria were used to reduce potential selection bias. However, because the study was conducted at a single center and included a relatively small number of patients undergoing multimodality imaging, selection bias and limited generalizability cannot be completely ruled out.

Imaging protocol and assessment

All enrolled patients underwent bilateral mammography, breast ultrasonography, and contrast-enhanced breast MRI according to the standard imaging protocols routinely followed at the study institution. Imaging findings were documented before correlation with histopathological and immunohistochemical results. The assessed imaging characteristics included lesion morphology and shape, margin characteristics, mammographic calcifications, posterior acoustic characteristics on ultrasonography, MRI enhancement patterns, and BI-RADS assessment. Imaging findings were described using standardized BI-RADS terminology where applicable. The multimodality approach was used to characterize complementary morphological and enhancement features across the three imaging techniques. However, because this analysis evaluated individual imaging characteristics rather than a combined predictive algorithm, we interpreted the results primarily as associations between imaging findings and molecular subtypes.

Image interpretation

Imaging findings were assessed with particular attention to lesion morphology, margins, calcifications, posterior acoustic characteristics, enhancement patterns, and BI-RADS category. The imaging characteristics were subsequently correlated with histopathological and immunohistochemical findings. We included only patients with complete imaging and pathological information in the final analysis, and we reported no missing data for the variables analyzed.

Important methodological clarification required

The original manuscript does not specify the number of radiologists involved in image interpretation, their experience level, whether images were independently assessed or reviewed by consensus, or whether the radiologists were blinded to histopathological and immunohistochemical findings. These details should be added. If more than one reader independently evaluated the images, report interobserver agreement.

Histopathological and immunohistochemical assessment

All included breast lesions were confirmed histopathologically. Immunohistochemical assessment was then used to classify tumors by molecular subtype. The study evaluated the major clinically relevant subgroups reported in the manuscript, including Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC). Because the manuscript does not provide detailed immunohistochemical methodology, the authors should explicitly report the exact criteria used for subtype assignment. These should include the ER and PR positivity thresholds, HER2 scoring criteria, the Ki-67 threshold used to distinguish Luminal A from Luminal B, and the specific criteria used to classify HER2-enriched tumors. The authors

should also clarify whether they determined molecular subtypes using immunohistochemical surrogate definitions or molecular assays. If the authors used immunohistochemical surrogate classification, they should consistently describe the groups as immunohistochemically defined molecular surrogate subtypes rather than implying that gene-expression profiling established intrinsic molecular subtypes.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Associations between categorical variables were assessed using contingency tables and the Chi-square test or Fisher's exact test, as appropriate. Univariate logistic regression analysis was performed to evaluate the association between selected imaging features and molecular subtype outcomes. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Because of the relatively small sample size and limited number of observations within individual molecular subgroups, multivariable logistic regression was not performed. Receiver operating characteristic (ROC) curve analysis was subsequently used to assess the discriminatory performance of selected imaging features. Diagnostic performance was summarized using the area under the curve (AUC), sensitivity, and specificity. A two-sided p-value $\leqslant 0.05$ was considered statistically significant. Given the small number of patients in some molecular subtype groups and the observed imbalance in certain imaging characteristics, interpret the reported ORs as exploratory estimates rather than definitive predictive measures. In particular, the complete or near-complete separation observed for some imaging characteristics warrants cautious interpretation of conventional logistic regression estimates. Where the original patient-level data permit, penalized logistic regression, such as Firth logistic regression, would be preferable for assessing these associations in future or revised analyses.

Interpretation of effect Estimates and confidence intervals

The magnitude of the reported associations was interpreted together with the corresponding 95% confidence intervals rather than on the basis of odds ratios alone. Several estimates showed wide confidence intervals, reflecting substantial uncertainty due to the limited sample size and small numbers within some molecular subtype groups. For example, posterior acoustic enhancement showed a strong association with TNBC (OR: 20.9, 95% CI: 10.5-415), while circumscribed margins were also associated with TNBC (OR: 18.75, 95% CI: 3.46–101.6). Although these associations were statistically significant, the wide confidence intervals indicate limited precision and should prevent interpreting these estimates as definitive clinical prediction effects. Similarly, mammographic calcification demonstrated an OR of 3.33 for HER2-enriched tumors, but the confidence interval included unity (95% CI: 0.62–18.0) and the association was not statistically significant (p=0.162). Therefore, this finding should be regarded as an observed trend rather than evidence of a statistically confirmed predictive association. Overall, interpret the statistical findings as exploratory associations that require confirmation in larger cohorts with adequate representation of each molecular subtype. Future studies should use appropriately powered multivariable or penalized regression models and external validation before considering these imaging characteristics for clinical prediction.

3. Results

In our study of 50 patients with breast cancer, the mean age was 51.56 ± 10.3 years, with the highest incidence in the 41–50 years age group (34%). Right-sided involvement was seen in 31 patients (62%). Table 1 summarizes the presentation and additional features of breast lumps. The most predominant breast mass shape is Irregular on USG (48%) and mammogram (50%) and Lobulated on MRI (34%). A non-circumscribed margin is seen on USG (64%) and mammogram (66%); among non-circumscribed masses, the most common type is microlobulated. In this study, the most common molecular subtype is Luminal A (30%), followed by Luminal B (28%). Calcification on mammogram is predominantly seen in the HER2-enriched type (77.77%) and is least associated with TNBC (25%). In the posterior features of breast mass on USG, 75% of TNBC cases show enhancement, 80% of Luminal A cases show shadowing, and 55.55% of HER2-enriched cases show a combined pattern. Enhancement is significantly associated with TNBC. 72% of cases show a heterogeneous enhancement pattern, 64% show low Intra-tumoral T2 hyperintensity, 80% show irregular margins, and 58% show washout time signal intensity on MRI.

Table 1. Presentation and additional features of breast mass.

Variable		n	%
Presentation			
Palpable lump		50	100
Breast Pain		17	34
Nipple discharge		4	8
Additional features			
Skin thickness	On USG	17	34
	On Mammogram	19	38
Axillary Lymphadenopathy	On USG	32	64
	On Mammogram	28	56

Mammographic calcification was significantly associated with TNBC status, with calcifications observed in 25.0% of TNBC cases compared with 65.8% of non-TNBC cases (p=0.0197). (Table 2, Fig. 1) Circumscribed margin on mammogram is significantly associated with TNBC, and non-circumscribed is associated with Luminal A. (Table 3, Fig. 2) Univariate analysis shows that Posterior acoustic enhancement and circumscribed margin are significant predictors of TNBC, and Posterior Shadowing is a significant predictor of Luminal A. (Table 4, Fig. 3)

Table 2. Association Between Mammographic Calcification and TNBC Status.

Molecular Subtype	Total, n	Calcification Present, n (%)	Calcification Absent, n (%)	P-value
TNBC	12	3 (25.0)	9 (75.0)	
Non-TNBC	38	25 (65.8)	13 (34.2)	0.0197
Total	50	28 (56.0)	22 (44.0)	

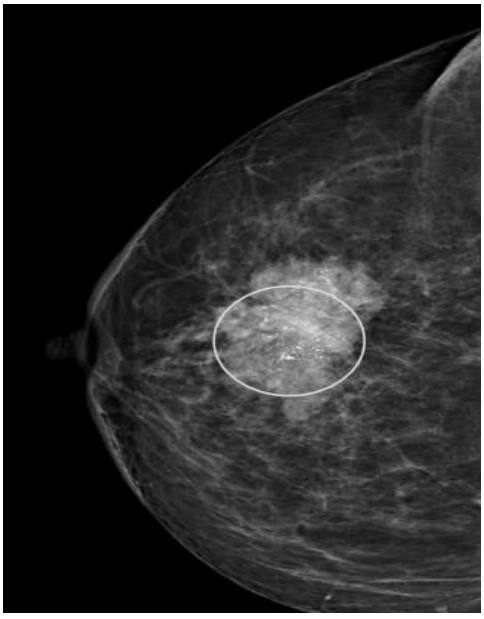

Fig. 1. Pleomorphic Calcification on mammogram.

Table 3. Association Between Mammographic Margin Characteristics and Breast Cancer.

Molecular Subtype	Total, n	Circumscribed Margin, n (%)	Non-circumscribed Margin, n (%)	P-value
TNBC	12	12 (100.0)	0 (0.0)	
Luminal A	15	2 (13.3)	13 (86.7)	
Luminal B	14	6 (42.9)	8 (57.1)	<0.001
HER2-enriched	9	1 (11.1)	8 (88.9)	
Total	50	21 (42.0)	29 (58.0)	

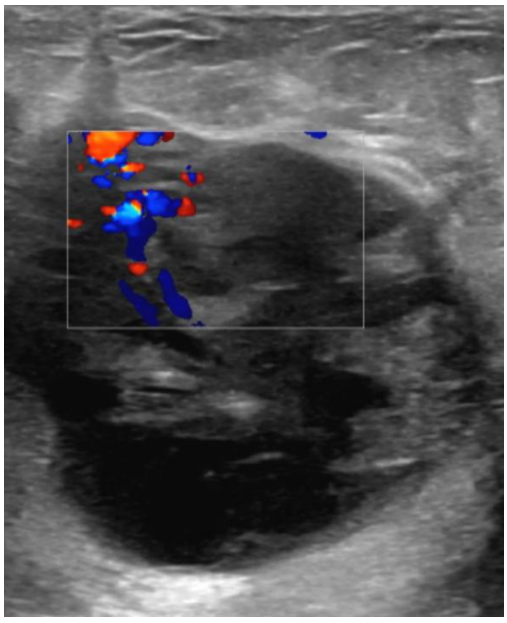

Fig. 2. Well circumscribed mass with posterior acoustic enhancement on breast USG.

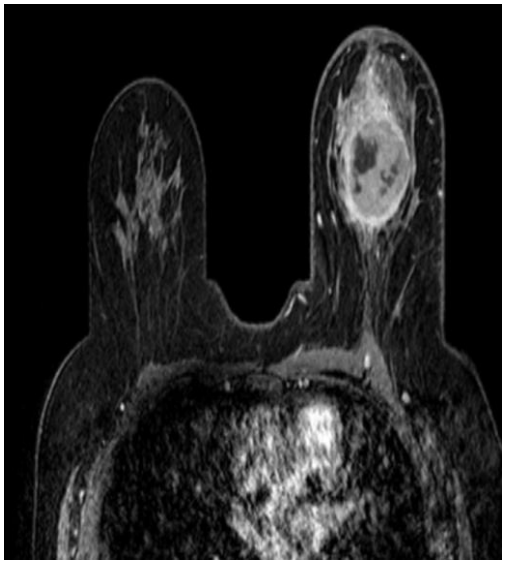

Fig. 3. Well-circumscribed margin with capsular/rim enhancement on MRI.

Table 4. Univariate regression analysis with predictive value of imaging features.

Imaging Feature	Characteristic Feature	Odd Ratio (OR)	Confidence Interval (CI)	P-value
Calcification	Her2 enriched vs Others	3.33	0.62-18	0.162
Posterior Shadowing	Luminal A vs Others	5.33	1.27-22.32	0.035
Posterior Enhancement	TNBC vs Others	20.9	10.5-415	<0.001
Circumscribed margin	TNBC vs Others	18.75	3.46-101.6	<0.001

In contrast, when HER2-enriched tumors were specifically compared with other molecular subtypes using univariate logistic regression, mammographic calcification was not significantly associated with HER2-enriched disease (OR=3.33, 95% CI: 0.62–18.0; p=0.162).

ROC analysis

Receiver operating characteristic (ROC) curve analysis was performed to assess the discriminatory performance of selected imaging characteristics for distinguishing specific molecular subtypes from the remaining breast cancer subtypes. The area under the curve (AUC), sensitivity, and specificity were calculated for posterior acoustic enhancement and circumscribed mammographic margins in distinguishing TNBC from non-TNBC, posterior acoustic shadowing in distinguishing Luminal A from other subtypes, and mammographic calcification in distinguishing HER2-enriched tumors from other subtypes. Circumscribed mammographic margins demonstrated good discriminatory performance for TNBC (AUC=0.86; sensitivity=83.3%; specificity=89.5%; p<0.001). Posterior acoustic enhancement showed a similarly high AUC for distinguishing TNBC from other subtypes (AUC=0.88; sensitivity=75.0%; specificity=99.9%; p<0.001). Posterior acoustic shadowing demonstrated modest discriminatory performance for Luminal A tumors (AUC=0.69; sensitivity=80.0%; specificity=57.0%; p=0.026). Mammographic calcification showed limited discriminatory performance for HER2-enriched tumors (AUC=0.63; sensitivity=77.8%; specificity=48.8%; p=0.220). These findings suggest that selected imaging characteristics may have discriminatory value in this cohort; however, interpret the ROC estimates cautiously because of the small sample size and the lack of an independently validated predictive model.

Table 5. Diagnostic Discrimination of Selected Imaging Features for Breast Cancer Molecular Subtypes.

Outcome	Imaging Feature	AUC	Sensitivity (%)	Specificity (%)	P-value
TNBC vs. others	Circumscribed margin	0.86	83.3	89.5	<0.001
TNBC vs. others	Posterior acoustic enhancement	0.88	75.0	99.9	<0.001
Luminal A vs. others	Posterior acoustic shadowing	0.69	80.0	57.0	0.026
HER2-enriched vs. others	Mammographic calcification	0.63	77.8	48.8	0.220

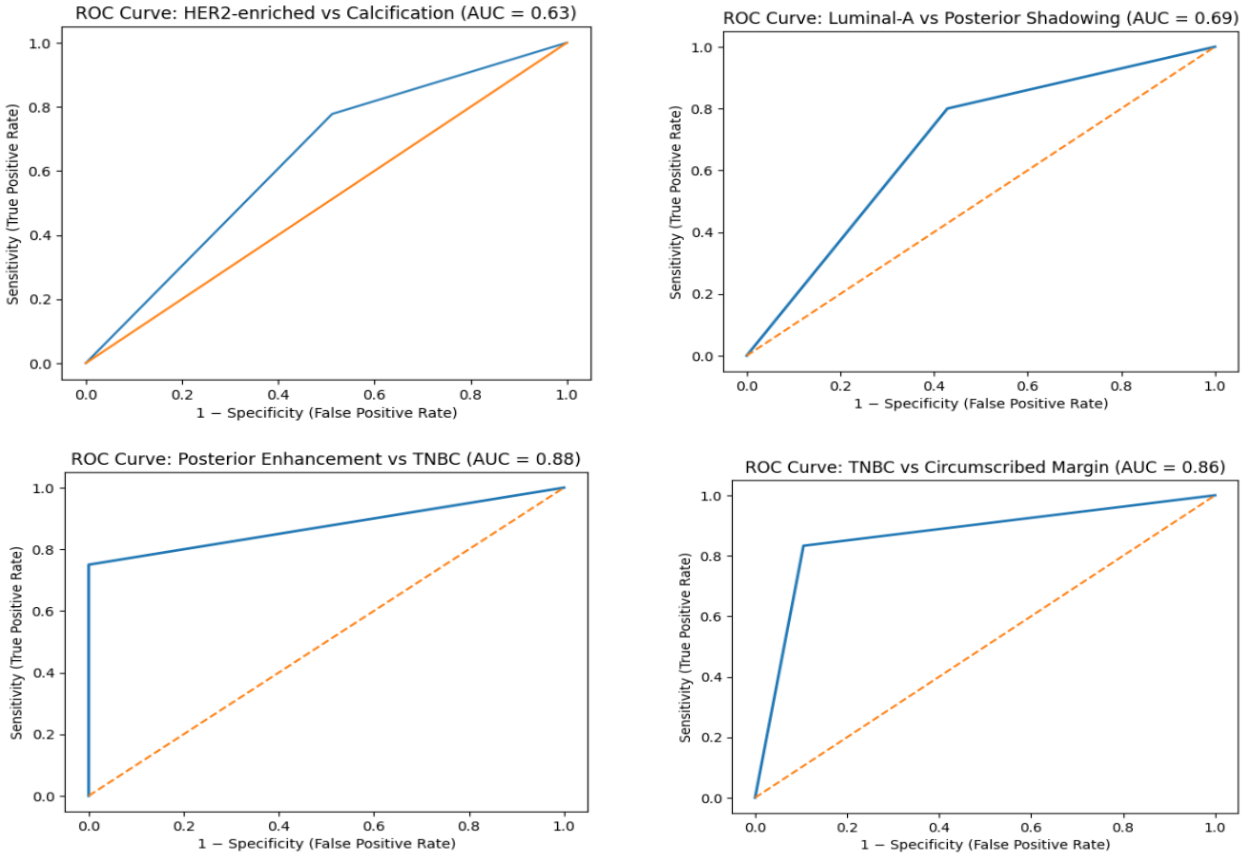

Fig. 4. ROC analysis for the predictor Imaging Features.

4. Discussion

The present study investigated the association between multimodality imaging characteristics and immunohistochemically defined molecular subtypes of breast cancer in 50 patients. The strongest associations were observed for TNBC and Luminal A tumors. Circumscribed margins and posterior acoustic enhancement were strongly associated with TNBC. In contrast, posterior acoustic shadowing was associated with Luminal A. Mammographic calcification showed a significant association with TNBC when TNBC was compared with non-TNBC, but was not significantly associated with HER2-enriched tumors in univariate logistic regression. These findings should therefore be interpreted as subtype-associated imaging characteristics rather than definitive non-invasive predictors. The mean patient age was 51.56 ± 10.3 years, with the highest proportion in the 41–50-year age group (34%), which is broadly consistent with the relatively younger age distribution of breast cancer reported among Indian women by Malvia et al.[5] All patients presented with a palpable breast lump, consistent with the findings of Azhar et al.[6] Because the present cohort consisted of symptomatic patients undergoing diagnostic evaluation, these demographic and clinical findings should be interpreted descriptively rather than as evidence of specific epidemiological or molecular subtype patterns. On mammography, irregular shape and non-circumscribed margins were common findings, consistent with BI-RADS principles that identify these features as suspicious for breast malignancy.[7] However, an important subtype-specific finding was that all TNBC lesions in the present cohort had circumscribed margins. This finding is consistent with Rashmi et al.,[14] who reported an association between circumscribed margins and TNBC, and with the broader imaging observations of Dogan et al.,[8] and Chen et al.,[9] who emphasized that TNBC may demonstrate relatively well-defined or less conventionally suspicious morphology despite its aggressive biological behavior. Thus, a circumscribed mass should not exclude TNBC from the differential diagnosis. Posterior acoustic enhancement was observed in 75% of TNBC cases and showed a strong association with TNBC (OR=20.9, 95% CI: 10.5–415; $p<0.001$), with an AUC of 0.88. This finding agrees with Rashmi et al.,[14] and Chen et al.,[9] who also described posterior acoustic enhancement as a characteristic feature of TNBC. Possible explanations include differences in tumor cellularity, necrosis, and stromal composition, although the present study did not directly evaluate these mechanisms. The combination of circumscribed margins and posterior acoustic enhancement is therefore particularly noteworthy because it may produce a relatively benign-appearing imaging phenotype in an aggressive tumor. Larger studies are needed to determine whether this combination has reproducible clinical value. Posterior acoustic shadowing was associated with Luminal A tumors (OR=5.33, 95% CI: 1.27–22.32; p=0.035), consistent with previous observations by Rashmi et al.,[14] A possible explanation is a greater desmoplastic or fibrous stromal response; however, the current study did not directly assess this histologically. The modest ROC performance (AUC=0.69) indicates that posterior shadowing alone has limited discriminatory ability and should not be considered an independent diagnostic marker of Luminal A disease. The relationship between mammographic calcification and molecular subtype was more complex. Calcification was present in 25% of TNBC cases compared with 65.8% of non-TNBC cases (p=0.0197), indicating a significant association with TNBC status. However, when HER2-enriched tumors were specifically compared with other subtypes, calcification was not statistically significant (OR=3.33, 95% CI: 0.62–18.0; p=0.162). Thus, the higher descriptive frequency of calcification in the HER2-enriched group should not be interpreted as evidence of a confirmed HER2-specific association. Nevertheless, the findings are consistent with previous work suggesting that mammographic calcification patterns may contain information related to molecular phenotype, including studies by Luo et al.,[12] and Rana et al.,[13] Differences in sample size, subtype distribution, patient characteristics, and imaging criteria may account for variations between studies. MRI findings in the present cohort included heterogeneous enhancement, low intratumoral T2 hyperintensity, irregular margins, washout kinetics, and relatively frequent rim or capsular enhancement, particularly in TNBC and HER2-enriched tumors. These findings are broadly compatible with previous reports emphasizing the value of MRI in characterizing TNBC and other molecular subtypes. Xie et al.,[10] demonstrated that multiparametric MRI and whole-tumor histogram analysis could differentiate TNBC from other subtypes, while Dogan et al.,[11] described characteristic multimodality imaging features of TNBC. However, the present study used descriptive MRI features rather than quantitative histogram or radiomic analysis; therefore, make direct methodological comparisons cautiously. The possible relationship between rim enhancement and central necrosis or peripheral vascularity is biologically plausible but was not directly evaluated in this study. Overall, the strongest agreement with previous research was observed for the association of TNBC with circumscribed margins and posterior acoustic enhancement, particularly the findings reported by Rashmi et al.[14] The association of posterior acoustic shadowing with Luminal A was also consistent with previous observations.[13, 14] In contrast, findings on calcification were more complex and highlight the importance of the comparison group and statistical method when interpreting imaging–subtype relationships. Differences from previous studies may reflect variations in sample size, demographic characteristics, stage at presentation, molecular subtype distribution, imaging equipment, interpretation criteria, and pathological classification. The clinical implication of these findings is that mammography, ultrasonography, and MRI may provide complementary information regarding breast cancer phenotype before definitive tissue diagnosis. However, the present study did not develop or externally validate a combined multimodality prediction model. Therefore, the observed associations and AUC values should not be interpreted as evidence that imaging can replace histopathological and immunohistochemical molecular classification. Several limitations should be considered. The study was conducted at a single center and included only 50 patients, with relatively small numbers in some molecular subgroups, particularly TNBC (n=12) and HER2-enriched tumors (n=9). Consequently, only univariate regression was performed, and the wide confidence intervals indicate limited precision of some effect estimates. The study did not assess interobserver agreement or external validation, and it did not include long-term follow-up or machine-learning/radiomic approaches. These limitations restrict generalizability and support interpreting the findings as exploratory and hypothesis-generating. Future prospective multicenter studies with larger and more diverse populations should validate these associations using standardized imaging protocols, clearly defined immunohistochemical subtype criteria, independent image interpretation, and appropriately powered multivariable or penalized regression models. Integrating mammographic, ultrasound, and MRI features may ultimately support the development of validated multimodality prediction models. Overall, the present study adds to the growing evidence that breast cancer molecular subtypes may exhibit distinct imaging phenotypes, particularly the association of TNBC with circumscribed margins and posterior acoustic enhancement. Nevertheless, these findings require confirmation before clinical implementation.

Limitations of the study

This study has some limitations. It was conducted at a single centre with a relatively small sample size, which may limit the generalizability of the

findings. Although patients were enrolled using predefined inclusion and exclusion criteria, some selection bias may still be present. Because of the small sample size, we performed only univariate regression analysis and could not conduct multivariable analysis. Interobserver agreement and external validation were not assessed. The short study period also did not allow long-term follow-up. In addition, this study did not include machine learning techniques. Future multicentre studies with larger sample sizes and external validation are needed to confirm these findings and further evaluate the role of advanced imaging analysis.

5. Conclusion

The findings of this study suggest that specific imaging characteristics on mammography, ultrasonography, and MRI are associated with different molecular subtypes of breast cancer. Circumscribed mammographic margins and posterior acoustic enhancement were strongly associated with TNBC, whereas posterior acoustic shadowing was associated with Luminal A tumors. Mammographic calcification was more frequent in non-TNBC tumors but was not significantly associated with HER2-enriched disease in univariate analysis. A multimodality imaging approach may provide complementary information for non-invasive preoperative assessment of breast cancer. When interpreted alongside clinical, histopathological, and immunohistochemical findings, it may help generate hypotheses about the underlying molecular subtype. However, because of the single-center observational design, relatively small sample size, and absence of multivariable analysis and external validation, these findings should be interpreted with caution and should not be considered definitive. Further large-scale, prospective, multicentre studies are required to validate these associations and determine their clinical applicability in routine practice.

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