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Research Article

Diagnostic Value of Mammographic Breast Density Patterns in Predicting Histopathological Tumor Grade and Molecular Subtype of Invasive Breast Carcinoma

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Abstract

Background: Mammographic breast density is a well-established independent risk factor for breast cancer development and can obscure lesions on screening mammography. However, its direct relationship with intrinsic tumor biology—specifically histological grade and surrogate molecular subtypes—remains a subject of clinical investigation.

Objective: To evaluate the diagnostic value of mammographic breast density patterns categorized by the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) in predicting histopathological tumor grade and molecular subtypes among women with invasive breast carcinoma.

Methods: This cross-sectional study evaluated 160 female patients with histologically confirmed invasive breast carcinoma who underwent diagnostic digital mammography followed by surgical resection or core needle biopsy at University of Lahore Teaching Hospital. Mammographic breast density was classified

according to ACR BI-RADS 5th edition density categories: non-dense (Category A: almost entirely fatty; Category B: scattered fibroglandular) and dense (Category C: heterogeneously dense; Category D: extremely dense). Histopathological tumor grade was determined using the Nottingham Combined Histological Grade system. Immunohistochemical (IHC) profiling was performed to categorize tumors into four surrogate molecular subtypes: Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC). Chi-square tests, Spearman rank correlations, and multivariable logistic regression analyses were conducted.

Results: Among 160 participants (mean age 51.4 ± 10.8 years), dense breast parenchyma (BI-RADS C/D) was present in 56.3% (n = 90) of patients, while 43.8% (n = 70) exhibited non-dense tissue (BI-RADS A/B). High-grade (Grade 3) tumors were significantly more prevalent in women with dense breasts compared to those with non-dense breasts (48.9% vs. 22.9%, p = 0.001). Distribution of molecular subtypes differed significantly across density categories (p = 0.002): HER2-enriched (18.9%) and Triple-Negative (25.6%) subtypes were disproportionately concentrated in the dense breast group (BI-RADS C/D), whereas Luminal A tumors predominated in non-dense breasts (48.6%). Multivariable logistic regression demonstrated that dense breast tissue (BI-RADS C/D) was an independent predictor of both high histological grade (Grade 3; adjusted OR = 2.84, 95% CI: 1.38–5.85, p = 0.005) and aggressive non-luminal molecular phenotypes (HER2-enriched/TNBC; adjusted OR = 3.12, 95% CI: 1.48–6.58, p = 0.003) after adjusting for age, BMI, and menopausal status.

Conclusion: Mammographic breast density patterns correlate significantly with adverse histopathological features and aggressive molecular phenotypes in invasive breast carcinoma. Heterogeneously and extremely dense breast tissue patterns are independently associated with high tumor grade, HER2 enrichment, and triple-negative subtypes, underscoring the role of mammographic density as a surrogate biomarker for adverse tumor biology.

Keywords: Mammographic density; BI-RADS; Invasive breast carcinoma; Histopathological grade; Molecular subtypes; Triple-negative breast cancer; Radiology; Pathology.

1. Introduction

Invasive breast carcinoma is the most common female malignancy globally and a primary cause of cancer-related mortality [1, 2]. Heterogeneity in clinical outcomes among patients with similar anatomical tumor stages has highlighted the critical role of intrinsic tumor biology [2, 3]. Histopathological tumor grading—typically assessed using the Nottingham Combined Histological Grade system—evaluates tubule formation, nuclear pleomorphism, and mitotic count, providing essential prognostic information [3, 4]. Furthermore, surrogate molecular subtyping based on immunohistochemical (IHC) expression of Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and Ki-67 proliferation index categorizes breast cancer into distinct biological classes: Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC) [4, 5].

Mammographic breast density reflects the relative proportion of radiodense epithelial and stromal tissue compared to radiolucent adipose tissue [6, 7]. The American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) standardizes mammographic parenchymal patterns into four distinct categories: A (almost entirely fatty), B (scattered fibroglandular density), C (heterogeneously dense), and D (extremely dense) [7, 8]. Elevated mammographic density is a well-established independent risk factor for breast cancer, conferring a 4- to 6-fold higher risk of disease development compared to fatty breasts, while simultaneously reducing the sensitivity of screening mammography due to lesion masking [6, 8, 9].

Beyond its role as a structural risk factor, dense fibroglandular tissue represents a microenvironment enriched with collagen type I, extracellular matrix proteins, transformed fibroblasts, and pro-inflammatory cytokines [10, 11]. This dense stromal microenvironment promotes epithelial-mesenchymal transition, enhances local paracrine signaling, and fosters genomic instability, potentially favoring the development of biologically aggressive tumor phenotypes [11, 12].

While the association between breast density and overall risk is well documented, the diagnostic utility of pre-treatment mammographic density patterns in predicting

specific tumor grades and IHC molecular subtypes remains actively investigated across diverse patient populations [13, 14]. Establishing a clear link between mammographic parenchymal patterns and underlying molecular characteristics could enhance pre-operative risk stratification, guide supplemental imaging modalities (e.g., automated breast ultrasound or contrast-enhanced mammography), and inform personalized management pathways [15, 16].

Therefore, this cross-sectional study was designed to evaluate the diagnostic value of ACR BI-RADS mammographic breast density patterns in predicting histopathological tumor grade and surrogate molecular subtypes among women with invasive breast carcinoma.

2. Rationale of the Study

Mammographic density is readily assessed during initial diagnostic imaging, prior to invasive biopsy or surgical extirpation [7, 8]. While histopathological grading and IHC molecular profiling remain the definitive benchmarks, understanding the correlation between radiologically dense parenchyma and aggressive intrinsic subtypes (such as Grade 3, HER2-enriched, and TNBC) provides clinicians with immediate diagnostic insight [11, 14]. Demonstrating that mammographic density correlates with adverse biological features supports the integration of density metrics into comprehensive pre-operative risk models, aiding choices regarding supplemental screening imaging, neoadjuvant treatment planning, and surgical margins.

3. Objectives

Primary Objective

- To evaluate the association between ACR BI-RADS mammographic breast density patterns and histopathological tumor grade in women diagnosed with invasive breast carcinoma.

Secondary Objectives

1. To assess the distribution of surrogate molecular subtypes (Luminal A, Luminal B, HER2-enriched, TNBC) across non-dense and dense mammographic parenchymal categories.

2. To determine whether dense mammographic parenchyma (BI-RADS C/D) independently predicts

high histological tumor grade (Grade 3) after controlling for age, body mass index (BMI), and menopausal status.

3. To evaluate the independent predictive value of mammographic density for aggressive non-luminal molecular subtypes (HER2-enriched and TNBC).

4. Materials and Methods

4.1 Study Design and Setting

A hospital-based cross-sectional study was conducted at University of Lahore Teaching Hospital.

4.2 Study Duration

The study was conducted over an eight-month period, encompassing diagnostic digital mammography acquisition, standardized BI-RADS density classification, tissue block sectioning, histopathological grading, IHC molecular profiling, and statistical modeling.

4.3 Study Population

Adult female patients with histologically confirmed primary invasive breast carcinoma who underwent pre-treatment diagnostic digital mammography and subsequent surgical resection or core needle biopsy.

4.4 Sample Size

A total sample size of 160 patients was evaluated. The sample size was calculated assuming a moderate effect size ($w = 0.28$) for the association between mammographic density categories and molecular subtypes using a Chi-square test, maintaining an alpha level of 0.05 and a statistical power of 85%.

4.5 Inclusion Criteria

1. Adult women aged 18 years or older.

2. Newly diagnosed, histologically proven primary invasive breast carcinoma (Invasive Ductal Carcinoma No Special Type [NST], Invasive Lobular Carcinoma, or other invasive subtypes).

3. Availability of standardized, high-quality full-field digital mammograms (FFDM) including cranio-caudal (CC) and medio-lateral oblique (MLO) views obtained prior to biopsy, surgery, or systemic therapy.

4. Complete histopathological evaluation including Nottingham tumor grade and IHC biomarker status (ER, PR, HER2, Ki-67).

4.6 Exclusion Criteria

1. Prior history of ipsilateral breast surgery, radiation therapy, or reduction/augmentation mammoplasty.

2. Receipt of neoadjuvant chemotherapy or endocrine therapy prior to mammography and tissue sampling.

3. Locally advanced breast cancer with total skin ulceration, diffusely distorting inflammation, or artifactual skin thickening obscuring parenchymal evaluation.

4. Synchronous bilateral invasive breast carcinomas or distant metastatic disease at initial presentation.

5. Incomplete medical, radiological, or pathological records.

4.7 Mammographic Evaluation and Density Categorization

Pre-treatment digital mammograms were independently reviewed on high-resolution (5 megapixel) diagnostic workstations by two experienced breast radiologists who were blinded to patient clinical and histopathological data.

Breast density was categorized according to the ACR BI-RADS 5th Edition criteria into four groups [7]:

- **Category A:** Almost entirely fatty; the breasts are almost entirely fat.

- **Category B:** Scattered areas of fibroglandular density.

- **Category C:** Heterogeneously dense, which may obscure small masses.

- **Category D:** Extremely dense, which lowers the sensitivity of mammography.

For analytical purposes, categories were grouped into **Non-Dense Breasts (BI-RADS A + B)** and **Dense Breasts (BI-RADS C + D)**. Discrepancies in density assignment were resolved by consensus review.

4.8 Histopathological Evaluation and Tumor Grading

Tissue sections (4 μm) obtained from core needle biopsies or surgical excision specimens were stained with Hematoxylin and Eosin (H&E). Histological tumor grade was determined using the **Nottingham Combined Histological Grade** system (Elston-Ellis modification of the Scarff-Bloom-Richardson system) by evaluating [3, 4]:

1. Tubule formation ($1-3$ points)
2. Nuclear pleomorphism ($1-3$ points)
3. Mitotic count ($1-3$ points)

Tumors were categorized as:

- **Grade 1 (Low Grade):** Total score $3-5$ points (well-differentiated)
- **Grade 2 (Intermediate Grade):** Total score $6-7$ points (moderately differentiated)
- **Grade 3 (High Grade):** Total score $8-9$ points (poorly differentiated)

4.9 Immunohistochemical Profiling and Molecular Subtyping

Immunohistochemical (IHC) staining was performed on formalin-fixed paraffin-embedded (FFPE) tissue sections using automated immunostainers with primary antibodies against ER, PR, HER2, and Ki-67 [4, 5].

- **ER and PR Positivity:** Defined as $\geq 1\%$ nuclear staining in tumor cells (Allred score ≥ 3).
- **HER2 Status:** Evaluated according to ASCO/CAP guidelines. 0 and $1+$ were defined as negative; $3+$ was defined as positive. Equivocal cases ($2+$) were evaluated using fluorescence in situ hybridization (FISH) for gene amplification (HER2/CEP17 ratio ≥ 2.0).
- **Ki-67 Index:** Expressed as the percentage of positively stained nuclei among at least 500 malignant cells. High proliferation was defined as Ki-67 $\geq 20\%$.

Surrogate molecular subtypes were classified as [5]:

1. **Luminal A:** ER^+, $PR^+(\geq 20\%)$, $HER2^-$, Ki-67 $< 20\%$
2. **Luminal B:** ER^+, $HER2^-$ with PR $< 20\%$ or Ki-67 $\geq 20\%$; OR ER^+, $HER2^+$
3. **HER2-Enriched:** ER^-, PR^-, $HER2^+$
4. **Triple-Negative (TNBC):** ER^-, PR^-, $HER2^-$

4.10 Statistical Analysis

Statistical processing was performed using SPSS version 26.0. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test and expressed as mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were presented as absolute numbers and percentages (n, %).

Differences in demographic parameters, tumor grade, and molecular subtypes across mammographic density groups were analyzed using Student's t-test or Mann-Whitney U test for continuous variables and Pearson's Chi-square (χ^2) test or Fisher's exact test for categorical variables. Spearman rank correlation coefficients assessed linear associations between BI-RADS density scores, histological grade, and Ki-67 index. Multivariable binary logistic regression models were developed to evaluate whether dense breasts (BI-RADS C/D) independently predicted high tumor grade (Grade 3) and aggressive molecular subtypes (HER2-enriched/TNBC), adjusting for age, BMI, and menopausal status. Statistical significance was set at a two-sided p-value < 0.05.

5. Results

5.1 Patient Demographics and Baseline Characteristics

The total study sample comprised 160 female patients (mean age 51.4 ± 10.8 years; 53.1% postmenopausal). Overall, 90 patients (56.3%) presented with dense breast parenchyma (BI-RADS C/D), while 70 patients (43.8%) had non-dense breasts (BI-RADS A/B). Women with dense breasts were significantly younger (47.2 ± 9.1 vs. 56.8 ± 10.6 years, $p < 0.001$), had lower mean BMI (25.4 ± 3.8 vs. 28.6 ± 4.5 kg/m^2, $p < 0.001$), and were predominantly

premenopausal (64.4% vs. 24.3%, $p < 0.001$).

Variable	Non-Dense (BI-RADS A/B) (n = 70)	Dense (BI-RADS C/D) (n = 90)	Total Cohort (n = 160)	p-value
Age, years	56.8 ± 10.6	47.2 ± 9.1	51.4 ± 10.8	<0.001
Body Mass Index (BMI), kg/m^2	28.6 ± 4.5	25.4 ± 3.8	26.8 ± 4.4	<0.001
Menopausal Status, n (%)				<0.001
- Premenopausal	17 (24.3)	58 (64.4)	75 (46.9)	
- Postmenopausal	53 (75.7)	32 (35.6)	85 (53.1)	
Pathological Tumor Size (pT), cm	2.4 ± 1.1	2.6 ± 1.3	2.5 ± 1.2	0.284
Pathological Lymph Node Positivity, n (%)	26 (37.1)	41 (45.6)	67 (41.9)	0.281
Histological Subtype, n (%)				0.412
- Invasive Ductal Carcinoma (NST)	58 (82.9)	78 (86.7)	136 (85.0)	
- Invasive Lobular Carcinoma	8 (11.4)	7 (7.8)	15 (9.4)	

Variable	Non-Dense (BI-RADS A/B) (n = 70)	Dense (BI-RADS C/D) (n = 90)	Total Cohort (n = 160)	p-value
- Others (Mucinous, Medullary, etc.)	4 (5.7)	5 (5.6)	9 (5.6)	

Table 1: Baseline demographic and pathological characteristics stratified by mammographic density.

5.2 Mammographic Density Patterns and Histopathological Tumor Grade

Evaluation of Nottingham histological tumor grades revealed a marked shift toward higher tumor grade with increasing mammographic density ($p = 0.001$). Grade 3 (high-grade) tumors were identified in 48.9% ($n = 44$) of patients in the dense breast group compared to 22.9% ($n = 16$) in the non-dense group. Conversely, Grade 1 tumors were significantly more common in non-dense breasts (25.7% vs. 6.7%).

Nottingham Tumor Grade	Non-Dense (BI-RADS A/B) (n = 70)	Dense (BI-RADS C/D) (n = 90)	Total Cohort (n = 160)	p-value
Grade 1 (Well Differentiated), n (%)	18 (25.7)	6 (6.7)	24 (15.0)	**0.001**
Grade 2 (Moderately Differentiated), n (%)	36 (51.4)	40 (44.4)	76 (47.5)	
Grade 3 (Poorly Differentiated), n (%)	16 (22.9)	44 (48.9)	60 (37.5)	

Nottingham Tumor Grade	Non-Dense (BI-RADS A/B) (n = 70)	Dense (BI-RADS C/D) (n = 90)	Total Cohort (n = 160)	p-value
BI-RADS Density Breakdown				<0.001
- BI-RADS Category A (n = 22), n Grade 3 (%)	3 (13.6)	—	3 (13.6)	
- BI-RADS Category B (n = 48), n Grade 3 (%)	13 (27.1)	—	13 (27.1)	
- BI-RADS Category C (n = 62), n Grade 3 (%)	—	27 (43.5)	27 (43.5)	
- BI-RADS Category D (n = 28), n Grade 3 (%)	—	17 (60.7)	17 (60.7)	

Table 2: Distribution of Nottingham histological tumor grades across mammographic density categories.

5.3 Association Between Mammographic Density and Molecular Subtypes

Surrogate molecular subtype distribution demonstrated statistically significant variation across mammographic density categories ($\chi^2 = 14.82, p = 0.002$). Luminal A tumors predominated in non-dense breasts (48.6%), whereas HER2-enriched (18.9%) and Triple-Negative (25.6%) subtypes were disproportionately concentrated in dense breasts. Furthermore, the mean Ki-67 proliferation index was significantly higher in the dense breast group ($32.4 \pm 18.2\%$ vs. $21.6 \pm 14.5\%$, $p < 0.001$).

Biomarker / Subtype	**Non-Dense (BI-RADS A/B) (n = 70)**	**Dense (BI-RADS C/D) (n = 90)**	**Total Cohort (n = 160)**	**p-value**
Molecular Subtype, n (%)				**0.002**
- Luminal A	34 (48.6)	22 (24.4)	56 (35.0)	
- Luminal B	21 (30.0)	28 (31.1)	49 (30.6)	
- HER2-Enriched	5 (7.1)	17 (18.9)	22 (13.8)	
- Triple-Negative (TNBC)	10 (14.3)	23 (25.6)	33 (20.6)	
Receptor Status, n (%)				
- Estrogen Receptor (ER) Positive	55 (78.6)	50 (55.6)	105 (65.6)	0.003
- Progesterone Receptor (PR) Positive	48 (68.6)	41 (45.6)	89 (55.6)	0.004
- HER2 Positive	11 (15.7)	29 (32.2)	40 (25.0)	0.018
Ki-67 Index (≥ 20%), n (%)	28 (40.0)	58 (64.4)	86 (53.8)	0.002

Table 3: Distribution of IHC receptor status, Ki-67 index, and surrogate molecular subtypes.

5.4 Correlation Analysis

Spearman rank correlation analysis revealed a significant positive correlation between four-category BI-RADS mammographic density (A to D) and Nottingham histological grade ($r_s = 0.38, p < 0.001$) as well as Ki-67 index ($r_s = 0.35, p < 0.001$). Significant inverse correlations were identified between BI-RADS density and ER positivity ($r_s = -0.28, p < 0.001$) and PR positivity ($r_s = -0.26, p = 0.001$).

Parameter Pair	Spearman Correlation (rs)	p-value
BI-RADS Density Category vs. Nottingham Tumor Grade	0.38	<0.001
BI-RADS Density Category vs. Ki-67 Index (%)	0.35	<0.001
BI-RADS Density Category vs. ER Positivity	-0.28	<0.001
BI-RADS Density Category vs. PR Positivity	-0.26	0.001
BI-RADS Density Category vs. Non-Luminal Subtypes (HER2+/TNBC)	0.32	<0.001

Table 4: Bivariate correlation analysis between mammographic density and pathological parameters.

5.5 Multivariable Logistic Regression Analysis

In multivariable logistic regression, dense breast parenchyma (BI-RADS C/D) remained an independent predictor of high tumor grade (Grade 3; adjusted OR = 2.84, 95% CI: 1.38–5.85, $p = 0.005$) after adjusting for patient age, BMI, and menopausal status. Similarly, dense breasts independently predicted aggressive non-luminal molecular subtypes (HER2-enriched and TNBC; adjusted OR = 3.12, 95% CI: 1.48–6.58, $p = 0.003$).

Dependent Outcome Model	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value
Model 1: High Histological Grade (Grade 3)				
Dense Breasts (BI-RADS C/D vs. A/B)	3.22 (1.62–6.42)	0.001	2.84 (1.38–5.85)	0.005
Age (per 10-year increase)	0.72 (0.52–0.98)	0.038	0.85 (0.60–1.21)	0.372
Body Mass Index (per 5 kg/m^2 increase)	0.78 (0.56–1.08)	0.138	0.88 (0.61–1.28)	0.512
Premenopausal Status	2.45 (1.26–4.78)	0.008	1.62 (0.78–3.38)	0.194
Model 2: Non-Luminal Subtypes (HER2+ / TNBC)				
Dense Breasts (BI-RADS C/D vs. A/B)	3.01 (1.48–6.12)	0.002	3.12 (1.48–6.58)	0.003
Age (per 10-year increase)	0.68 (0.48–0.95)	0.024	0.81 (0.55–1.18)	0.274
Premenopausal Status	2.18 (1.08–4.42)	0.029	1.42 (0.66–3.05)	0.368

*Adjusted for age, BMI, and menopausal status.

Table 5: Multivariable logistic regression modeling predictors of high grade and aggressive molecular subtypes.

6. Discussion

This cross-sectional study evaluated the diagnostic relationship between ACR BI-RADS mammographic breast density patterns, histopathological tumor grade, and surrogate molecular subtypes in invasive breast carcinoma. The findings demonstrate that dense breast tissue (BI-RADS C/D) is significantly associated with high-grade (Grade 3) tumors, high Ki-67 proliferation indices, and aggressive non-luminal molecular phenotypes (HER2-enriched and TNBC) [6, 11, 14].

6.1 Biological Mechanisms Linking Density to Aggressive Phenotypes

The link between mammographic density and adverse pathological features involves the biology of the dense microenvironment [10, 11]. Dense fibroglandular tissue is characterized by excessive extracellular matrix (ECM) deposition, high collagen cross-linking, increased stromal stiffness, and dense populations of cancer-associated fibroblasts (CAFs) [10, 12]. Mechanotransduction signals triggered by elevated tissue stiffness activate integrin pathways and focal adhesion kinase (FAK), driving tumor cell hyperproliferation, loss of cell polarity, and genomic instability [11, 12].

Furthermore, dense stroma secretes pro-inflammatory cytokines (such as IL-6, TNF-α, and TGF-β) and vascular endothelial growth factor (VEGF), creating an immunosuppressive and angiogenic niche that favors the emergence of hormone receptor-negative, highly proliferative cell clones [11, 13]. This provides a mechanistic basis for why HER2-enriched and triple-negative subtypes—which lack hormone receptor expression—are disproportionately found in dense breast tissue [14, 16].

6.2 Comparison with Existing Literature

Our findings align with several epidemiological and radiological investigations [13, 14, 17]. Yaghjyan et al. and Olsen et al. reported that high mammographic density was more strongly associated with ER-negative, high-grade, and high-mitotic-index breast cancers than with low-grade hormone receptor-positive tumors [13, 17]. Similarly, studies examining automated volumetric density measurements

have confirmed that dense parenchyma correlates with elevated Ki-67 nuclear expression and HER2 amplification [14, 18]. The pre-dominance of Luminal A tumors in non-dense, fatty breasts (48.6%) observed in our study reinforces the concept that fatty tissue environments—often associated with age-related lobular involution—are more hospitable to slow-growing, highly differentiated hormone-sensitive neoplasms [6, 11].

6.3 Clinical and Diagnostic Implications

Evaluating pre-treatment mammographic density offers diagnostic value beyond simple risk estimation [7, 15]. Identifying dense parenchymal patterns (BI-RADS C/D) on baseline screening or diagnostic mammograms alerts radiologists and oncologists to a higher likelihood of an underlying aggressive tumor phenotype [15, 16]. Because high density also reduces mammographic sensitivity via acoustic and X-ray attenuation masking, women with dense breasts presenting with suspicious lesions benefit from supplemental imaging modalities—such as hand-held or automated breast ultrasound (ABUS), contrast-enhanced mammography (CEM), or breast magnetic resonance imaging (MRI)—to accurately map disease extent, screen for multifocality, and assess therapeutic response [8, 15].

Furthermore, recognizing that dense breasts harbor higher rates of Grade 3 and TNBC tumors can inform surgical planning and time-to-biopsy triage, ensuring rapid histological processing and prompt initiation of neoadjuvant systemic therapy where indicated [2, 5].

6.4 Limitations

Several limitations of this study should be acknowledged. First, the cross-sectional design evaluates density and tumor parameters at a single diagnostic timepoint, preventing longitudinal assessment of density changes over time. Second, breast density was assessed using qualitative ACR BI-RADS categories rather than fully automated 3D volumetric density software (e.g., Volpara or Quantra), though BI-RADS categorization reflects standard clinical practice [7, 8]. Third, while major confounders (age, BMI, menopausal status) were controlled for in multivariable models, systemic hormone replacement therapy (HRT) history was not fully documented for all patients.

7. Conclusion

Pre-treatment ACR BI-RADS mammographic breast density patterns demonstrate strong diagnostic value in predicting histopathological tumor grade and molecular subtypes in women with invasive breast carcinoma. Heterogeneously dense (BI-RADS C) and extremely dense (BI-RADS D) breast tissue patterns are independent predictors of high histological grade (Grade 3) and aggressive non-luminal molecular subtypes (HER2-enriched and Triple-Negative Breast Cancer). Pre-operative assessment of mammographic density provides valuable biological insight, supporting personalized diagnostic imaging workflows and risk-stratified multidisciplinary care.

8. Recommendations

1. Include qualitative or quantitative mammographic breast density reporting systematically in all pre-operative radiological reports for suspicious breast lesions.

2. Utilize supplemental diagnostic imaging—such as automated breast ultrasound (ABUS) or contrast-enhanced mammography—for women with dense breasts (BI-RADS C/D) to overcome masking effects and evaluate for multifocal disease.

3. Prioritize rapid core needle biopsy and urgent IHC biomarker processing for suspicious lesions identified in extremely dense breasts due to the higher probability of high-grade or triple-negative disease.

4. Integrate mammographic density metrics into multidisciplinary pre-operative decision-making models alongside clinical and core-biopsy parameters.

5. Conduct prospective multi-center studies utilizing 3D automated volumetric density software combined with genomic sequencing to further elucidate the molecular pathways driving carcinogenesis in dense breast microenvironments.

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