

Pre-operative Imaging Risk Factors for Lympho-Vascular Invasion in Breast Cancer as Determined by Mammography and Ultrasound Findings of Primary Breast Masses

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Author's Contribution

^{1,2}Substantial contributions to the conception or design of the work, acquisition, Data Collection, Analysis, ⁴draft of manuscript ³Final Approval.

Funding Source: None

Conflict of Interest: None

Received: Jan 25, 2026

Revised: May 03, 2026

Accepted: May 19, 2026

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ABSTRACT

Objective: To determine pre-operative mammographic and ultrasound features predictive of lymphovascular invasion in patients with breast cancer presenting to a tertiary care center in Pakistan.

Methodology: This retrospective descriptive study was conducted at SIUT Breast Oncology OPD and Radiology department. The data were retrieved from the archival records of the Hospital covering the duration from 2017 to 2021. Medical data record of the patients with histopathologically proven breast cancer whose pre-treatment mammograms, ultrasounds and histopathology reports were available, patients who have undergone upfront mastectomy or breast-conserving surgery and LVI status confirmed by immunohistochemistry were incorporated. Imaging features were assessed for ultrasound, and mammography. LVI status was assessed on histopathology and correlated with imaging findings using univariate and multivariate logistic regression.

Results: The mean age of 201 patients enrolled in the study was 48.04 ± 11.65 years. The LVI was observed in 131 (65.2%) patients. According to univariate analysis, non-circumscribed ultrasound margins (OR 22.08), posterior shadowing (OR 3.29), irregular shape of mass by ultrasound (OR 3.03), raised size of mass on ultrasound (OR 1.18/cm), and the dense breast tissue (OR 2.27) were significantly linked to LVI ($p < 0.05$). Additionally, on multivariable analysis, the breast density (adjusted OR 2.3), posterior shadowing (adjusted OR 3.17), and ultrasound mass size (adjusted OR 1.23/cm remained significant independent predictors for LVI, ($p < 0.05$).

Conclusion: Mammographic and ultrasound features, specifically irregular margins, mass shape, posterior shadowing, and breast density, observed as helpful preoperative predictors of LVI. Due few significant limitations further larger prospective studies are needed to validate this approach before routine clinical practice.

Keywords: Breast cancer, LVI, Mammography; Ultrasound, Pre-operative prediction, Histopathology

Cite this article as: Shaikh S, Anwar K. Pre-operative Imaging Risk Factors for Lympho-Vascular Invasion in Breast Cancer as Determined by Mammography and Ultrasound Findings of Primary Breast Masses. *Ann Pak Inst Med Sci.* 2026; 22(3):307-312. doi. 10.48036/apims.v22i3.1549

Introduction

The breast carcinoma remains a most frequently diagnosed malignancy in women throughout the world, with the estimates of GLOBOCAN reporting approximately 2.30 million new patients and 666,103 deaths worldwide, corresponding to 23.8% of all new malignances and 15.4% of cancer-related mortality rate among women.¹ The Asian population bears the highest regional burden, with 985,817

patients documented in 2022, followed by the Northern America and Europe.² In Pakistan the breast malignancy occurs around two and a half times more compared to the neighboring countries of India and Iran, with at least 90,000 women affected per years nationwide and a described frequency of around 69.1 per 100,000 in Karachi.³ Worldwide the breast cancer cases are projected to exceed 6 million by 2050, with the greatest significant rise anticipated in Asia and Africa, underlining the urgent

need for reliable, non-invasive prognostic markers, predominantly in limited resources regions where access to advanced molecular testing remains limited.³

In the histopathological features that effect the prognosis and planning of treatment, lymphovascular invasion (LVI) has come to be regarded as a critical contributing factor. It is a pivotal prognostic factor that in a direct manner of influences the patient survival outcomes and guides case-specific strategies of the treatment, including the selection of adjuvant chemotherapy regimens and the magnitude of the surgical intervention.⁵ The LVI, can be defined as the presence of tumor cells within lymphatic or vascular channels, is significantly linked to a higher risk of lymph node metastasis and decreased disease-free survival.⁵ Conventionally, the status of LVI is confirmed only postoperatively by the histopathological assessment, which limits its utility in preoperative surgical and systemic planning of treatment.

Such limitations have motivated growing interest in preoperative imaging as a surrogate means of predicting the status of LVI. Few previous research studies have revealed that the preoperative breast mammography, three-dimensional mammography, and MRI could be potentially used for the predictive estimation of LVI.⁶

Ultrasonography, specifically offers distinct practical improvements, as it is relatively low-cost, real-time, and capable of being replicated compared with other cross-sectional imaging approaches.⁶ Latest radiomics-basis work has reinforced this evidence base: ultrasound radiomics-basis clinical prediction tools have been developed to estimate the lymphovascular invasion in invasive breast carcinoma through large scale retrospective research studies.⁷ The contrast-enhanced ultrasound considerations have also shown discriminatory value, with LVI positive tumors representing significantly advanced peak intensity and shorter time-to-peak values in contrast to LVI-negative tumors, resulting in an area under the curve of 0.81 for the prediction of LVI.⁵

Correspondingly, MRI-based imaging analysis and clinicopathological clinical prediction tools have been assessed comprehensively, including dynamic contrast-enhanced and diffusion-weighted MRI observations for the prediction of LVI in node-negative invasive breast carcinoma,⁸ multiparametric MRI-based radiomic assessment models validated across multiple centers,⁹ and deeply learning approaches incorporating prior clinical and radiological features to enhance the accuracy prediction.^{10,11}

Regardless of this expanding body of published evidence on radiomics and multiparametric imaging, conventional sonographic and mammographic morphological features of the primary breast mass consistently accessible in routine low-resource clinical practices remain relatively underexplored as preoperative predictors of the LVI.

Previous studies of gray scale ultrasound-basis in T1 breast invasive ductal carcinoma have proposed that the features of simple conventional ultrasonography, independent of complex radiomics modelling workflows, may associated with meaningful predictive information.⁶

Correspondingly, the worldwide rise in the burden of breast carcinoma and its greater than expected impact in the populations of Asian countries further reinforces the relevance of reachable, imaging-based risk stratification tools for the regions where advanced imaging analysis infrastructure is limited usually,² and data specifically correlating standard, readily available mammographic and sonographic features with LVI remain limited and inconsistent. Present study was therefore planned, to determine the specific mammographic and ultrasound imaging characteristics of the primary breast masses as risk factors for LVI, with the purpose of offering a practical, supporting pre-operative risk stratification and patient-specific surgical and systemic treatment planning.

Methodology

This retrospective, descriptive study was carried out at the Breast Oncology Outpatient Department (OPD) and the Radiology Department of the Sindh Institute of Urology and Transplantation (SIUT). Study was done after obtaining the ethical approval from the Institutional Review Board/Ethics Review Committee of SIUT (SIUT-ERC-2021/A-295). The data were retrieved from the archival records of the Hospital covering the duration from 2017 to 2021. The record of the cases that were diagnosed with breast carcinoma histopathologically, along with pre-treatment ultrasound diagnosis, mammograms, and histopathological reports were available, and who had undergone either upfront mastectomy or breast-conserving surgeries with confirmed LVI status through immunohistochemistry, was incorporated for the study.

On the other hand, the records of the patients whose pre-treatment mammograms, ultrasounds, or histopathological records were completely unavailable or controversial or incomplete radiological or clinical data record was not projected. The non-probability consecutive sampling technique was utilized to select cases meeting the inclusion

criteria over the duration of study. The case files of the patients were reviewed, and only cases with biopsy-proven breast carcinoma were included. Sonographic, radiology and the histopathological diagnostic records of the patients were searched for mammograms and ultrasounds for the breast performed for the evaluation of primary breast tumors, together with corresponding breast and axillary lymph node biopsy reports, in order to correlate the preoperative findings of images with status of LVI. All the relevant features of mammography and sonography of the primary breast mass comprising the shape, margin, echogenicity, vascularity, and BI-RADS category of the masses were recorded and analyzed in the correlation to LVI status. Subsequently the data were entered and analyzed using SPSS version 26, with appropriate descriptive statistics and association statistical tests application to assess the association between imaging findings and the positivity of LVI taking p-value ≤ 0.05 as statistically significant.

Results

A total of 346 patients were included with a mean age of 56.91 ± 10.89 years; 61.8% were male. Mean BMI was 27.49 ± 4.28 kg/m², and 26.6% were obese. Diabetes and hypertension were present in 37.0% and 44.5%, respectively, while 12.1% had chronic kidney disease and 8.1% had COPD. CABG was the most common procedure

(57.2%). Mean CPB and cross-clamp times were 112.42 ± 27.51 min and 73.22 ± 18.98 min, respectively. (Table I).

The mean vasoactive-inotropic score (VIS) was 9.98 ± 6.02 at CICU admission and 12.53 ± 8.03 at 24 hours postoperatively, while the mean peak VIS during the first 24 postoperative hours was 23.13 ± 6.14 , (Table II).

The most frequent event occurred was composite outcome in 118 (34.1%) of patients. Acute kidney injury 65 (18.5%) and prolonged ventilation >48 hours 58 (16.8%) were the most common individual complications. In-hospital mortality was 32 (9.2%), while reoperation 24 (6.9%), renal replacement therapy 22 (6.4%), reintubation 18 (5.2%), and stroke 12 (3.5%) were less frequent.

Table I: Demographic and clinical characteristics of the patients. (n=102)

Characteristic	Statistics
Age (years) — Mean $\pm$ SD / Median (Range)	48.04 $\pm$ 11.65 / 48.0 (22–74)
Family history of breast cancer	Yes 69 (34.3%) No 132 (65.7%)
Postmenopausal status	Yes 102 (50.7%) No 99 (49.3%)
Lactation history	Yes 160 (79.6%) No 41 (20.4%)
Breast side	Right 99 (49.3%) Left 102 (50.7%)
Presenting complaint	Lump 183 (91.0%) Pain 11 (5.5%) Lump and pain 04 (2.0%) Nipple discharge 03 (1.5%)

Table II: Mammographic findings by lymphovascular invasion status.

Mammographic Feature	Category	LVI Positive	LVI Negative	p-value
Mass shape	Oval	8 (6.1%)	8 (11.4%)	0.322
	Round	1 (0.8%)	0 (0.0%)	
	Irregular	122 (93.1%)	62 (88.6%)	
Mass margins	Circumscribed	3 (2.3%)	2 (2.9%)	0.409
	Micro lobulated	7 (5.3%)	8 (11.4%)	
	Irregular	112 (85.5%)	54 (77.1%)	
	Indistinct	9 (6.9%)	6 (8.6%)	
Micro calcifications	None	100 (76.3%)	61 (87.1%)	0.178
	Within the mass	25 (19.1%)	9 (12.9%)	
	Outside the mass	1 (0.8%)	0 (0.0%)	
	Both in and out of mass	5 (3.8%)	0 (0.0%)	
Breast density (BI-RADS category)	A	11 (8.4%)	18 (25.7%)	0.001
	B	45 (34.4%)	26 (37.1%)	
	C	75 (57.3%)	26 (37.1%)	
Overall mammographic finding	Only mass	98 (74.8%)	56 (80.0%)	0.086
	Mass + microcalcifications	25 (19.1%)	9 (12.9%)	
	Focal asymmetry	3 (2.3%)	5 (7.1%)	
	Focal asymmetry with calcifications	5 (3.8%)	0 (0.0%)	
Architectural distortion / trabecular thickening	Yes	118 (90.1%)	60 (85.7%)	0.483
	No	13 (9.9%)	10 (14.3%)	
Asymmetry	Focal	7 (5.3%)	5 (7.1%)	0.049
	Global-small breast	3 (2.3%)	3 (4.3%)	
	Global-enlarged breast	32 (24.4%)	6 (8.6%)	
	No	89 (67.9%)	56 (80.0%)	
Multifocality	Yes	19 (14.5%)	13 (18.6%)	0.583
	No	112 (85.5%)	57 (81.4%)	

At CICU admission, mean VIS was 13.12 ± 6.72 in non-survivors versus 9.65 ± 5.85 in survivors ($p = 0.001$). This difference remained significant at 6 hours (16.42 ± 7.63 vs 10.84 ± 6.67), 12 hours (17.63 ± 8.28 vs 11.92 ± 7.03), and 24 hours (17.41 ± 8.59 vs 12.03 ± 7.82), all $p < 0.001$. Peak VIS within the first 24 hours was also markedly higher among non-survivors (29.25 ± 6.53 vs 22.51 ± 5.75 ; $p < 0.001$). (Table III). Patients with CKD had 1.95 times

higher odds of the outcome compared with those without CKD (AOR = 1.955; 95% CI: 0.741–5.156; $p = 0.176$).

Similarly, patients with COPD had 1.85 times greater odds of the outcome (AOR = 1.854; 95% CI: 0.583–5.891; $p = 0.295$), although this association was not statistically significant. Higher age category and BMI were also associated with increased odds of the outcome; however, these findings were not significant after adjustment for

Table III: Ultrasound findings by lymphovascular invasion status.

Ultrasound Feature	Category	LVI Positive	LVI Negative	p-value
Ultrasound mass shape	Oval	8 (6.1%)	11 (15.7%)	0.0361
	Round	2 (1.5%)	3 (4.3%)	
	Irregular	121 (92.4%)	56 (80.0%)	
Ultrasound mass orientation	Parallel	23 (17.6%)	10 (14.3%)	0.5716
	Antiparallel	101 (77.1%)	58 (82.9%)	
	Cannot be assessed	7 (5.3%)	2 (2.9%)	
Ultrasound mass boundary	Abrupt	63 (48.5%)	44 (62.9%)	0.0721
	Echogenic halo	67 (51.5%)	26 (37.1%)	
Ultrasound echo pattern	Anechoic	1 (0.8%)	0 (0.0%)	0.6005
	Hypoechoic	111 (84.7%)	62 (88.6%)	
	Hyperechoic	2 (1.5%)	0 (0.0%)	
	Isoechoic	2 (1.5%)	0 (0.0%)	
	Complex	15 (11.5%)	8 (11.4%)	
Ultrasound mass margins	Circumscribed	0 (0.0%)	5 (7.1%)	0.0041
	Microlobulated	11 (8.4%)	9 (12.9%)	
	Irregular/spiculated	120 (91.6%)	56 (80.0%)	
Ultrasound posterior features	Enhancement	14 (10.7%)	12 (17.1%)	0.0049
	Shadowing	39 (29.8%)	8 (11.4%)	
	Both	77 (58.8%)	46 (65.7%)	
	None	1 (0.8%)	4 (5.7%)	
Posterior acoustic shadowing	Yes	39 (29.8%)	8 (11.4%)	0.0059
	No	92 (70.2%)	62 (88.6%)	

Table IV: Univariate relationship n of mammographic and ultrasound features with LVI

Imaging Feature	Comparison	OR	95% CI	p-value
Mammographic Features				
Breast density	Dense vs Non-dense	2.27	1.25–4.11	0.0071
Microcalcifications	Present vs Absent	2.10	0.94–4.71	0.0715
Asymmetry	Present vs Absent	1.89	0.95–3.77	0.0716
Mammographic mass size (cm)	per 1 cm increase	1.10	0.96–1.25	0.1645
Mammographic mass shape	Irregular vs Oval/Round	1.75	0.64–4.76	0.2733
BI-RADS category	5-6 vs 3-4	1.23	0.62–2.43	0.5494
Mammographic mass margins	Non-circumscribed vs Circumscribed	1.25	0.20–7.69	0.8061
Ultrasound Features				
Ultrasound mass margins	Non-circumscribed vs Circumscribed	22.08	1.20–405.49	0.0047
Posterior acoustic shadowing	Present vs Absent	3.29	1.44–7.50	0.0048
Ultrasound mass shape	Irregular vs Oval/Round	3.03	1.27–7.23	0.0128
Ultrasound mass size (cm)	per 1 cm increase	1.18	1.02–1.37	0.0288
Ultrasound mass boundary	Echogenic halo vs Abrupt	1.80	0.99–3.26	0.0527
Ultrasound echo pattern	Non-hypoechoic vs Hypoechoic	1.40	0.58–3.36	0.4555
Ultrasound mass orientation	Non-parallel vs Parallel	0.78	0.35–1.75	0.5515

Table V: Multivariable logistic regression: independent pre-operative imaging predictors of LVI

Imaging Feature	Adjusted OR	95% CI	p-value
Mammographic Predictors			
Breast density (dense category C vs non-dense A/B)	2.39	1.25–4.60	0.0088
Microcalcifications (present vs absent)	1.51	0.62–3.66	0.3644
Asymmetry (present vs absent)	1.20	0.55–2.65	0.6482
Ultrasound Predictors			
Posterior acoustic shadowing (present vs absent)	3.17	1.24–8.15	0.0164
Ultrasound mass shape (irregular vs oval/round)	2.40	0.86–6.68	0.0941
Ultrasound mass size (per 1 cm increase)	1.23	1.04–1.45	0.0148
Ultrasound mass boundary (echogenic halo vs abrupt)	1.31	0.64–2.66	0.4607

confounding variables. Diabetes and hypertension likewise showed no significant independent association with the outcome ($p>0.050$). (Table IV).

Discussion

The LVI is a very imperative prognostic feature of the breast carcinoma and is related with a higher risk of lymph node involvement and the progression of disease. Usually, it is confirmed through postoperative histopathological assessment, creating a requirement for reliable preoperative indicators. Present evidence suggests that the routine mammographic and ultrasound features of may contribute as the useful marks to the LVI before surgery. This study enrolled the data record of 201 patients retrospectively with as overall mean age of 48.04 ± 11.65 years, with over half of the women were postmenopausal (50.7%). The results were in close to the study by Borghesan DH et al¹² where mean age of the women with breast cancer was 52.53 ± 11.94 years and majority of postmenopausal women 83/100. Few other studies also found almost similar demographic pattern.^{13,14}

The findings of this study were consistent within a growing body of recent literature examining preoperative imaging prediction of lymphovascular invasion (LVI) in breast carcinoma. According to a Chinese cohort of 192 patients conducted Xu et al⁶ with T1 invasive ductal carcinoma, reported an incidence of LVI around 29.2%, somewhat higher than the 13-27% range demonstrated in earlier studies, and observed that the tumor margin as a key independent ultrasound predictor, closely reflecting to this study where non-circumscribed margins carried the strongest univariate relationship with the LVI. The findings of this study closely align with the study by Tong YY et al¹⁵ where posterior echo shadowing, age of the patient and suspicious findings on axillary ultrasound imaging were independent predictors of LVI and axillary lymph node metastasis in invasive breast carcinoma along with calcification also identified as an independent predictor of the LVI ($p=0.013$). The findings of this study were broadly consistent with the study by Liu Z et al¹⁶ on 122 breast carcinoma cases to assess the mammography values in predicting LVI of breast carcinoma and reported that the interstitial edema, blurring of subcutaneous fat, and skin thickening were noted as independent risk factors for LVI. Almost similar pattern was reported by the Bahrami M et al¹⁷ who demonstrated that the mammographic and sonographic findings from 187 cases of breast carcinoma at a single center were categorized by the status of LVI, with ultrasound features including tumor margin, calcification, and vascularity, and mammographic

features like tumor calcification, density, and shape, compared between the LVI-positive and LVI-negative groups and concluded that the mammographic calcifications and vascularity by ultrasound Doppler were significantly related to LVI (<0.05).

However, Nijati et al⁹ observed that the ADC-based radiomic model exhibited an encouraging accuracy (AUC of 0.87) in predicting the LVI prior to surgery in patients with breast carcinoma, indicating it could significantly support clinical treatment decisions. In keeping with the present findings, a broader meta-analysis accumulating multiple MRI radiomics studies demonstrated a diagnostic odds ratio of 23, sensitivity of 89%, and specificity 82% for predicting the LVI, supporting that imaging-based features, whether conventional or the radiomic, contributing genuine predictive value for LVI status across the modalities. According to additional support for imaging morphology as a marker of tumor biology, Huang Y et al¹⁹ reported that the greater elastic heterogeneity was substantially linked to LVI, emphasizing that the stiffness of tumor and structural irregularity, likewise to the present study the ultrasound margin irregularity identified in this cohort, reflects the similar underlying infiltrative biology.

The pattern is further supported by Song EJ et al²⁰ who demonstrated that the LVI-positive tumors noted significantly higher maximum elasticity and higher elasticity standard deviation ($p<0.05$) in contrast to LVI-negative tumors, more supporting that heterogeneity of the structural tumor, whether taken by elastography, radiomics, or conventional grayscale morphological features, consistently differentiates the status of LVI across the imaging modalities. Some inconsistencies in the findings of this study and prior literature may be due to a substantial difference in the sample size of studies, differences in which features were measured or how finely they were characterized, radiological expertise, used instruments and natural differences between patient populations across the health facilities and countries.

Based on expected common reasons for the variation across the studies and limited large-scale local evidences underscoring the need for further larger, multicenter research studies specially at local level incorporating supplementary features like vascularity and lymph node estimation to build a more reliable prediction tool for LVI pre-operatively.

Conclusion

Study revealed that the growing recognition that mammography and ultrasound are not conventional tools

for detecting breast masses, but can also provide valuable preoperative insights into the biology of tumor. The features including irregular margins of mass, shape of the mass, posterior acoustic shadowing, and dense breast tissue emerged as radiological indicators pointing toward the possibility of LVI that were typically confirmed only after surgery by histopathology. In the limited resource regions, the routine and affordable imaging can help to identify the high-risk tumors prior to surgery in the supporting of better planning of treatment, where advanced molecular and radiomic tools remain unreachable. Though, due to several substantial limitations and before implement of this evidence, future large, prospective studies are strongly recommended to prove these imaging markers validity into reliable preoperative risk-stratification for routine clinical practice.

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