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Independent and Incremental Value of Breast Mass Orientation Angle in Ultrasound-Based Malignancy Prediction

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Abbreviations

ACR, American College of Radiology; AUC, area under the ROC curve; BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index; CI, confidence interval; ICC, intraclass correlation coefficient; IQR, interquartile range; LR, likelihood ratio; NPV, negative predictive value; OR, odds ratio; PACS, Picture Archiving and Communication System; PPV, positive predictive value; ROC, receiver operating characteristic; US, ultrasonography; VIF, variance inflation factor

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Objectives—Orientation of breast masses on ultrasonography is a well-recognized feature for differentiating benign from malignant lesions. Recent studies suggest that quantitative assessment of the orientation angle may improve diagnostic discrimination. This study aimed to evaluate the diagnostic performance of the orientation angle in a real-world cohort and to determine its incremental value when integrated with established clinical and sonographic predictors.

Methods—This retrospective study included 502 biopsy-proven breast lesions evaluated with ultrasound between 2019 and 2025. The orientation angle was defined as the acute angle between the longest axis of the lesion and the skin surface measured on transverse images. Inter-reader reliability was assessed using intraclass correlation coefficients (ICCs). Diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis. Multivariable logistic regression models were constructed with and without the orientation angle to assess independent predictors of malignancy and incremental model performance.

Results—Of the 502 lesions, 258 (51.4%) were malignant. Measurement reliability was excellent, with ICC values exceeding 0.96. Malignant lesions demonstrated significantly larger orientation angles than benign lesions and showed a stepwise increase across Breast Imaging Reporting and Data System categories. An optimal cut-off value of 25.3° yielded an AUC of 0.72, specificity of 90.2%, and a positive likelihood ratio of 4.66. In multivariable analysis, orientation angle remained independently associated with malignancy (odds ratio 1.03 per degree increase; $p < .001$).

Conclusion—Quantitative orientation angle is a reproducible and independent predictor of breast malignancy and provides incremental diagnostic value beyond conventional ultrasound descriptors, supporting its role as a complementary imaging biomarker in breast ultrasound assessment.

Key Words—breast cancer; breast imaging reporting and data system; orientation angle; ultrasonography

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, with a steadily increasing global incidence that reflects both demographic transitions and improvements in cancer detection. Recent global

estimates indicate that approximately 2.3 million new cases were diagnosed in 2022, with incidence rates rising in the majority of countries, particularly those with low- and middle-income economies, while mortality reductions have been observed mainly in very high-income regions with established screening and treatment infrastructures.[1] Projections suggest that by 2050, the global burden of breast cancer will increase substantially, underscoring persistent disparities in access to early detection and care. In high-resource settings such as the United States, contemporary cancer statistics demonstrate continued increases in breast cancer incidence—especially for localized disease—alongside long-term declines in mortality, trends largely attributed to widespread mammographic screening and advances in systemic therapy.[2]

Mammography remains the cornerstone of population-based breast cancer screening, contributing to increased detection of early-stage and in situ disease and corresponding stage migration, which has played a critical role in improving survival outcomes.[1,2] Ultrasonography (US) serves as an important adjunct imaging modality, particularly in women with dense breast tissue, where it enhances lesion characterization and detection sensitivity when used in conjunction with mammography.[1,2] Together, these imaging strategies have significantly influenced observed epidemiologic patterns, increasing reported incidence through earlier diagnosis while contributing to mortality reductions in settings with adequate screening coverage and treatment capacity.

The utility of breast ultrasound in determining benign and malignant breast masses has come a long way. In the past, breast ultrasound was reserved only to differentiate between cystic and solid lesions.[3] There was a frequent overlap of benign and malignant breast signs, leading to many unnecessary biopsies and anxiety for the patients.[4] With the advent of newer ultrasound technology and the latest 5th version of Breast Imaging Reporting and Data System (BI-RADS), breast ultrasound plays a pivotal role in assessing breast masses.[5]

According to the American College of Radiology (ACR) Appropriateness Criteria for the evaluation of a palpable breast mass, US is preferred over mammography in specific clinical contexts, primarily driven by patient age, breast tissue characteristics, and safety considerations.[6] Ultrasound is the recommended initial imaging modality for women younger than 30 years because it avoids ionizing radiation and has superior performance in dense breast tissue, allowing reliable differentiation between cystic and solid lesions.[7] In women aged 30–39 years, ultrasound is often favored as the initial study due to lower cancer prevalence and higher breast density, although diagnostic mammography remains appropriate depending on clinical suspicion and risk factors. Additionally, ultrasound is recommended when mammography is negative or inconclusive in the setting of a persistent palpable abnormality and plays a critical complementary role in lesion characterization and image-guided biopsy.[6]

Despite much evidence pointing out that mass orientation is one of the most reliable features for differentiating benign from malignant lesions,[4,8,9] BI-RADS only classifies the orientation into parallel and non-parallel, where it signifies benign and malignant lesions, respectively.[10] A non-parallel orientation on sonography may indicate extension of the lesion across normal tissue planes.[11]

Chen and Wu[5] demonstrated that quantitative assessment of orientation angle could improve discrimination between benign and malignant breast masses and showed its value within a multivariable framework. However, further evaluation across different study designs, pathological spectra, and clinical workflows is warranted. The present study addresses this need by examining the performance of orientation angle in a retrospective, real-world cohort and assessing its relative contribution alongside established clinical and sonographic predictors. A secondary aim was to integrate orientation angle with other clinical and imaging variables in a multivariable model to identify independent predictors of malignant breast masses. Unlike prior studies conducted in controlled or prospective settings, this study evaluates orientation angle in a retrospective clinical cohort and examines its incremental value within a multivariable framework.

Methods

Ethical Approval

This study was approved by the Ethics Review Committee of Universitas Pelita Harapan (231/K-LKJ.

ETIK/VII/2024) and was conducted in accordance with the Declaration of Helsinki. No written consent has been obtained from the patients, as there is no patient-identifiable data included.

Study Design and Population

This retrospective study was conducted at a private tertiary hospital for cancer referrals between 2019 and September 14, 2025. A total of 21,910 individuals who underwent breast US screening or presented with symptoms such as palpable mass, nipple discharge, or breast pain and subsequently received US examinations were assessed for eligibility. The inclusion criteria were female sex, with an age range of 18–90 years, and histopathology results were available. Exclusion criteria included: (1) male sex; (2) absence of ultrasound results before surgery, chemotherapy, or radiotherapy; (3) pregnancy or lactation; and (4) non-mass lesions and breast lesions with indistinct lower margins on sonography. A flowchart illustrating the initial subject selection process is presented in Figure 1.

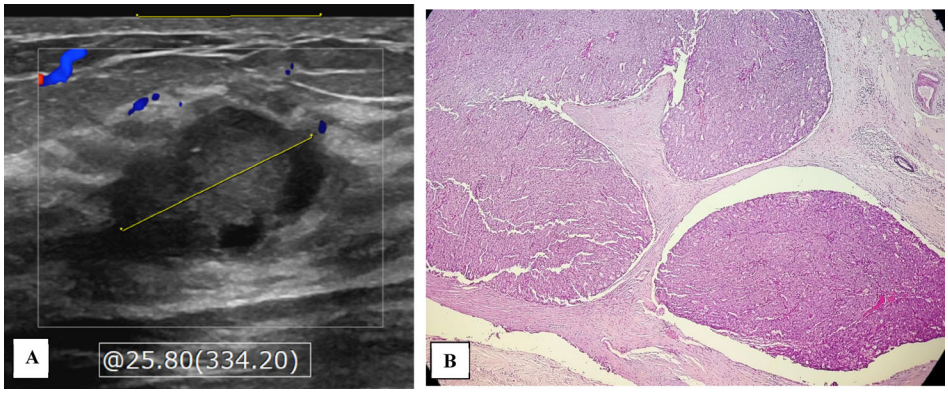
Breast US examinations were performed and interpreted in accordance with the fifth edition of the BI-RADS US Atlas. Imaging descriptors, including shape, orientation, margin, echogenicity, posterior acoustic features, calcifications within or outside a mass, intraductal calcifications, and architectural distortion, were used for lesion characterization and image interpretation.[10] When multiple breast masses were detected in a single subject, only the lesion that was biopsied would be measured.[3] Several tissue samples underwent immunohistochemical evaluation, and a lesion initially classified as benign on routine histopathology may be reclassified as malignant when immunohistochemical findings demonstrate features consistent with malignancy.

Measurement of the Orientation Angle of the Breast Mass

The methodology of measuring the orientation angle had been discussed by Chen & Wu.[5] Breast US was performed using high-frequency ultrasound systems (GE LOGIQ S8 and Philips EPIQ 7) equipped with linear array transducers (5–15 MHz) and optimized for breast imaging. Standardized patient positioning and scanning protocols were applied to ensure comprehensive evaluation of the breast and axillary regions. Lesions were characterized according to the fifth edition of the BI-RADS US lexicon, and color Doppler imaging was used to assess lesion vascularity. BI-RADS categorization was independently assigned by 2 experienced breast radiologists (N.K., who has 8 years of professional experience, and N.I.S.H.S., who has 15 years of professional experience).

Lesion orientation was evaluated by measuring the acute angle between the longest axis of the lesion and the breast skin surface using the Picture Archiving and Communication System (PACS) (Figures 1 and 2, where Figure 1 depicts a malignant lesion with a higher orientation angle and Figure 2 illustrates a representative benign lesion with a lower orientation

Figure 1. A 40-year-old female with a chief complaint of a right breast lump for 3 months. **A**, Her breast ultrasound reveals an intracystic lobulated solid mass with well-defined margins, exhibiting lobulated contours with focal microlobulations, measuring approximately 1.8 × 1.2 cm, located at the 10–11 o'clock position in the periareolar region. The orientation angle is 25.8 degrees, above the cut-off line of 25.3 degrees. **B**, The histopathology (Hematoxylin [HE], 50×) reveals a papillary ductal carcinoma in situ.



angle for comparison). Only the transverse plane was used for measurement, and the tails or spiculations were not included in the measurement. Initial measurements were performed by a breast radiologist (N.K.) and 4 senior radiology residents to assess inter-observer agreement. Subsequently, all measurements were conducted by the 4 residents, with any discrepancies resolved by consensus involving 1 of 2 experienced breast radiologists. All measurements were made while being blinded to the histopathology result.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics (version 26; IBM Corp., Armonk, NY). Continuous variables were summarized as mean ± standard deviation or median (interquartile range [IQR]), as appropriate, while categorical variables were expressed as frequencies and percentages.

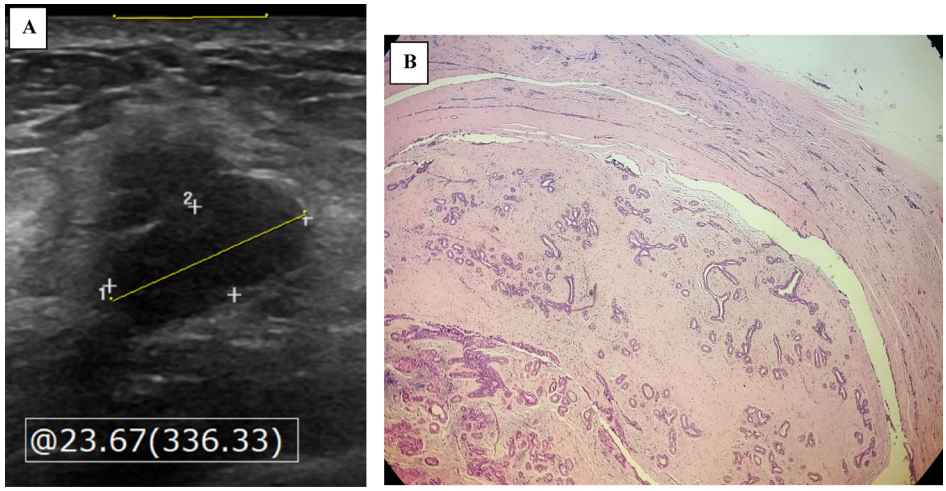
The average measures of inter-reader intraclass correlation coefficients (ICCs) were interpreted according to the criteria proposed by Koo and Li,[12] with values <0.50 indicating poor reliability, 0.50–0.75 indicating moderate reliability, 0.75–0.90 indicating good reliability, and values exceeding 0.90 indicating excellent reliability.

Univariable analyses were initially conducted to screen potential predictors of malignancy. Variables with a *p*-value <.25 on univariable analysis were considered potentially relevant and were entered into multivariable analysis, in accordance with recommended modeling strategies to avoid exclusion of clinically important covariates. Because the outcome variable (benign versus malignant) was dichotomous, multivariable binary logistic regression was used to identify independent factors associated with malignancy. Variables were entered using the enter method. Categorical variables were entered as binary or dummy-coded variables, with 1 category designated as the reference group. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Multicollinearity among covariates was assessed using variance inflation factors (VIFs), with VIF values <5 indicating the absence of significant multicollinearity. To evaluate the incremental diagnostic contribution of the angle variable, a hierarchical modeling strategy was applied. Two multivariable logistic regression models were constructed, where the first model included all selected significant covariates except angle, and the second model was the first model with the addition of the orientation angle.

Model fit was assessed using the −2 log likelihood (−2LL) statistic. Improvement in model fit after inclusion of angle was evaluated using the likelihood ratio test, calculated as follows:

$$x^2 = (-2\mathrm{LL}_{\mathrm{Model1}}) - (-2\mathrm{LL}_{\mathrm{Model2}})$$

Figure 2. A 25-year-old female with a chief complaint of a right breast lump. **A**, Breast ultrasound reveals an oval, well-circumscribed, solid hypoechoic mass with smooth margins, measuring approximately 1.2 × 0.9 cm. The orientation angle is 23.6 degrees, below the cut-off line of 25.3 degrees. **B**, The histopathology (HE, 50×) reveals a fibroadenoma of the breast.



With degrees of freedom equal to the number of additional variables entered into Model 2. A significant likelihood ratio test indicated improved model fit with the inclusion of the angle.[13]

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) would be evaluated. The optimal cut-off point would be determined using Youden's index. This study also compared the derived cut-off point with that reported by Chen and Wu[5] using our dataset. To assess and compare the discriminative performance of the 2 models, predicted probabilities were saved from each logistic regression model and used to generate receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) with 95% CIs was calculated for Model 1 and Model 2. The AUC was calculated to assess diagnostic performance, with values of 0.9–1.0 reflecting excellent accuracy, 0.8–0.9 very good accuracy, 0.7–0.8 good accuracy, 0.6–0.7 fair accuracy, and 0.5–0.6 indicating poor diagnostic accuracy.[14] The improvement in diagnostic performance following the inclusion of angle was evaluated by comparing the AUC values between the 2 models. All statistical tests were 2-tailed, and a p-value <.05 was considered statistically significant.

Results

Patient Recruitment

There are 21,910 patients undergoing breast ultrasound between 2019 and September 14, 2025. Following application of the eligibility criteria, a total of 502 breast lesions were included in the final analysis. Of these, 244 lesions (48.6%) were benign, and 258 lesions (51.4%) were malignant, as confirmed by histopathological examination. The patient recruitment process is summarized in Figure 3.

Intrarater Reliability

The measurement reliability of the orientation angle was excellent. In the initial subset of 30 lesions, the ICC between the breast radiologist and each of the 4 senior radiology residents was at least 0.81, indicating good reliability. In the full dataset, all inter-reader ICC values exceeded 0.96, indicating excellent agreement across all readers (Table 1).

Figure 3. Flowchart of patient recruitment.

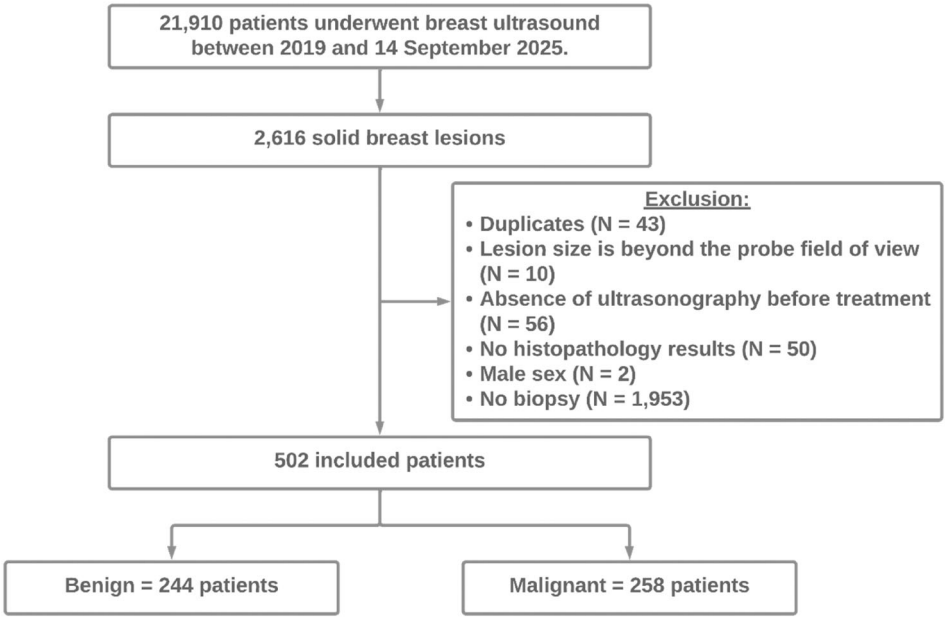


Table 1. Inter-Rater Intraclass Correlation Coefficient Between Readers

Rater	ICC	95% CI	*p*-Value
Initial dataset			
N.K. vs reader 1 ($N = 30$)	0.816	0.612–0.912	<.001
N.K. vs reader 2 ($N = 30$)	0.811	0.602–0.910	<.001
N.K. vs reader 3 ($N = 30$)	0.812	0.604–0.910	<.001
N.K. vs reader 4 ($N = 30$)	0.815	0.611–0.912	<.001
Full dataset			
Reader 1 vs reader 2 ($N = 122$)	0.983	0.976–0.977	<.001
Reader 1 vs reader 3 ($N = 54$)	0.991	0.985–0.995	<.001
Reader 1 vs reader 4 ($N = 75$)	0.965	0.943–0.979	<.001
Reader 2 vs reader 3 ($N = 142$)	0.994	0.992–0.996	<.001
Reader 3 vs reader 4 ($N = 109$)	0.970	0.954–0.980	<.001

ICC, intraclass correlation.

Clinical, Imaging, and Pathological Characteristics

Patients with malignant breast lesions were significantly older than those with benign lesions (49.1 ± 10.9 years versus 35.3 ± 11.0 years, *p*-value <.001). Malignant lesions demonstrated significantly higher body mass index (BMI), short-axis-to-long-axis ratio, and orientation angle compared with benign lesions (all *p*-values ≤.001).

Malignant masses were more frequently associated with the presence of calcifications (34.1% versus 9.0%), axillary lymph node enlargement (33.3% versus 9.0%), irregular shape (68.7% versus 14.8%), spiculated margins (26.7% versus 1.6%), and posterior acoustic shadowing (35.3% versus 13.1%) (all *p*-values <.001). Detailed comparisons are presented in Table 2.

Pathologic analysis revealed that fibroadenoma was the most common benign lesion (54.1%), while invasive carcinoma of no special type was the most common malignant diagnosis (36.0%). The full distribution of benign and malignant pathologies is summarized in Table 3.

Diagnostic Performance of Orientation Angle

Orientation angle demonstrated a progressive increase with higher BI-RADS categories. Median orientation angles increased from 6.6° (IQR: 2.8–14.5°) in BI-RADS 3 lesions to 39.9° (IQR: 10.7–81.6°) in BI-RADS 5 lesions (Table 4), indicating a positive association between increasing orientation angle and higher suspicion of malignancy.

ROC curve analysis identified an optimal orientation angle cut-off value of 25.3°, yielding an AUC of 0.72 (95% CI: 0.68–0.77). At this cut-off, sensitivity was 45.7% (95% CI: 41.4–50.1), and specificity was 90.2% (95% CI: 87.6–92.3). The corresponding LR+ was 4.66 (95% CI: 3.33–6.59), and the LR− was 0.60 (95% CI: 0.53–0.68), indicating moderate rule-in capability but limited rule-out performance (Table 5). When compared with the previously reported cut-off of 22.9°, the higher threshold improved specificity and PPV, with a modest reduction in sensitivity.

Multivariable Analysis and Incremental Diagnostic Value

In Model 1, which incorporated established clinical and sonographic predictors without the orientation angle, several variables emerged as independent factors associated with malignancy. Axillary lymph node enlargement (OR 2.54, $p = .007$), spiculated margins (OR 5.72, $p = .008$), irregular shape (OR 5.44, $p < .001$), older age (OR 1.07 per year increase, $p < .001$), and heterogeneous echotexture (OR 0.19, $p = .001$) were significant contributors to malignancy risk. The overall performance of Model 1 was strong, with a −2 log likelihood of 387.3 and a Nagelkerke R^2 of 0.607, indicating good explanatory power based on conventional BI-RADS–related descriptors and clinical factors.

Upon inclusion of the orientation angle in Model 2, the angle demonstrated an independent and statistically significant association with malignancy (OR 1.03 per degree increase, 95% CI 1.015–1.039; $p < .001$). Importantly, the inclusion of this variable resulted in a meaningful improvement in overall model performance. The −2 log likelihood decreased from 387.3 to 365.3, corresponding to a statistically significant

Table 2. Characteristics of Benign and Malignant Masses

Variable	Benign Mass ($N = 244$)	Malignant Mass ($N = 258$)	*p*-Value
Age (year)	35.3 ± 11	49.1 ± 10.9	<.001
Body mass index (kg/m^2) (25th and 75th percentile)	22.4 (20.3; 24.6)	23.4 (21.2; 26.6)	.001
Short axis to long axis ratio (25th and 75th percentile)	0.6 (0.5; 0.75)	0.68 (0.52; 0.83)	.001
Orientation angle (25th and 75th percentile)	6.7 (2.9; 15.2)	19.2 (7.2; 74.8)	<.001
Family history of breast cancer			.163
Yes	15 (6.1)	9 (3.5)	
No	229 (93.9)	249 (96.5)	
Breast pain			.553
Yes	45 (18.4)	53 (20.5)	
No	199 (81.6)	205 (79.5)	
Nipple discharge			.13
Yes	6 (2.5)	13 (5)	
No	238 (97.5)	245 (95)	
Laterality of mass			.359
Left	112 (45.9)	131 (50.6)	
Right	132 (54.1)	128 (49.4)	
Quadrant			.164
Upper outer	139 (57)	169 (65.5)	
Upper inner	41 (16.8)	34 (13.2)	
Lower inner	14 (5.7)	17 (6.6)	
Lower outer	50 (20.5)	38 (14.7)	
Calcification			<.001
Present	22 (9)	88 (34.1)	
Absent	222 (91)	170 (65.9)	
Enlarged lymph node in the axillary region			<.001
Yes	22 (9)	86 (33.3)	
No	222 (91)	172 (66.7)	
Shape			<.001
Oval	208 (85.2)	81 (31.4)	
Irregular	36 (14.8)	177 (68.7)	
Margin			<.001
Angular	1 (0.4)	2 (0.8)	
Circumscribed	187 (76.6)	104 (40.3)	
Indistinct	4 (1.6)	28 (10.9)	
Microlobulated	48 (19.7)	55 (21.3)	
Spiculated	4 (1.6)	69 (26.7)	
Echo pattern			<.001
Anechoic	7 (2.9)	9 (3.5)	
Heterogenous	25 (10.2)	19 (7.4)	
Hypoechoic	212 (86.9)	230 (89.1)	
Posterior features			<.001
Acoustic shadowing	32 (13.1)	91 (35.3)	
Combined	7 (2.9)	8 (3.1)	
Negative	73 (29.9)	103 (39.9)	
Posterior enhancement	132 (54.1)	56 (21.7)	

likelihood ratio test ($\chi^2 = 22.03$, $p < .001$), while the Nagelkerke R^2 increased from 0.607 to 0.639. These findings indicate that the orientation angle provides incremental explanatory value beyond established morphologic and clinical predictors, rather than merely duplicating their effects (Table 6).

VIF values ranged from 1.021 to 2.023 for each item in both models, well below commonly accepted thresholds for concern, confirming the absence of problematic collinearity among predictors. This suggests that the orientation angle contributes unique and independent diagnostic information and does not

Table 3. Distribution of Breast Lesions

Pathology	Number (%)
Benign lesion ($N = 244$)	
Fibroadenoma	132 (54.1)
Adenosis/usual ductal hyperplasia spectrum	19 (7.8)
Fibrocystic changes	47 (19.3)
Intraductal papilloma	12 (4.9)
Phylloides tumor/fibroepithelial tumor	7 (2.9)
Chronic mastitis/inflammatory lesions	6 (2.5)
Sclerosing adenosis	5 (2)
Ductal ectasia	4 (1.6)
Columnar cell change/lesion	3 (1.2)
Apocrine metaplasia	3 (1.2)
Others	6 (2.5)
Malignant lesion (N = 258)	
Invasive carcinoma, no special type (NST)	93 (36)
Invasive carcinoma of a special type	32 (12.4)
Intraductal papilloma	3 (1.2)
Ductal carcinoma in situ (DCIS)	21 (8.1)
Microinvasive carcinoma (DCIS with microinvasion)	18 (6.9)
Invasive carcinoma with mixed NST + special features (not classifiable as pure special type)	16 (6.2)
Carcinoma with extensive in situ component (EIC-positive)	14 (5.4)
Paget disease of the nipple (± underlying carcinoma)	7 (2.7)
Malignant phyllodes tumor	6 (2.3)
Borderline phyllodes tumor	5 (1.9)
Neuroendocrine carcinoma of the breast	5 (1.9)
Metaplastic carcinoma (unclassifiable subtype)	5 (1.9)
Lymphoma or hematologic malignancy involving the breast	4 (1.6)
Other rare malignant epithelial tumors	13 (5)

Table 4. Distribution of the Orientation Angle of Breast Mass According to the BI-RADS Classification

BI-RADS Category	Number (%)	Orientation Angle (25th and 75th IQR)
3	233 (46.4)	6.6 (2.8; 14.5)
4A	87 (17.3)	13.1 (4.6; 40.8)
4B	34 (6.8)	16.4 (6.9; 72.5)
4C	63 (12.5)	22.1 (6.6; 78.9)
5	85 (16.9)	39.9 (10.7; 81.6)

IQR, interquartile range.

substantially overlap with other sonographic descriptors included in the model.

Discussion

In this study, we demonstrate that the orientation angle of breast masses on US is a reproducible and clinically relevant imaging parameter with independent diagnostic value for malignancy. Malignant lesions exhibited significantly larger orientation angles than benign lesions, and the angle showed a clear stepwise increase across ascending BI-RADS categories, supporting its biological plausibility as a marker of infiltrative growth. Using ROC analysis, an optimal cut-off value of 25.3° achieved high specificity (90.2%) and a moderate LR+ (4.66), indicating moderate rule-in capability for malignancy, albeit with limited sensitivity. Importantly, multivariable analysis confirmed that the orientation angle remained independently associated with malignancy after adjustment for established clinical and sonographic predictors, and its inclusion significantly improved overall model fit and discriminative performance. In contrast to the study by Chen and Wu,[5] which evaluated orientation angle as a standalone parameter in a prospective setting, our study demonstrates its independent and incremental contribution within a multivariable model in a real-world clinical cohort, thereby providing evidence of its practical utility in routine breast ultrasound assessment. These findings suggest that quantitative assessment of lesion orientation provides incremental diagnostic information beyond conventional BI-RADS descriptors and may serve as a useful adjunct in breast ultrasound risk stratification.

A clinically reliable imaging descriptor must, first and foremost, demonstrate high inter-reader reliability. This requirement is particularly critical for BI-RADS descriptors that are strongly associated with malignancy, as consistent interpretation is essential for the reliable identification of women with breast cancer.[9] Previous studies have shown that inter-observer agreement for dichotomous outcomes, such as mass orientation (parallel versus non-parallel) and vascularity (absent or minimal versus exuberant), generally ranges from moderate to substantial, which is consistent with expectations for these qualitative descriptors.[8] In this study, the dichotomous outcome of parallel and non-parallel is quantified. The inter-reader agreement between the senior breast radiologist and senior residents was in the good range, while agreement among senior residents was excellent,

Table 5. Comparison of Diagnostic Test Accuracy Performance

Cut-Off Angle	Sensitivity	Specificity	LR(+)	LR(−)	PPV	NPV
≥22.9 (from Chen and Wu [2024])[5]	47.7% (41.4–53.9)	88.1% (83.4–91.9)	4.01 (2.79–5.78)	0.59 (0.52–0.67)	80.9% (74.7–85.9)	67.3% (63–71.4)
≥25.3	45.7% (41.4–50.1)	90.2% (87.6–92.3)	4.66 (3.33–6.59)	0.6 (0.53–0.68)	83.1% (79.8–86.3)	61.1% (56.9–65.4)

LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table 6. Multivariable Categorical Regression Analysis of Factors Associated with the Outcome

	Model 1 (Without Orientation Angle)		Model 2 (With Orientation Angle)	
Variable	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Presence of lymph node enlargement	2.54 (1.29–4.99)	.007	2.54 (1.25–5.17)	.001
Margin: spiculated	5.72 (1.58–20.7)	.008	4.91 (1.23–19.58)	.024
Age	1.069 (1.069–1.124)	<.001	1.092 (1.064–1.121)	<.001
Presence of family history	0.24 (0.06–0.94)	.04	0.24 (0.06–0.94)	.04
Presence of calcification	1.89 (0.97–3.72)	.063	2.16 (1.07–4.36)	.031
Shape: irregular	5.44 (2.98–9.94)	<.001	4.65 (2.49–8.69)	<.001
Echo: heterogeneous	0.19 (0.07–0.52)	.001	0.18 (0.066–0.51)	.001
Orientation angle	—	—	1.03 (1.015–1.039)	<.001
Model diagnostics	−2 Log likelihood = 387.3 Nagelkerke R^2 = 0.607		−2 Log likelihood = 365.3 Nagelkerke R^2 = 0.639	

OR, odds ratio.

indicating that measurement of the breast mass orientation angle is a clinically reliable imaging descriptor.

Our results show that the optimal cut-off to differentiate benign and malignant lesions is 25.3°. This finding indicates that quantitative assessment of lesion orientation has the potential to complement the conventional dichotomous BI-RADS orientation descriptor by improving objectivity and reproducibility in clinical practice. Using a cut-off value of 22.9° in our dataset resulted in only a marginal reduction in sensitivity and NPV, while all other diagnostic performance parameters increased. In their original study, Chen and Wu[5] reported that the orientation angle achieved a sensitivity of 88%, specificity of 87.4%, PPV of 81.1%, NPV of 92.2%, and an AUC of 92.5% for distinguishing benign from malignant breast masses. Subgroup analyses based on arbitrarily defined orientation angle ranges were not performed, as such stratification may introduce selection bias and reduce statistical robustness. Moreover, intermediate angle ranges do not correspond to clinically actionable categories, given that lesions within this spectrum are typically managed based on established BI-RADS assessment.

The differences in sensitivity and specificity between our findings and the previously published study are likely attributable to several methodological and population-related factors rather than inconsistency in the diagnostic value of orientation-related ultrasound features. A key distinction is study design. Our study was retrospective, whereas Chen and Wu[5] employed a prospective methodology. Prospective designs benefit from standardized acquisition protocols and real-time interpretation, while retrospective analyses rely on archived images and reports with variable quality and completeness. Such design-related differences are well recognized to influence estimates of diagnostic accuracy.[15]

Sample size and case composition also differed substantially. Our cohort was larger and maintained a balanced benign-to-malignant ratio of approximately 1:1, whereas prospective studies often reflect real-world prevalence or selectively include clinically suspicious lesions. Balanced case distributions tend to

stabilize specificity but may reduce apparent sensitivity by incorporating a broader range of equivocal lesions, whereas enriched cohorts may inflate sensitivity.[16]

Additionally, the histopathological spectrum of benign lesions in our study was more comprehensive. We included inflammatory entities such as chronic mastitis, which were not explicitly represented in the comparator study. These lesions frequently mimic malignant sonographic features, including non-parallel orientation and irregular margins, and their inclusion is expected to increase false-positive interpretations and lower specificity, consistent with spectrum bias.[11,15]

Reader-related factors may have further contributed. Our analysis involved multiple readers, whereas the comparator study did not specify the number of readers. Inclusion of multiple readers introduces inter-observer variability, which may modestly reduce sensitivity and specificity but enhances generalizability. In contrast, single-reader or expert-only studies often report higher performance that may not reflect routine clinical practice.[17]

Finally, differences in orientation definitions, diagnostic thresholds, ultrasound equipment, and verification strategies may also influence performance metrics. Retrospective studies are particularly susceptible to partial verification bias, as histopathology is more often available for suspicious lesions, potentially affecting sensitivity and specificity estimates.[3]

Our multivariable analysis reveals that the presence of lymph node enlargement, spiculated margin, presence of calcification, and irregular margin predict malignancy. An orientation angle of ≥25.3° and older age also predict malignancy, but with a lower odds ratio. Meanwhile, the absence of family history and heterogeneous echotexture results in lower odds of malignant breast mass.

Irregular shape, spiculated margins, and non-parallel orientation are among the most consistent sonographic features predictive of malignancy.[11,18,19] Spiculated margins reflect infiltrative extension of a lesion into adjacent tissues, while an irregular shape suggests uneven growth and progressive advancement of the lesion border. A non-parallel orientation on sonography may indicate extension across normal tissue planes.[19] In a study of non-palpable BI-RADS 4 lesions, irregular shape demonstrated a PPV of 66%, spiculated margins a PPV of 80%, and non-parallel orientation a PPV of 58.9%.[18] Li et al (2020) employed multimodality ultrasound imaging in BI-RADS 4 lesions and found that age ≥40 years old is an independent risk factor for the prediction of breast malignancy.[20] Breast cancer risk increases with age due to the cumulative accumulation of genetic mutations, prolonged lifetime exposure to estrogen, and age-related declines in DNA repair and immune surveillance mechanisms.[21,22]

The presence of calcification, especially intralesional microcalcification, is a reliable diagnostic sign for carcinoma.[19] The association between calcifications and malignancy in our study is biologically plausible and aligns with our finding that a proportion of malignant lesions were ductal carcinoma in situ. Calcifications are a hallmark imaging feature of ductal carcinoma in situ, arising from intraductal necrosis and secretory debris that subsequently undergo dystrophic calcification.[23] Their presence on ultrasound, particularly when associated with a mass, therefore reasonably correlates with malignancy and supports calcification as an independent predictive feature in our multivariable analysis.

Echogenicity is one of the least useful descriptors in differentiating benign from malignant masses.[7,19,24] The significance observed in our model likely reflects the histopathological composition of our cohort, which included a high proportion of benign proliferative and inflammatory lesions (eg, adenosis and chronic mastitis) that commonly demonstrate heterogeneous echotexture. When adjusted for stronger malignant predictors such as spiculated margins, calcifications, and lymph node enlargement, heterogeneous echotexture functioned as a benign-associated feature, thereby yielding a low odds ratio. This result underscores that echogenicity should be interpreted in conjunction with other sonographic features rather than in isolation.

The association between lymph node enlargement and malignancy observed in our study is clinically expected, as malignant breast lesions frequently spread via lymphatic channels to regional axillary lymph nodes.[25] Metastatic involvement leads to cortical thickening, loss of the fatty hilum, and nodal enlargement, which are well-established imaging markers of nodal metastasis.[26] Consequently, the presence of lymphadenopathy reflects more advanced

disease and serves as a strong predictor of malignancy in breast imaging evaluation.

In our multivariable analysis, the absence of a family history of breast cancer was associated with lower odds of malignancy, consistent with its established role as a clinical risk factor rather than an imaging feature.[27] A positive family history reflects inherited genetic susceptibility and long-term hormonal or environmental influences that increase baseline cancer risk, whereas patients without such a history are more likely to harbor sporadic and benign breast lesions.[21] After adjustment for strong sonographic predictors of malignancy, the low odds ratio observed in our study suggests that the absence of family history functions as a protective clinical variable, reinforcing that malignant risk is multifactorial and influenced by both imaging findings and underlying patient risk profiles.

This study has several limitations. First, this was a retrospective study in which radiologists reviewed images from the PACS. Image interpretation was based on static images, whereas real-time assessment may have provided additional information and potentially led to the assignment of more suspicious descriptors. Although static image review does not fully reflect routine clinical practice, it remains a common method for interpreting clinical breast sonograms.[11] Second, the analysis was limited to biopsy-confirmed lesions and therefore did not assess the predictive performance of BI-RADS features in lesions considered definitively benign or managed with imaging follow-up. Third, this was a single-center study conducted at a tertiary cancer referral hospital, which may have introduced referral bias and limited the generalizability of our findings to screening populations or lower-acuity clinical settings. Fourth, sample bias could not be avoided in this retrospective study. While most benign lesions do not require surgical intervention, some patients choose to undergo biopsy or surgery. Therefore, patients who decline such procedures may be underrepresented, introducing potential selection bias. Fifth, the near-equal distribution of benign and malignant lesions in our cohort does not reflect real-world disease prevalence and may have influenced estimates of diagnostic performance, particularly predictive values. Sixth, although measurement reliability was high, most final angle measurements were performed by senior residents, and performance may differ among readers with varying levels of experience. Seventh, the proposed orientation angle cut-off was derived and evaluated within the same cohort, and external validation in an independent dataset is required before clinical implementation. Despite these limitations, the large sample size, excellent inter-reader reliability, and comprehensive multivariable adjustment support the robustness of our findings and highlight the potential clinical utility of quantitative orientation assessment as an adjunct to BI-RADS descriptors. Lastly, this study did not evaluate the association between orientation angle and specific histopathological subtypes or molecular biomarkers such as Ki-67. Such analyses were beyond the primary objective of this study, which focused on binary diagnostic discrimination (benign versus malignant). Moreover, incomplete availability of molecular data, particularly from externally obtained histopathological results, and the imbalanced distribution of pathological subtypes limited the feasibility and statistical robustness of subtype-level analyses. Future studies with standardized molecular profiling and adequately powered subtype-specific cohorts are warranted to explore these relationships.

Conclusion

This study demonstrates that quantitative orientation angle is a reproducible and independent imaging biomarker for breast malignancy, with high specificity and moderate ability to rule in malignancy. An angle ≥25.3° is associated with increased malignancy risk and shows a progressive relationship with BI-RADS categories. Importantly, incorporation of orientation angle into a multivariable model significantly improves diagnostic performance beyond conventional ultrasound descriptors. These findings support the role of orientation angle as a complementary parameter in breast ultrasound, with potential utility in refining risk stratification and supporting biopsy decision-making, pending external validation.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

The data are not publicly available due to privacy or ethical restrictions.

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