Original Article

Diagnostic test of conventional ultrasonography combined with contrast-enhanced ultrasound in the subcategorization of suspicious Breast Imaging-Reporting and Data System (BI-RADS) 4 breast lesions

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Background: Although conventional ultrasonography (CUS) and contrast-enhanced ultrasound (CEUS) play a critical role in cancer detection, diagnosis, and image-guided biopsies, there is no standardized diagnostic approach for the clinical evaluation of suspected Breast Imaging-Reporting and Data System (BI-RADS) category 4 breast lesions. This diagnostic test evaluates the complementary roles of CUS and CEUS in addressing limitations of conventional imaging, such as microvascular visualization. This study aimed to evaluate the diagnostic value of combining CUS with CEUS in subcategorizing suspicious breast lesions classified as BI-RADS for ultrasound (US-BI-RADS) category 4.

Methods: The data of 131 patients with BI-RADS category 4 breast lesions, examined between February 2017 and March 2023, were retrospectively analyzed. All lesions underwent pathological examination following surgery and served as the gold standard for diagnosis. Key features such as lesion margins, echogenicity, size, microcalcification, blood flow distribution via color Doppler flow imaging (CDFI), and CEUS characteristics were assessed. CEUS scores were calculated using a five-point scoring system. Stepwise logistic regression was applied to evaluate the odds ratios (ORs) of the lesion characteristics on US and CEUS. The combination of the US-BI-RADS and CEUS scores (termed the CEUS-BI-RADS) was compared to the US-BI-RADS alone, and a receiver operating characteristic (ROC) curve analysis was conducted to determine the diagnostic performance of these methods.

Results: Of the 131 lesions, 62 (47.3%) were benign, and 69 (52.7%) were malignant. The multivariate logistic regression identified the primary indicators of malignancy as calcification [OR =1.58, 95% confidence interval (CI): 0.25–2.91, P=0.02], suspicious or abnormal axillary lymph nodes (OR =2.51, 95% CI: 0.59–4.44, P=0.01), obscure margins after enhancement (OR =2.67, 95% CI: 0.35 to 4.99, P=0.02), and increased lesion size (OR =4.89, 95% CI: 1.45–8.33, P=0.005). The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the US-BI-RADS were 73.9%, 74.2%, 74.0%, 71.9%, and 76.1%, respectively, while those of the CEUS-BI-RADS were 92.8%, 79.0%, 86.3%, 90.7%, and 83.1%, respectively. The areas under the ROC curves for the US-BI-RADS and CEUS-BI-RADS were 0.741 and 0.859, respectively.

Conclusions: The CEUS-BI-RADS significantly enhances diagnostic efficacy for BI-RADS category 4 breast lesions, outperforming the US-BI-RADS and could reduce unnecessary biopsies.

Keywords: Conventional ultrasonography (CUS); contrast-enhanced ultrasound (CEUS); Breast Imaging-Reporting and Data System category 4 (BI-RADS 4); breast cancer (BC); diagnosis

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Introduction

Breast cancer (BC) is the most common malignant tumor among women, it poses a significant threat to their physical and mental health (1,2). About 25% of women are affected by breast diseases at some point in their lives (3). However, the spectrum of breast lesions ranges from benign physiological glandular changes to highly invasive malignant tumors, making accurate diagnosis challenging. Early detection via population screening can significantly improve patient outcomes, and the 5-year survival rate of BC patients diagnosed at an early stage exceeds 90% (4). Therefore, the early diagnosis and timely treatment of BC are crucial for improving patient prognosis (5).

Highlight box

Key findings

- Conventional ultrasonography (CUS) and contrast-enhanced ultrasound (CEUS) are effective diagnostic tools for breast lesions, especially for Breast Imaging-Reporting and Data System (BI-RADS) category 4 lesions.
- The CEUS-BI-RADS approach significantly enhances diagnostic efficacy for BI-RADS category 4 breast lesions compared to BI-RADS for ultrasound (US-BI-RADS) alone.

What is known, and what is new?

- In recent years, advancements in CUS and CEUS technologies have provided promising solutions for more accurate breast cancer diagnoses.
- The combination of CUS and CEUS significantly enhances diagnostic efficacy for BI-RADS category 4 breast lesions, outperforming the US-BI-RADS and reducing unnecessary biopsies.

What is the implication, and what should change now?

- CEUS serves as a valuable complement to traditional US by providing additional diagnostic information. The combination of CUS and CEUS improves diagnostic efficacy for suspected BI-RADS category 4 breast lesions while reducing unnecessary biopsies.

Conventional ultrasonography (CUS) is one of the most widely used imaging modalities for evaluating breast lesions. For decades, CUS has played a critical role in cancer detection, diagnosis, and image-guided biopsies. In 2003, the American College of Radiology (ACR) introduced the standardized Breast Imaging-Reporting and Data System (BI-RADS), which was subsequently updated in 2013 (6). The BI-RADS standardizes the reporting and classification of breast lesions, enhancing diagnostic efficacy, and is widely employed in cancer screening programs worldwide. However, CUS has limitations in detecting blood flow in small vessels or microvasculature, which can reduce its reliability in evaluating certain breast lesions (7).

According to the ACR BI-RADS, there is considerable overlap in the imaging characteristics of BI-RADS category 4 benign and malignant lesions, which have a malignancy probability ranging from 3% to 94% (8,9). The positive predictive value (PPV) for malignancy of BI-RADS 4 lesions is relatively low, ranging from 15.5% to 20.0% (10). Consequently, patients with BI-RADS 4 lesions often undergo biopsy or even surgery, which may lead to unnecessary risks, patient anxiety, overtreatment, and economic burden.

Contrast-enhanced ultrasound (CEUS) represents a significant advancement in diagnostic imaging technology. By using blood-pool contrast agents, CEUS can visualize the microcirculation of lesions, which may be undetectable by conventional color Doppler ultrasonography (US) due to low blood flow velocity or artifacts caused by breathing and heartbeat. The microcirculation status of breast lesions is an important pathological indicator of malignancy (11). Previous studies have shown that CEUS provides valuable diagnostic insights for distinguishing between benign and malignant breast lesions (12,13). The integration of CUS with CEUS has been shown to improve the diagnostic accuracy for malignant lesions (14,15). Despite these advancements, there is no standardized diagnostic approach

for the sonographic evaluation of suspected BI-RADS 4 lesions. To address this gap, we conducted a retrospective study to assess the clinical value of combining CUS and CEUS in diagnosing suspicious BI-RADS 4 breast lesions to enhance diagnostic accuracy and reduce unnecessary interventions. While BI-RADS standardizes lesion classification, its accuracy for category 4 lesions remains suboptimal due to overlapping imaging features. CEUS overcomes CUS limitations by visualizing microvascular perfusion, a hallmark of malignancy. Recent studies highlight CEUS's diagnostic equivalence to MRI but lack standardized protocols for BI-RADS 4 lesions (16,17). Our study integrates CEUS-derived microvascular parameters into BI-RADS, addressing this gap and validating its utility in a retrospective cohort. We present this article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-485/rc).

Methods

Study population

This was a retrospective study analyzing patients who presented with BI-RADS 4 breast lesions. This study included 131 female patients (131 lesions) treated at The First Affiliated Hospital of Soochow University and Suzhou Xiangcheng People's Hospital between February 2017 and March 2023. The included cases were all patients who visited the outpatient clinic due to breast discomfort. All patients underwent routine color Doppler US and CEUS imaging examinations. The average age of the patients was 46.1±12 years (range, 22–71 years), and the average lesion diameter was 21.2±14.3 mm (range, 3.8–86 mm).

To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: have a lesion classified as BI-RADS for ultrasound (US-BI-RADS) category 4 based on CUS imaging; have pathological confirmation of the diagnosis via histopathological examination; and have not previously undergone a clinical intervention before the US examination. Patients were excluded from the study if they met any of the following exclusion criteria: were pregnant or lactating females; had contraindications to CEUS; had undergone chemotherapy or radiotherapy; had multiple lesions on the same side of the breast; and/or had incomplete clinical data. This retrospective diagnostic test included 131 lesions to achieve 80% power (α=0.05) based on prior CEUS studies. Histopathological examinations were conducted by two pathologists blinded to imaging results, using hematoxylin-eosin staining and immunohistochemistry. Discrepancies were resolved by a third pathologist.

Written informed consent was obtained from all the patients. The study was approved by the Institutional Ethics Committee of Suzhou Xiangcheng People's Hospital (approval number: 2016-014) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The First Affiliated Hospital of Soochow University was informed and agreed with this study.

Instruments and examination methods

CUS and CEUS were performed by four senior radiographers with more than 5 years of experience (Y.Z., L.J., M.F.P. and D.Z.) using a LOGIQ E9 ultrasonic scanner (GE Healthcare, Milwaukee, WI, USA). A linear transducer (ML6-15) with a frequency of 8–13 MHz was used for CUS, and a linear transducer (9L) with a frequency of 8.4 MHz was used for CEUS. The mechanical index was set to <0.16, and the gain was adjusted between 100–120 dB.

Contrast agent preparation and administration

The contrast agent, SonoVue (Bracco Imaging S.P.A., Milan, Italy), was prepared by mixing 5 mL of saline with 59 mg of lyophilized powder. The mixture was shaken and left to stand for 1 minute before use (18).

Examination protocol

CUS examination

Conventional B-mode and color Doppler flow imaging (CDFI) were performed to evaluate the lesion characteristics, including margin, echogenicity, size, microcalcification, and blood flow distribution.

CEUS examination

The CEUS mode was activated, centering the lesion in the image frame while using peripheral glandular tissue as a control. Patients were instructed to breathe calmly and maintain their position. A 3.0 mL bolus of sulfur hexafluoride suspension was injected into the elbow vein, followed by a 5 mL saline flush. Imaging began simultaneously with the injection and was recorded continuously for 120 seconds. Observations included enhancement intensity, shape, margins, timing, homogeneity, filling defects, vasa vasorum, and the presence of a "crab claw-like" sign.

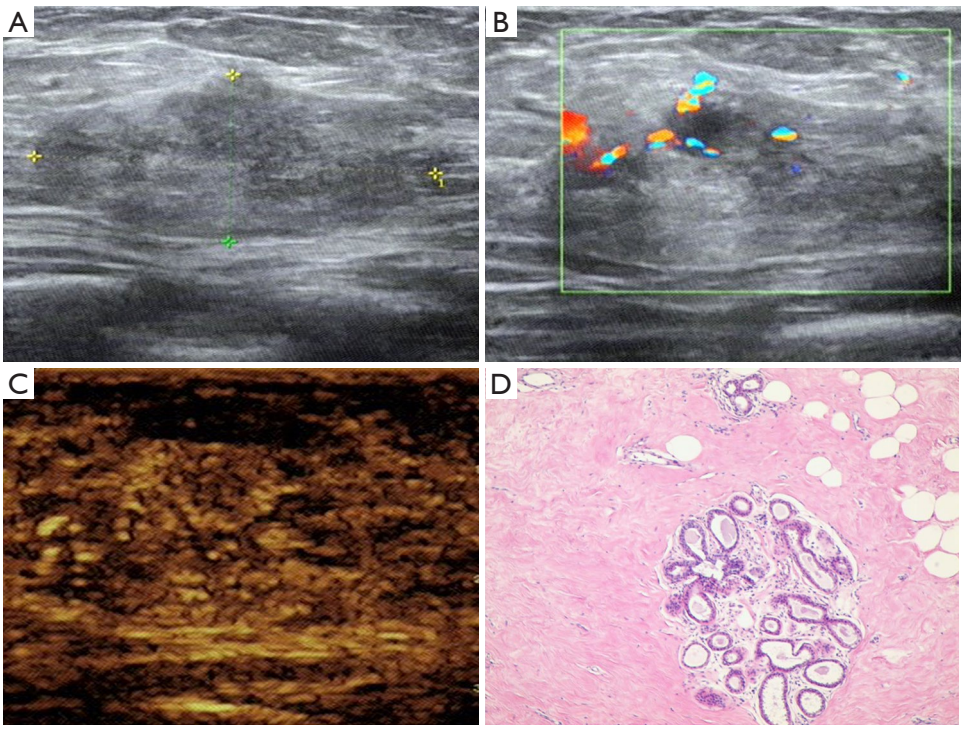

Figure 1 US and CEUS images of a 51-year-old female diagnosed with fibrocystic breast disease at histopathology. (A) Gray-scale US image showing low echo and unclear boundaries in the left breast. Asterisks indicate the borders of the nodules. (B) Color Doppler US showing abundant blood vessels in the lesion. The lesion was diagnosed as BI-RADS 4B on US. (C) CEUS image showing no enlargement of the lesion, clear boundaries, regular morphology, and no crab claw-like sign, which were diagnosed as benign features on CEUS. (D) Histopathological analysis revealed fibrocystic breast disease (hematoxylin and eosin staining; original magnification, ×100). BI-RADS, Breast Imaging-Reporting and Data System; CEUS, contrast-enhanced ultrasound; US, ultrasonography.

Image analysis

All the CUS images were independently reviewed by two senior sonographers (with over five years of experience each) who were blinded to the clinical and pathological results. Discrepancies were resolved via discussion until a consensus was reached.

Lesions were classified as categories 4A, 4B, and 4C according to the BI-RADS, with the diagnostic cut-off set between categories 4A and 4B (6). Lesions in category 4A were considered as likely benign (while those in categories 4B and 4C were classified likely as malignant.

The CEUS five-point scoring method was used to assess lesion malignancy (19). The CEUS-BI-RADS categories were determined by adjusting the US-BI-RADS classification based on the CEUS scores as follows: CEUS scores of 1–3: downgrade the US-BI-RADS classification by one category; CEUS scores of 4–5: upgrade the US-BI-RADS classification by one category. The new classification system was referred to as the CEUS-BI-RADS (*Figure 1*).

Statistical analysis

The statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). The measurement data are expressed as the mean ± standard deviation. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. The independent sample *t*-test was used to compare the normally distributed variables. The Chi-squared test was used to compare the non-normally distributed variables. Sensitivity, specificity, accuracy, the PPV, and the negative predictive value (NPV) were calculated for each diagnostic method. Stepwise logistic regression was used to develop a multivariate logistic regression model for breast lesions; P values of 0.05 and 0.10 were set as the entry and exclusion criteria, respectively. Stata version 15.1 (StataCorp, College Station, TX, USA) was used to construct a multivariate analysis forest

Table 1 Comparison of the clinicopathological data of the benign and malignant breast lesions

Characteristics	Benign (n=62)	Malignant (n=69)	Z/χ^2 value	P value
Age (years)	39.4±9.79 [22–61]	50.8±11.20 [23–71]	–5.216	<0.001
Lesion size (mm)	16.48±11.88 [3.8–53]	25.36±15.13 [4.9–86]	–4.229	<0.001
Side			–0.395	0.69
Right	30	31		
Left	32	38		
Pathological result			–	–
Fibroadenoma	20 (32.3)	–		
Adenopathy	15 (24.2)	–		
Intraductal papilloma	10 (16.1)	–		
Fibrocystic mastopathy	8 (12.9)	–		
Chronic inflammation	5 (8.1)	–		
Benign phyllodes tumor	1 (1.6)	–		
Others	3 (4.8)	–		
Invasive ductal carcinoma	–	54 (78.3)		
Papillary carcinoma	–	10 (14.5)		
Ductal carcinoma in situ	–	4 (5.8)		
Tubular carcinoma	–	1 (1.4)		

Data were presented as mean ± standard deviation [range], n, or n (%).

plot. The areas under the curves (AUCs) of the receiver operating characteristic (ROC) curves for the US-BI-RADS and CEUS-BI-RADS were compared using a Z-test with MedCalc version 19.0.4 (MedCalc Software Ltd., Ostend, Belgium). CUS and CEUS parameters were combined using logistic regression to generate CEUS-BI-RADS scores. All P values were two-sided. AUC >0.8, sensitivity >85%, and specificity >75% were considered indicative of strong diagnostic performance. Statistical significance was set at P<0.05.

Results

Clinical and pathological findings of lesions

All the patients underwent surgical treatment. As *Table 1* shows, of the 131 lesions, 62 were benign and 69 were malignant lesions. The benign lesions included 20 cases of fibroadenoma, 15 cases of adenopathy (including 1 case of sclerosing glandular disease, 2 cases of glandular disease with cysts, and 2 cases of glandular disease with ductal dilation), 10 cases of intraductal papilloma, 8 cases of fibrocystic mastopathy, 5 cases of chronic inflammation, 1 case of lobular benign tumor, and 3 cases of other benign lesions. The malignant lesions included 54 invasive ductal carcinomas, 10 intraductal papillary carcinomas, 4 ductal carcinomas *in situ*, and 1 tubular carcinoma. There was a statistically significant difference in the age and lesion size between the patients with benign and malignant lesions (both P<0.05).

Screening of risk factors for breast lesions

The univariate analysis of the 131 breast nodules showed that there were statistically significant differences between the benign and malignant nodules in terms of patient age, margin, size, calcification, axillary lymph nodes, blood flow, enhancement intensity, enhancement scope, enhancement homogeneity, vasa vasorum, crab claw-like sign, enhancement margin, and shape (*Tables 1-3*). The results of the multivariate logistic regression analysis showed that the main signs of malignant breast masses were intratumoral

Table 2 Comparison of the US characteristics between the benign and malignant breast lesions

Parameter	Pathology		Z/χ^2 value	P value
	Benign (n=62)	Malignant (n=69)		
Shape			–1.930	0.054
Regular	14	7		
Irregular	48	62		
Margin			–2.564	0.01
Clear	40	29		
Obscure	22	40		
Echogenicity			–0.441	0.66
Hypoechogenicity	58	63		
Isoechogenicity	1	0		
Hyperechogenicity	2	1		
Mixed echo	1	5		
Rear features			–0.407	0.68
Attenuation	10	26		
No attenuation	48	25		
Augmentation	4	18		
Calcification			–3.937	<0.001
Yes	14	39		
No	48	30		
Axillary lymph nodes			–3.155	0.002
Yes	4	19		
No	58	50		
Blood flow			–3.623	<0.001
Yes	42	64		
No	20	5		
Aspect ratio			–0.878	0.38
<1	47	46		
1	2	4		
>1	13	19		

US, ultrasonography.

calcification [odds ratios (OR) =1.58, 95% confidence interval (CI): 0.25 to 2.91, P=0.02], suspicious or abnormal axillary lymph nodes (OR =2.51, 95% CI: 0.59 to 4.44, P=0.01), obscure margin after enhancement (OR =2.67, 95% CI: 0.35 to 4.99, P=0.02), and enlarged lesion size (OR =4.89, 95% CI: 1.45 to 8.33, P=0.005) (*Figure 2*).

Diagnostic performance of CUS and CEUS

As *Table 4* shows, using the US-BI-RADS 64 cases were diagnosed as category 4A (48.85%), 55 as category 4B (41.98%), and 12 as category 4C (9.16%). The malignancy rates of the US-BI-RADS 4A, 4B, and 4C lesions were

Table 3 Comparison of the CEUS characteristics between the benign and malignant breast lesions

Parameter	Pathology		Z/χ^2 value	P value
	Benign (n=62)	Malignant (n=69)		
Enhancement intensity			–2.340	0.02
Hypoechogenicity/isoechogenicity	7	1		
Hyperechogenicity	55	68		
Enhancement scope			–8.466	<0.001
Not enlarged	50	5		
Enlarged	12	64		
Enhancement time			–1.255	0.21
Fast-forward	58	60		
Same or slow-forward	4	9		
Enhancement homogeneity			–3.358	0.001
Homogeneous	32	16		
Inhomogeneous	30	53		
Filling defect			–1.866	0.06
Yes	24	38		
No	38	31		
Vasa vasorum			–5.109	<0.001
Yes	43	52		
No	19	17		
Crab claw-like sign			–4.749	<0.001
Present	6	33		
Absent	56	36		
Margin			–3.068	0.002
Clear	46	33		
Obscure	16	36		
Shape			–7.700	<0.001
Regular	44	4		
Irregular	18	65		

CEUS, contrast-enhanced ultrasound.

28.13% (18 cases), 72.73% (40 cases), and 91.67% (11 cases), respectively. Under the five-point scoring system, 2.3% (3/131) of the lesions were scored as 1 point, 3.8% (5/131) as 2 points, 35.9% (47/131) as 3 points, 28.2% (37/131) as 4 points, and 29.8% (39/131) as 5 points. For the CEUS-BI-RADS, this study modified the BI-RADS category based on a re-scoring scheme using CEUS scores, and 34.35% (45/131) of the lesions were diagnosed as category 3, 6.9% (9/131) as category 4A, 15.3% (20/131) as category 4B, 35.1% (46/131) as category 4C, and 8.4% (11/131) as category 5. The malignancy rates of the lesions based on the CEUS-BI-RADS 3, 4A, 4B, 4C, and 5 scores were 8.9%, 11.1%, 70.0%, 84.8%, and 100%, respectively. Using pathology as the gold standard, the sensitivity,

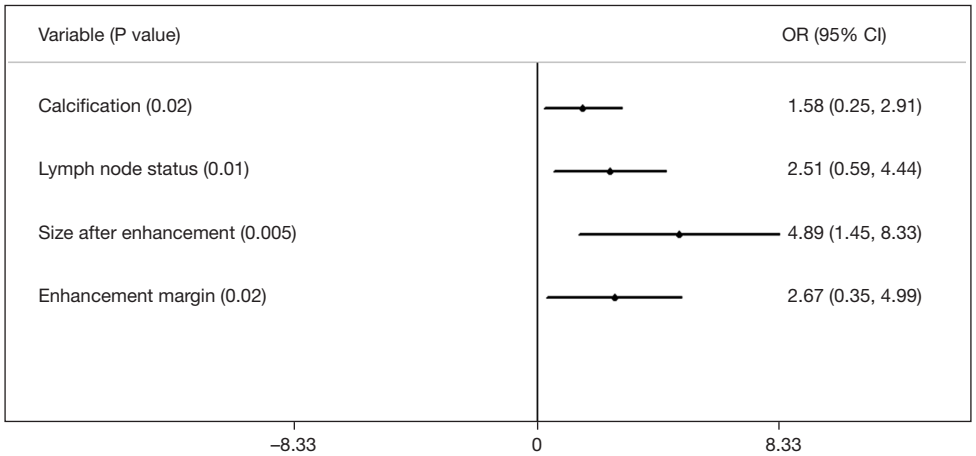

Figure 2 Multivariate logistic regression analysis results of benign and malignant breast lesions. CI, confidence interval; OR, odds ratio.

Table 4 Comparison of the malignant breast lesions detected through histopathological confirmation and use of the US-BI-RADS, CEUS score, and CEUS-BI-RADS

Lesion [n]	Pathological results	
	Benign (n=62)	Malignant (n=69)
US-BI-RADS		
4A [64]	46	18
4B [55]	15	40
4C [12]	1	11
CEUS		
1 [3]	2	1
2 [5]	5	0
3 [47]	43	4
4 [37]	6	31
5 [39]	6	33
CEUS-BI-RADS		
3 [45]	41	4
4A [9]	8	1
4B [20]	6	14
4C [46]	7	39
5 [11]	0	11

CEUS, contrast-enhanced ultrasound; CEUS-BI-RADS, the combination of US-BI-RADS and CEUS scores; US-BI-RADS, Breast Imaging-Reporting and Data System for ultrasound.

specificity, and accuracy of the US-BI-RADS diagnosis were 73.9%, 74.2%, and 74.0%, respectively. While the diagnostic sensitivity, specificity, and accuracy of the CEUS-BI-RADS were 92.8%, 79.0%, and 86.3%, respectively (*Table 5*). As *Figure 3* shows, the AUCs of the ROC curves for the US-BI-RADS and CEUS-BI-RADS diagnoses were 0.741 and 0.859, respectively (P=0.002).

Discussion

BC has the highest incidence and mortality rates among female malignancies worldwide. Traditional breast imaging techniques include magnetic resonance imaging (MRI), mammography, and CUS (20,21). Recent studies have found that combining enhanced scoring with clinical indicators based on the BI-RADS score can improve the efficiency of spectral mammography in diagnosing BC (16,22). However, MRI is limited by its inability to dynamically observe imaging features of lesions in real time, its time-consuming and costly nature, and contraindications such as severe contrast agent allergies, nephrotoxicity, claustrophobia, and metal implants. As a result, MRI is primarily used as a supplementary examination to CUS (20,23-25). Currently, CUS is the most widely used method for breast tumor screening. However, early BI-RADS category 4 lesions often exhibit unclear imaging features on CUS, leading to potential misdiagnoses.

CEUS improves lesion characterization by using contrast agents to enhance the contrast between blood vessels and surrounding tissues. Integration of CEUS with clinical factors may reduce unnecessary interventions in low-risk patients and ensure adequate monitoring of high-risk individuals (26). CEUS provides critical information about microcirculation perfusion, including the number, thickness, shape, and spatial distribution of new blood

Table 5 Comparison of the diagnostic performance between the US-BI-RADS and the CEUS-BI-RADS

Diagnostic methods	SE (%)	SP (%)	ACC (%)	PPV (%)	NPV (%)	AUC (95% CI)
US-BI-RADS	73.9	74.2	74.0	71.9	76.1	0.741 (0.657 to 0.813)
CEUS-BI-RADS	92.8	79.0	86.3	90.7	83.1	0.859* (0.787 to 0.914)

*, US-BI-RADS versus CEUS-BI-RADS (P=0.002 <0.05). ACC, accuracy; AUC, area under the curve; CEUS, contrast-enhanced ultrasound; CEUS-BI-RADS, the combination of US-BI-RADS and CEUS scores; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity; US-BI-RADS, Breast Imaging-Reporting and Data System for ultrasound.

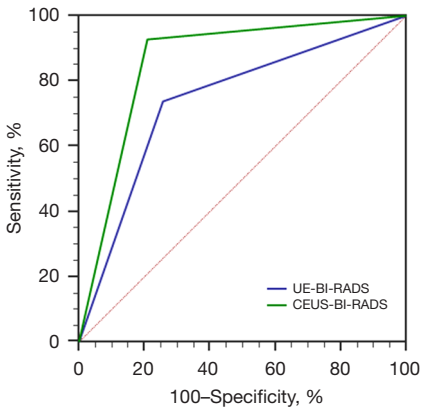

Figure 3 ROC curves of diagnostic efficacy for the US-BI-RADS and the CEUS-BI-RADS. BI-RADS, Breast Imaging-Reporting and Data System; CEUS, contrast-enhanced ultrasound; CEUS-BI-RADS, the combination of US-BI-RADS and CEUS scores; ROC, receiver operating characteristic; US, ultrasonography; US-BI-RADS, BI-RADS for ultrasound.

vessels. These capabilities give CEUS a distinct advantage in differentiating between benign and malignant breast lesions. CEUS has already been widely adopted for the qualitative diagnosis of liver and other abdominal organ tumors (27,28). Despite extensive research on the CEUS features of breast malignancies, the lack of standardized diagnostic criteria has limited its widespread use in breast disease diagnosis.

Microvascular information is a critical factor in distinguishing benign from malignant breast lesions (29). While gray-scale CUS cannot detect microvascular structures, CDFI and CEUS provide valuable blood flow information. Benign lesions typically exhibit minimal blood flow, while malignant lesions are characterized by higher angiogenesis and maximum flow velocity (30,31). However, CDFI faces challenges in detecting vessels with slow flow rates (<1 cm/s) or small diameters (<0.1 mm) (32,33). CEUS overcomes these limitations, offering the real-time visualization of microvascular details, including blood flow at speeds <1 mm/s and vessel diameters <1 μm (11,34). This allows CEUS to provide detailed insights into tumor blood flow and perfusion, aiding both diagnosis and post-treatment follow-up.

CEUS, as a pure blood-pool imaging technology, employs contrast agents approximately 2–6 μm in size, which are comparable to red blood cells and unable to penetrate endothelial cell spaces. This enables CEUS to display real-time microcirculation perfusion in lesions and surrounding tissues (20). Recent studies have shown that the diagnostic performance of CEUS for breast lesions rivals that of contrast-enhanced MRI, with diagnostic outcomes closely linked to histological features (35-38). CEUS has gained popularity due to its simplicity, real-time dynamic observation, and suitability for repeated examinations. Second-generation CEUS contrast agents, such as SonoVue, further enhance diagnostic precision by revealing real-time microcirculation in breast lesions, aiding in the differentiation of malignant tumors (39,40).

In this study, consistent with previous research, nine CUS and 10 CEUS diagnostic indicators were analyzed (20,41,42). The univariate analysis revealed statistically significant differences between the benign and malignant lesions in terms of age, margin, size, calcification, axillary lymph nodes, blood flow, enhancement intensity, enhancement scope, enhancement homogeneity, vasa vasorum, crab claw-like sign, enhancement margin, and shape. The multivariate logistic regression analysis identified calcification, axillary lymph nodes, enhancement margin, and enhancement scope as major risk factors for malignancy. Among these, the enlargement of the lesion's enhancement range was the most significant predictor, corroborating earlier findings (43,44).

Some studies have reported that abnormal blood vessels observed via CEUS are characteristic features of malignant tumors (45,46). Conversely, our findings suggest that the primary predictive factors are the extent of enhancement

and the presence of irregular enhancement margins. This discrepancy could be attributed to variations in sample populations, US machines, contrast agents, and the subjective interpretations of different sonographers. Notably, almost all relevant studies have consistently highlighted an enlarged enhancement range as a robust indicator, underscoring its potential as an effective criterion for distinguishing between benign and malignant breast lesions.

The AUC of the ROC curve for the CEUS-BI-RADS in distinguishing between benign and malignant lesions was 0.859, and it had a diagnostic accuracy of 86.3%. This underscores the value of combining CUS and CEUS for improved diagnostic accuracy, and supports the findings of previous studies (41,47,48). The CEUS-BI-RADS correctly diagnosed 113 of the 131 lesions. However, misdiagnoses occurred in a few cases. Five malignant tumors were misdiagnosed as benign. This was likely due to intact margins, uniform perfusion, and the absence of the crab claw-like sign on CEUS. 13 benign lesions were misclassified as malignant. This might have been due to overlapping imaging characteristics such as increased enhancement and the presence of the crab claw-like sign. These findings suggest that small lesions, deep locations, and operator-dependent factors may influence CEUS accuracy (19).

This study had some limitations. This study was a retrospective analysis and thus may be subject to selection bias. In addition, both CUS and CEUS may be highly operator-dependent, with varying levels of expertise, which may have contributed to the discrepancies. The sample size was small, and CEUS quantitative parameters were not analyzed. Further, the pathological subtypes were limited, which might have introduced selection bias into the study. Additionally, the absence of a unified CEUS classification standard might have introduced inter-operator variability. The consensus between the two sonographers in interpreting the imaging features might have also introduced observer bias. Future research with larger, multicenter datasets and long-term follow-up is needed to validate these findings and enhance the clinical utility of CEUS.

Conclusions

CEUS can serve as a valuable complement to CUS by providing additional diagnostic information. The combination of CUS and CEUS improves diagnostic efficacy for suspected BI-RADS category 4 breast lesions while reducing unnecessary biopsies.

Acknowledgments

None.

Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from all the patients. The study was approved by the Institutional Ethics Committee of Suzhou Xiangcheng People's Hospital (approval number: 2016-014) and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The First Affiliated Hospital of Soochow University was informed and agreed with this study.

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