

ORIGINAL RESEARCH

Analysis of the value of the combined application of multiple ultrasound modalities in the early diagnosis of breast cancer

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Abstract

Background: The aim of this study was to analyze the clinical value of the combined application of color Doppler ultrasound (CDUS), ultrasound elastography (UE) and real-time three-dimensional ultrasound (3D-US) in the early diagnosis of breast cancer. **Methods:** A retrospective analysis was conducted on 202 female patients with solitary breast nodules who were admitted to the Affiliated Wuxi People's Hospital of Nanjing Medical University between March 2022 and October 2024. All patients underwent examinations using CDUS, UE, and 3D-US. **Results:** Pathological findings identified 98 malignant and 104 benign lesions among the 202 solitary breast nodules. Ultrasonographic findings revealed that the malignant group exhibited a significantly higher prevalence of irregular tumor shape, ill-defined margins, posterior acoustic attenuation, a taller-than-wide orientation (aspect ratio ≥ 1), penetrating arterial blood supply, a resistance index (RI) > 0.7 , a UE score ≥ 4 compared to the benign group ($p < 0.05$). Diagnostic performance of the individual modalities was as follows: 3D-US diagnosed 97 malignant and 105 benign nodules, demonstrating 78.57% sensitivity, 80.77% specificity, 79.38% positive predictive value (PPV), 80.00% negative predictive value (NPV), 79.70% accuracy, and moderate agreement with pathology (Kappa = 0.594, $p < 0.001$). CDUS identified 101 malignant and 101 benign nodules, with 83.67% sensitivity, 81.73% specificity, 81.19% PPV, 84.16% NPV, 82.67% accuracy, and good agreement (Kappa = 0.654, $p < 0.001$). UE detected 98 malignant and 104 benign nodules, achieving 81.63% sensitivity, 82.69% specificity, 81.63% PPV, 82.69% NPV, 82.18% accuracy, and good agreement (Kappa = 0.643, $p < 0.001$). The combined diagnostic approach yielded superior performance, with sensitivity 90.82%, specificity 80.77%, PPV 81.65%, NPV 90.32%, accuracy 85.64%, and strong agreement with pathology (Kappa = 0.716, $p < 0.001$). **Conclusions:** CDUS, UE, and 3D-US each demonstrate diagnostic value in the early detection breast cancer, while their combined application significantly enhances overall diagnostic efficacy.

Keywords

Breast cancer; Multiple ultrasound modalities; Diagnosis; CDUS; UE; 3D-US

1. Introduction

Breast cancer remains one of the most common malignancies among women worldwide. According to recent global cancer statistics, it accounts for approximately 24.5% of all new cancer cases in females. Importantly, the proportion of patients diagnosed before the age of 40 has increased significantly over the past decade, contributing to the rising disease burden [1]. This malignancy originates from the epithelial tissues of the mammary ducts or lobules. Due to the lack of typical clinical symptoms in early stages, the majority of patients are diagnosed at an advanced disease state, which significantly adversely affects prognosis [2]. Therefore, early screening, diagnosis and treatment are of critical importance for improving

the prognosis of breast cancer patients.

Ultrasound plays a pivotal role in early detection owing to its non-invasive nature, lack of ionizing radiation, and high reproducibility [3]. Ultrasound, as a widely utilized imaging modality in clinical practice, plays a pivotal role in the early diagnosis of breast cancer. However, reliance on a single ultrasound technique has certain limitations and often fails to meet growing clinical demands. Color Doppler ultrasound (CDUS) distinguishes benign from malignant lesions based on the resistive index (RI) of blood flow. Nevertheless, its limited sensitivity in detecting microvascular signals may result in missed diagnoses, particularly in malignancies with sparse vascularization [4]. Ultrasound elastography (UE) evaluates tissue stiffness to characterize lesions; however, its

diagnostic accuracy may be reduced when lesions are located at the periphery of glandular tissue or adjacent to the pectoralis major muscle, where elastic interference from surrounding structures can affect measurements [5]. Although real-time three-dimensional ultrasound (3D-US) provides detailed spatial visualization of lesions, it has limited ability to identify microcalcifications (diameter <0.5 mm), and its post-processing accuracy is highly operator-dependent [6]. These limitations have prompted research into the combined use of multiple ultrasound techniques. However, existing studies remain exploratory and face two major shortcomings: first, the absence of standardized operational protocols undermines the comparability of findings across studies; second, many adopt an oversimplified diagnostic approach in which a malignant indication from any single technique is defined as positive. This approach often reduces specificity due to the cumulative effect of false positives from individual modalities. Therefore, based on standardized operating procedures, this study adopted a multimodal approach combining CDUS, UE, and 3D-US to systematically evaluate its diagnostic value in early-stage breast cancer, using postoperative histopathological findings as the gold standard. We anticipate that our findings will help optimize combined ultrasound strategies and provide a more robust evidence base for selecting diagnostic modalities in early breast cancer detection.

2. Materials and methods

2.1 Patients

This retrospective study enrolled 202 consecutive female patients with solitary breast nodules who were admitted to the Affiliated Wuxi People's Hospital of Nanjing Medical University between March 2022 and October 2024. All patients' lesion specimens were obtained by puncture biopsy or surgical excision within two weeks after ultrasonography and submitted to the Department of Pathology for histological confirmation. Inclusion criteria were as follows: (1) pathologically confirmed diagnosis of either breast cancer or benign breast lesion; (2) newly diagnosed cases without prior treatment; (3) tumor diameter ranging from 1.0 to 5.0 cm; (4) completion of CDUS, UE, and 3D-US examinations with complete imaging data; (5) age ≥ 18 years; (6) Tumor, Node, Metastasis (TNM) stage I–II for patients in the malignant group. The following patients were excluded from the study: (1) Patients with other malignant tumors ($n = 8$). The presence of additional malignancies may confound physiological status, alter treatment plans, and influence ultrasonographic findings, thereby interfering with the accurate assessment of combined ultrasound techniques. (2) Patients with severe dysfunction of major organs such as heart or liver ($n = 7$). Organ dysfunction may alter metabolic and immune functions, compromise tolerance to ultrasound procedures, and affect diagnostic accuracy and prognosis. (3) Pregnant or lactating women ($n = 12$). Hormonal fluctuations during these periods may alter breast tissue architecture and ultrasonic features, making it difficult to distinguish benign from malignant lesions. (4) Patients with severe infection or active bleeding ($n = 5$). Systemic inflammatory or coagulopathic states—such as fever, leukocytosis, or bleeding—may

impair image quality, reduce diagnostic reliability, and limit procedural tolerance. This study was approved by the Ethics Committee of the Affiliated Wuxi People's Hospital of Nanjing Medical University (Approval No. KY25113).

2.2 Sample size calculation

The sample size for a single group was calculated using the following formula (Eqn. 1):

$$n = \frac{Z_{\alpha/2} \sqrt{2p(1-p)} + Z_{\beta} \sqrt{p_0(1-p_0) + p_1(1-p_1)}}{(p_1 - p_0)^2} \quad (1)$$

Where $\alpha = 0.05$ (two-tailed test), $Z_{\alpha/2} = 1.96$; $\beta = 0.10$ (test power $1 - \beta = 0.90$, $Z_{\beta} = 1.28$), $p_1 = 0.91$ (expected sensitivity), and $p_0 = 0.685$ (sensitivity of the single technique). Substituting these values into the formula yielded a minimum of 89 subjects per group. Accounting for a potential dropout rate of 10%, the sample size for each group was adjusted to $89/(1 - 0.10) \approx 99$. Thus, the total required sample size was at least 198 participants. This study ultimately enrolled 202 participants, which meets the statistical power requirements (Fig. 1).

2.3 Baseline data collection

Baseline clinical data were collected for all enrolled patients, including age, body mass index (BMI), menopausal status (premenopausal or postmenopausal), and lesion size.

2.4 Ultrasonography

All examinations in this study were performed using color Doppler ultrasound systems (ACUSON Oxana 2, Siemens; Mindray; GE, Milwaukee, WI, USA) equipped with a high-frequency linear array transducer (model: L6-15) operating at a bandwidth of 4–12 MHz. During the examination, patients were positioned supine with both breasts and axillary regions fully exposed. Multi-directional scans were performed across all quadrants of each breast, using the nipple as the central reference point. All examinations were performed following equipment calibration. Each day after startup, parameter verification was conducted using the built-in standard phantom, and examinations were initiated only after calibration met the established criteria. Baseline parameters for all ultrasound modes were pre-set according to a unified protocol, and operators were not permitted to modify them without justified clinical reasons. The multimodal ultrasound protocol in this study was based on our institution's conventional CDUS examination. To achieve the research objective of evaluating the combined value of multimodal ultrasound in the early diagnosis of breast cancer, three protocol-specific components were designed in addition to the routine examination, focusing on the integrated application of multiple modalities.

2.4.1 3D-US mode

The 3D acquisition mode was activated with a mechanical probe that automatically performed a volumetric sweep across a 15° angle. The acquisition time was approximately 5 seconds. During scanning, the probe was gently placed on the

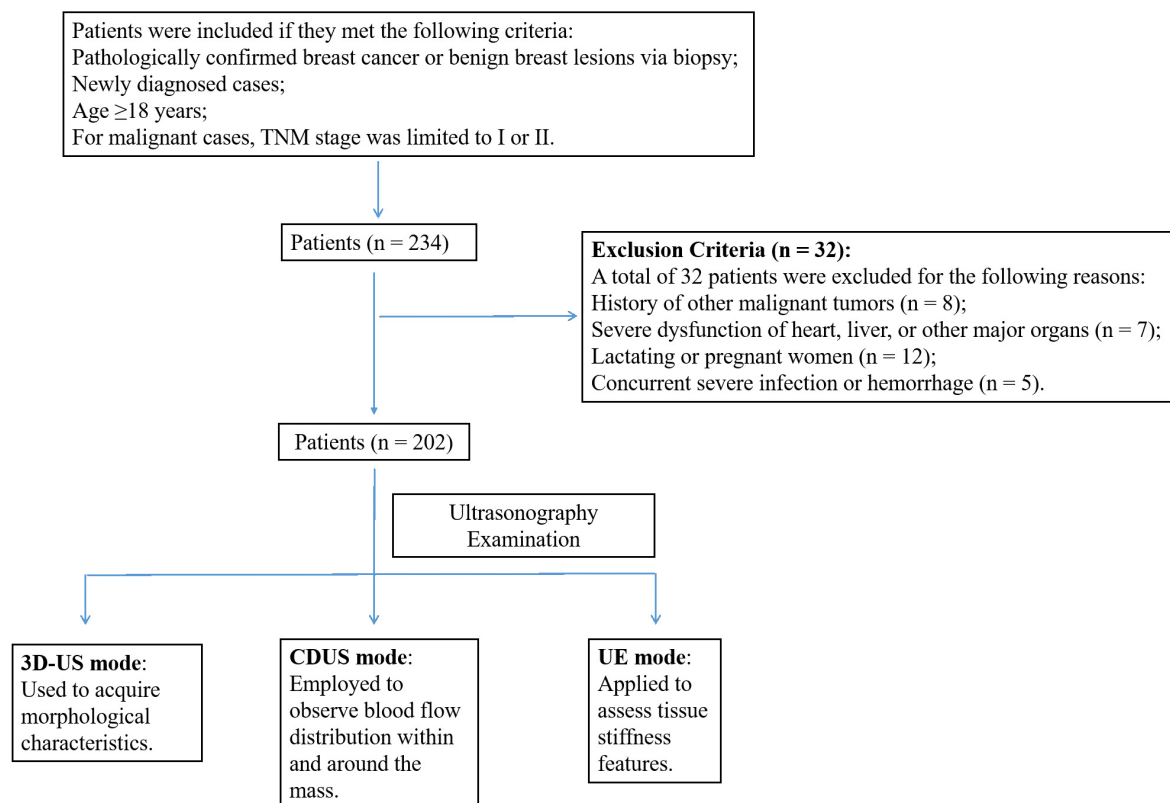


FIGURE 1. Flowchart of participant enrollment. 3D-US: Three-Dimensional Ultrasound; CDUS: Color Doppler ultrasound; UE: Ultrasound Elastography; TNM: Tumor, Node, Metastasis.

breast surface, kept perpendicular to the skin, and moved smoothly and steadily. The morphology, margins, and posterior echogenicity of the lesion were carefully observed. Lymph nodes in both axillae were also scanned, and the lesion's aspect ratio was evaluated in the sagittal plane. Malignant nodules were identified based on the following criteria: irregular morphology, unclear borders, posterior acoustic attenuation, and taller-than-wide orientation (aspect ratio ≥ 1).

2.4.2 CDUS mode

Color Doppler ultrasonography (CDUS) was performed with the pulse repetition frequency (PRF) set between 10 and 15 cm/s. The color gain was adjusted to a level just below the threshold of noise appearance, and the wall filter was set in the range of 50–100 Hz. Blood flow distribution within the mass and its periphery was observed, with the detection of perforating vessels within the lesion considered a positive finding. For hemodynamic parameter measurements, a standardized protocol was followed: the arterial vessel with the highest flow velocity within or around the lesion was selected, and the probe angle was adjusted to maintain a Doppler angle $<60^\circ$ relative to the blood flow direction. The resistive index (RI) was measured continuously over three cardiac cycles, with the mean value recorded as the final result. An RI value >0.7 was defined as a positive indicator of malignancy [7].

2.4.3 UE mode

Strain elastography was performed by the operator using a high-frequency probe, applying gentle and rhythmic manual compression and decompression over the target lesion. Uni-

form, moderate pressure was maintained throughout the procedure, and the built-in pressure indicator bar was monitored in real time to ensure that the applied stress remained within the optimal range (typically corresponding to levels 3–4). Elasticity imaging analysis of the region of interest (ROI) was conducted using a modified 5-point scoring system [8], described as follows: Score 1: The entire lesion is soft and deformable, appearing predominantly green. Score 2: The lesion is largely deformable and exhibits a mosaic pattern of green and blue, with green as the dominant color. Score 3: The central portion of the lesion appears blue, indicating increased stiffness, while the peripheral area remains green. Score 4: The entire lesion appears blue, suggesting high stiffness, with limited green areas at the periphery. Score 5: Both the lesion and the surrounding tissue appear blue, and the lesion exhibits an irregular shape, indicating widespread stiffness. An elasticity score of ≥ 4 was considered indicative of a malignant nodule.

2.4.4 Combined 3-item ultrasound for diagnosis

Combined ultrasound examination was defined as the integration of three ultrasonographic modalities: CDUS, UE, and 3D-US. A result was considered positive if any one of the three modalities indicated features suggestive of malignancy. A result was considered negative only when all three modalities showed no malignant features. This adjudication logic aligns with the design rationale of similar multimodal ultrasound integrated diagnosis studies. With reference to Wang *et al.* [9] on differentiating benign and malignant thyroid nodules, we ultimately adopted the “either-positive” rule as the com-

bined diagnostic criterion to balance diagnostic sensitivity with clinical practicality. A schematic diagram of the multimodal diagnostic workflow is presented in Fig. 2.

2.5 Operator consistency assurance

All six participating specialists (four sonographers and two technicians) completed standardized training prior to the study. The training covered operational protocols for three ultrasound modes, breast segmentation criteria, and image acquisition standards. Only those who passed the qualification assessment were permitted to perform examinations. To ensure operational consistency, a simple random sampling method was used to select 10% of cases for pre-experimental evaluation. The Cohen’s Kappa value for core operational indicators such as probe placement and scanning angle was 0.821, indicating good inter-operator consistency. Additionally, each operator was required to complete an Ultrasound Examination Record Form, documenting examination time, patient positioning, transducer usage, parameter adjustments (or “standard settings” if unmodified), and any anomalies during the procedure. A quality control specialist conducted weekly random audits of these records to ensure adherence to protocol, with an acceptance criterion of $\geq 98\%$ compliance.

2.6 Imaging protocol quality control

A comprehensive quality control system was implemented to ensure the reliability of imaging data. (1) Image Acquisition Quality Control: After each examination, operators performed

an initial review of acquired images before saving. Acceptable images met the following criteria: clear visualization without significant artifacts, complete depiction of the lesion, and measurability of key indicators. (2) Data Storage and Management: All ultrasound images and 3D volume data were stored in the hospital’s Picture Archiving and Communication System (PACS) with restricted access: operators could upload but not modify or delete data; reviewing physicians could view and analyze but not alter original data. Data were uniformly named using the format “Patient ID–Examination Date–Ultrasound Mode” to ensure traceability. (3) Offline Analysis Quality Control: Static images and 3D volume data were independently analyzed by two senior sonographers, each with over 10 years of breast ultrasound experience and no involvement in the initial scans. (4) Inter-Equipment Variability Control: Phantom tests ensured $<5\%$ acoustic velocity deviation, but software algorithm differences were not quantified.

To verify interobserver agreement, a simple random sampling method was used to select 10% of cases (20 cases in total) for consistency testing. Cohen’s Kappa coefficient analysis was applied to assess the nature of lesions (benign/malignant). The results showed a Kappa value of 0.753, indicating good diagnostic agreement between the two observers. In cases of disagreement (*e.g.*, discrepant lesion characterization or $>10\%$ difference in key measurements), a third senior sonographer (≥ 15 years of experience) arbitrated. The final diagnosis was determined by majority rule.

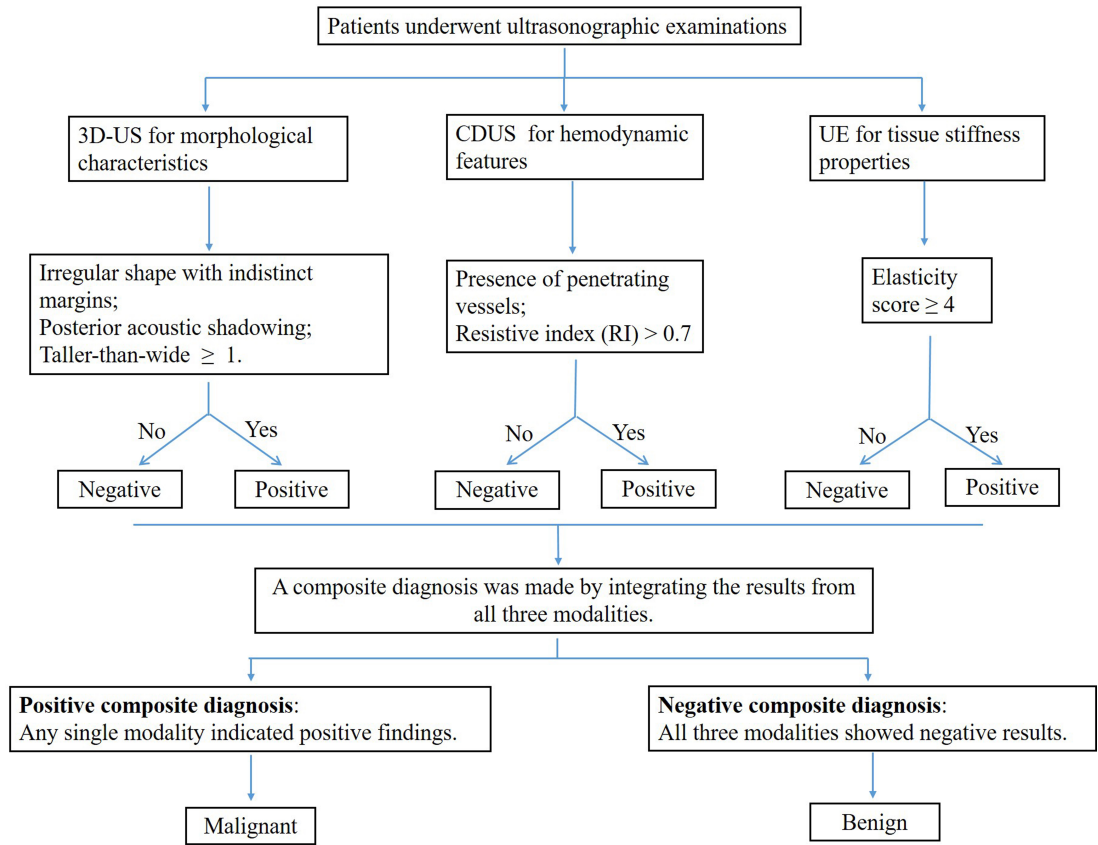


FIGURE 2. Schematic diagram of the multimodal diagnostic workflow. 3D-US: Three-Dimensional Ultrasound; CDUS: Color Doppler ultrasound; UE: Ultrasound Elastography.

2.7 Implementation of blinding in the study

As a retrospective study, double-blinding was applied to minimize bias: clinical information and results from pathology or other imaging modalities were concealed. During case selection, a research assistant extracted patient data from the hospital records, removing all clinical diagnostic details and retaining only basic demographic information. During ultrasound examinations, operators had access solely to the study ID, examination date, and procedure type, with no visibility into clinical symptoms, medical history, or prior test results, thereby ensuring complete blinding to clinical context. In the offline analysis phase, the two senior sonographers could only review ultrasound images and 3D volume data via PACS, with no access to the electronic medical record system. After all ultrasound diagnoses were finalized, the research assistant compared the imaging findings with pathological results to verify the integrity of the blinding process.

2.8 Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess the normality of continuous variables. A p -value > 0.05 indicated a normal distribution. Normally distributed continuous data were expressed as mean $\pm$ standard deviation (SD), and intergroup comparisons were made using the independent samples t -test. For non-normally distributed data, the Mann-Whitney U test was applied. Categorical variables were described as counts (percentages), using the chi-square test or Fisher's exact probability method. Positive and negative predictive values were calculated using the diagnostic 2×2 contingency table. Consistency between diagnostic modalities and pathological findings was assessed using the Kappa statistic. A Kappa value > 0.80 was interpreted as very good agreement, 0.60 – 0.80 as good agreement, and < 0.60 as fair agreement. A p -value < 0.05 was considered statistically significant.

3. Results

3.1 Pathologic examination results

Pathological examination revealed that among the 202 patients with solitary breast nodules, 98 (48.51%) had malignant lesions and 104 (51.49%) had benign lesions. Based on these pathological findings used as the gold standard, patients were categorized into a malignant group ($n = 98$) and a benign group ($n = 104$). There were no statistically significant differences in baseline characteristics such as age, body mass index (BMI), or menopausal status between the two groups ($p > 0.05$; Table 1).

3.2 Sonographic characterization of 3D-US examination

Compared with the benign group, malignant lesions exhibited significantly higher frequencies of irregular morphology, ill-defined margins, posterior acoustic attenuation, and a taller-than-wide orientation (aspect ratio ≥ 1). All differences were statistically significant ($p < 0.05$, Table 2).

3.3 Sonographic characterization of CDUS examination

The presence of perforating arterial supply and the proportion of lesions with a resistive index $RI > 0.7$ were significantly higher in the malignant group compared with the benign group ($p < 0.05$, Table 3).

3.4 Distribution of UE scores

The proportion of patients with ultrasound elastography (UE) scores ≥ 4 was significantly higher in the malignant group compared to the benign group ($p < 0.001$, Table 4), indicating that high UE scores are strongly associated with malignancy.

3.5 Comparison of different ultrasonographic modalities in detecting breast cancer

3D-US examination identified 97 malignant nodules and 105 benign nodules, demonstrating a sensitivity of 78.57%, specificity of 80.77%, positive predictive value (PPV) of 79.38%, negative predictive value (NPV) of 80.00%, and overall accuracy of 79.70%. The agreement with the gold standard was moderate (Kappa = 0.594, $p < 0.001$).

The CDUS modality detected 101 malignant and 101 benign nodules, with a sensitivity of 83.67%, specificity of 81.73%, PPV of 81.19%, NPV of 84.16%, and accuracy of 82.67%, showing good agreement with the gold standard (Kappa = 0.654, $p < 0.001$).

The UE examination identified 98 malignant and 104 benign nodules, demonstrating a sensitivity of 81.63%, specificity of 82.69%, PPV of 81.63%, NPV of 82.69%, and accuracy of 82.18%, also indicating good agreement (Kappa = 0.643, $p < 0.001$).

When all three modalities were combined, diagnostic performance improved significantly, with a sensitivity of 90.82%, specificity of 80.77%, PPV of 81.65%, NPV of 90.32%, and overall accuracy of 85.64%. Agreement with the gold standard was good (Kappa = 0.716, $p < 0.001$; Table 5).

Weekly audits showed 98% compliance, but image quality differences were not quantified.

3.6 Diagnostic performance of multimodal ultrasound combined examination for breast cancer

ROC analysis showed that the area under the curves (AUCs) for diagnosing breast cancer using 3D-US, CDUS, and UE alone were 0.797, 0.827, and 0.822, respectively. The combined diagnostic approach yielded an AUC of 0.858, which was significantly higher than that of each individual modality ($Z = 3.679$, $p < 0.001$; $Z = 1.992$, $p = 0.046$; $Z = 2.248$, $p = 0.025$; Table 6 and Fig. 3).

4. Discussion

Early-stage breast cancer is often asymptomatic and lacks specific clinical manifestations. As the disease progresses, malignant cells may invade surrounding tissues and metastasize to distant organs, leading to significantly reduced survival rates

TABLE 1. Comparison of baseline characteristics between malignant and benign groups.

Parameters	Malignant group (n = 98)	Benign group (n = 104)	t/χ^2	p
Age (yr)	46.55 ± 8.12	44.61 ± 7.42	1.744	0.078
BMI (kg/m ²)	21.45 ± 1.88	21.89 ± 1.75	1.723	0.086
Menopausal Status				
Premenopausal	51 (50.04)	62 (59.62)	1.175	0.278
Postmenopausal	47 (47.96)	42 (40.38)		
Lesion Size				
>2.0 cm	53 (54.08)	43 (41.35)	3.281	0.070
≤2.0 cm	45 (45.92)	61 (58.65)		

BMI: body mass index.

TABLE 2. Sonographic characterization of 3D-US examination in patients with different pathological properties.

Sonographic features (n (%))	Malignant group (n = 98)	Benign group (n = 104)	χ^2	p
Tumor morphology				
Regular	43 (43.88)	89 (85.58)	38.743	<0.001
Irregular	55 (56.12)	15 (14.42)		
Border				
Clear	37 (37.76)	90 (86.54)	51.439	<0.001
Unclear	61 (62.24)	14 (13.46)		
Posterior acoustic attenuation				
Yes	66 (67.35)	12 (11.54)	66.297	<0.001
No	32 (32.65)	92 (88.46)		
Taller-than-wide				
≥1	60 (61.22)	13 (12.50)	51.903	<0.001
<1	38 (38.78)	91 (87.50)		

TABLE 3. Sonographic characterization of CDUS examination in patients with different pathological outcomes.

Sonographic features (n (%))	Malignant group (n = 98)	Benign group (n = 104)	χ^2	p
Penetrating arterial blood supply				
Yes	70 (71.43)	14 (13.46)	69.793	<0.001
No	28 (28.57)	90 (86.54)		
RI				
>0.7	63 (64.29)	13 (12.50)	57.656	<0.001
≤0.7	35 (35.71)	91 (87.50)		

RI: resistance index.

TABLE 4. Comparison of UE score distribution between malignant and benign groups.

Sonographic features (n (%))	Malignant group (n = 98)	Benign group (n = 104)	χ^2	p
UE score				
≥4 points	80 (81.63)	18 (17.31)	73.598	<0.001
1~3 points	18 (18.37)	86 (82.69)		

UE: ultrasound elastography.

TABLE 5. Analysis of the diagnostic efficacy of different ultrasound examinations for breast cancer.

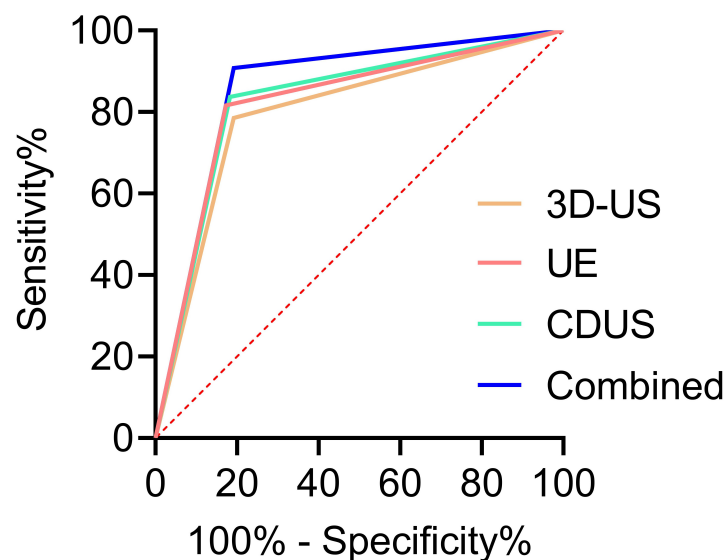
Method	Pathological diagnosis		Total
	Malignant	Benign	
3D-US			
Malignant	77	20	97
Benign	21	84	105
Total	98	104	
CDUS			
Malignant	82	19	101
Benign	16	85	101
Total	98	104	
UE			
Malignant	80	18	98
Benign	18	86	104
Total	98	104	
Combined			
Malignant	89	20	109
Benign	9	84	93
Total	98	104	

3D-US: Three-Dimensional Ultrasound; CDUS: Color Doppler ultrasound; UE: Ultrasound Elastography.

TABLE 6. Diagnostic performance of multimodal ultrasound combined examination for breast cancer.

Methods	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	Youden's index
3D-US	0.797	0.735–0.850	-	78.57 (77/98)	80.77 (84/104)	0.593
CDUS	0.827	0.768–0.876	-	83.67 (82/98)	81.73 (85/104)	0.654
UE	0.822	0.762–0.872	-	81.63 (80/98)	82.69 (86/104)	0.643
Combined	0.858	0.802–0.903	-	90.82 (89/98)	80.77 (84/104)	0.716

3D-US: Three-Dimensional Ultrasound; CDUS: Color Doppler ultrasound; UE: Ultrasound Elastography; AUC: Area under the curve; CI: Confidence Interval.

**FIGURE 3. ROC curves of multimodal ultrasound for diagnosing breast cancer.** 3D-US: Three-Dimensional Ultrasound; CDUS: Color Doppler ultrasound; UE: Ultrasound Elastography.

[10]. Therefore, early screening to detect suspicious lesions followed by precise diagnosis to determine their nature is of paramount importance.

Histopathological examination is the gold standard for breast cancer diagnosis, as it confirms whether a lesion is benign or malignant and allows molecular characterization through tissue biopsy. However, because it is invasive and technically difficult for micro or occult lesions, it is not suitable for routine screening. In recent years, imaging modalities have played a crucial role in breast cancer evaluation, primarily including ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) have become essential in the evaluation of breast cancer. Among these, ultrasonography offers distinct advantages such as ease of operation, high soft-tissue resolution, and excellent reproducibility, allowing for the acquisition of cross-sectional images of the breast with high sensitivity in assessing tumor size and morphology. Furthermore, by evaluating the vascularity of breast lesions, ultrasonography aids in differentiating the nature of breast masses, making it the preferred diagnostic tool for breast cancer.

In the early diagnosis of breast cancer 3D-US examination can present the tumor morphology and structure in three dimensions by acquiring multi-dimensional images such as coronal and sagittal sections of the breast. The main advantage of this technique is its ability to clearly demonstrate the spatial location of the tumor and its relationship with surrounding tissues, and it is particularly useful in capturing features such as irregular morphology and ill-defined borders [11]. However, 3D-US also has limitations, including reduced ability to display microcalcifications and fine intratumoral blood flow signals. These shortcomings may lead to missed or incorrect diagnoses of early breast cancers, thereby affecting diagnostic efficacy [12]. The moderate agreement observed between 3D-US and the pathological gold standard in this study may be attributable to these limitations. CDUS allows visualization of tumor vascularity and assists in differentiating benign from malignant lesions by assessing indicators such as penetrating arterial blood supply and the RI. The results of the study showed that the percentage of patients in the malignant group with perforating arterial blood supply and $RI > 0.7$ was higher than that in the benign group, which reflects the important value of CDUS in assessing tumor angiogenesis. However, CDUS has certain limitations. A study by Alamdaran SA *et al.* [13] reported that CDUS demonstrated a sensitivity of 69% and a specificity of 71% in differentiating malignant from benign thyroid nodules. Its performance is particularly limited in tumors with low vascularity, such as intraductal carcinoma, for which sensitivity may be as low as 68%. Furthermore, the interpretation of blood flow patterns is highly operator-dependent, and subjectivity in grading can lead to diagnostic errors.

UE is an emerging imaging technique that evaluates tissue stiffness to help distinguish between benign and malignant lesions. It provides a visual reference for clinical diagnosis by assigning color codes based on the hardness of the mass [14]. According to a previous study [15], malignant tumors typically exhibit greater stiffness than benign or normal tissues, likely due to abnormal cellular proliferation and excessive fibrous

tissue deposition following malignant transformation.

In this study, a higher proportion of patients with malignant lesions had UE scores ≥ 4 compared to those with benign lesions, consistent with findings reported by Zhou *et al.* [16]. However, some degree of misclassification was observed. This may be attributable to factors such as rapid tumor growth, large tumor volume, insufficient blood supply, or central liquefaction and necrosis, all of which can lead to heterogeneity in lesion stiffness. As a result, portions of the tumor, particularly the center may exhibit lower elasticity, thereby reducing the accuracy of the UE scoring system. Moreover, the inherent heterogeneity of breast cancer, including uneven distribution of internal tissue hardness, further complicates elasticity assessment and may contribute to diagnostic variability.

Given that each ultrasonography technique has its own advantages and limitations in the early diagnosis of breast cancer, this study further investigated the diagnostic value of combining multiple ultrasound modalities. Our findings demonstrated that the multi-modal ultrasound approach achieved a diagnostic accuracy of 85.64%, showing good agreement with the gold standard ($Kappa = 0.716$). These findings suggest that integrating three ultrasound techniques can leverage the strengths of each modality while compensating for their individual limitations. Specifically, 3D-US provides three-dimensional morphological information, CDUS evaluates tumor vascularity through hemodynamic assessment, and UE reflects differences in tissue stiffness. Together, these complementary parameters offer a more comprehensive representation of the biological features of tumors. This integration enhances the clinical utility of ultrasound, offering detailed information on tumor size, location, vascularity, and elasticity. Such data can assist surgeons in planning more precise surgical approaches and aid radiation oncologists in tailoring individualized radiotherapy plans. Inspired by predictive models used in agriculture, such as crop disease prediction systems that integrate multidimensional data (*e.g.*, climate, soil conditions, and crop growth) and apply machine learning techniques like random forests or neural networks to improve predictive performance, future exploration of machine learning for multimodal integration.

This study did not include a formal Patient and Public Involvement (PPI) component. (1) Study Design: This was a retrospective analysis of existing clinical and imaging data. The study design and protocol were developed based on the review of patient records. Due to the retrospective nature of the study, prospective patient involvement in the planning phase was not feasible. (2) Primary Research Focus: The primary aim of this study was to technically evaluate and compare the diagnostic performance of different ultrasound modalities. This analysis was conducted using imaging and pathological data obtained after all patient procedures were completed, with no prospective interventions or patient-facing components. (3) Practical Constraints: As a single-center, data-focused study, there were no direct patient interactions, recruitment activities, or opportunities to incorporate patient input during the study period. In future related studies, we plan to take the following steps to enhance patient and public involvement: (1) Consultation: Engage with patient advocates or representatives from breast cancer support groups during the study design phase to ensure alignment with patient priorities and values.

(2) Dissemination: Collaborate with patient representatives to develop lay summaries of our findings and disseminate the results in an accessible format more accessible to the wider patient community.

However, this study has several limitations. (1) The retrospective design (March 2022–October 2024) may introduce biases in patient selection, data completeness, and blinding procedures. Despite anonymization and independent analysis (2.7), incomplete medical records and potential blinding gaps may persist. Future research should aim to expand the sample size, conduct multicenter prospective studies, and include patients with diverse characteristics to more comprehensively evaluate the value of combining multiple ultrasound modalities in the early diagnosis of breast cancer. (2) Although daily calibration of all devices followed standardized manufacturer protocols, variations in calibration phantoms may have led to subtle differences in baseline parameters such as acoustic velocity and resolution among devices, potentially introducing additional uncertainty into the results. (3) No formal interobserver agreement analysis (*e.g.*, Kappa between sonographers) was conducted, potentially limiting diagnostic reproducibility. Future studies should include such analyses. (4) Given the biomechanical differences in male breast tissue, the diagnostic performance observed in this study cannot be directly extrapolated to male patients, and the value of multimodal ultrasound for this population requires separate validation. (5) Although a unified probe (L6-15, 4–12 MHz) was used, differences in calibration, software algorithms, and image quality across ultrasound systems (Siemens, Mindray, GE) may impact elastography and 3D imaging accuracy, particularly in stiffness assessment and volumetric reconstruction. (6) Histopathological confirmation within two weeks of ultrasound enhanced diagnostic accuracy but may reflect local practice rather than a universal standard, limiting generalizability.

5. Conclusions

The combined application of multiple ultrasonographic modalities shows strong clinical applicability in diagnosing solitary breast nodules and early-stage breast cancer in female patients. However, further targeted studies are needed to validate its diagnostic value in cases involving multiple nodules, advanced-stage disease, and male patients. Prospective multicenter studies with interobserver agreement analyses are needed to validate multimodal ultrasound's clinical value.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YS—designed the study and carried them out. YS, FSZ—supervised the data collection; prepared the manuscript for publication and reviewed the draft of the manuscript. YS, FSZ, XMZ, YZ, HSW—analyzed the data. YS, FSZ, XMZ, YZ—

analyzed and interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the Wuxi People's Hospital (Approval No. KY25113). Written informed consent was obtained from legally authorized representatives for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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