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Dual contrast-enhanced ultrasound for diagnosing pathologic nipple discharge associated with papillary lesions

Yanchun Zhao[1,2†], Songsong Wu[2†], Zhongtao Bao[3], Yucheng Lin[4], Ziwei Xu[2], Xing Chen[5], Lingpeng Tang[2] and Guorong Lyu[1*]

Abstract

Background The goal of this research study is to determine the efficacy of dual contrast-enhanced ultrasound (US) in evaluating ductal papillary lesions associated with pathological nipple discharge.

Methods A prospective multicenter study was conducted between January 2020 and December 2022. All participants were examined using dual contrast-enhanced US and had re-adjustment of BI-RADS classification. Genuine ductal papillary lesions were identified using US features and subsequently subjected to biopsy or excision. Using pathological results and clinical follow-up as the reference standard as a standard reference, we compared the diagnostic efficacy of dual contrast-enhanced US to conventional US in detecting papillary lesions.

Results The study included 102 female participants ranging in age from 29 to 80 years (average 47.6 ± 9.4), of whom 87 were retained for analysis. We precisely localized discharging ducts with papillary lesions in 85 patients, with 68 showing varying degrees of enhancement in papillary lesions. Compared to conventional US, dual contrast-enhanced US was more accurate in locating and detecting papillary lesions ($P < 0.001$). The optimized BI-RADS classification allowed for a more informed prediction of the malignancy risk associated with papillary lesions. Multivariate logistic regression analysis revealed that ductal continuity, the boundary between the nodule and duct, and peak intensity are independent risk factors for malignancy. The area under the curve for detecting malignant papillary lesions was 0.937.

Conclusions Dual contrast-enhanced US is effective at precisely locating lactiferous ducts in pathological nipple discharge, detecting and differentiating papillary lesions, and improving the accuracy of BI-RADS classification.

Keywords Nipple discharge, Contrast-enhanced ultrasonography, Papillary lesion, Diagnostic efficacy

†Yanchun Zhao and Songsong Wu contributed equally to this work.

*Correspondence:
Guorong Lyu
lgr_feus@sina.com
[1]Department of Ultrasound, The Second Affiliated Hospital of Fujian Medical University, Licheng District, Quanzhou, Fujian 362000, China
[2]Department of Ultrasonography, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou, China
[3]Department of Ultrasound, The First Affiliated Hospital of Fujian Medical University, Fuzhou, China
[4]Department of Medical Ultrasonics, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Maternity and Child Health Hospital, Fujian Medical University, Fuzhou, China
[5]Department of Basic Surgery, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou, China

Introduction

Pathological nipple discharge (PND) is a common symptom found in 2 to 10% of breast pathology patients in clinical settings [1]. Approximately 80% of PND cases involve benign lesions caused by intraductal papillary lesions or secretory breast diseases such as plasma cell mastitis, mammary duct ectasia, and fibrocystic changes [2]. While benign papillomas are the most common papillary lesions, the spectrum includes atypical papillomas, in situ papillary carcinoma, ductal carcinoma in situ, and invasive ductal carcinomas, among other malignancies [3]. Thus, PND is now recognized as one of the risk factors for breast cancer. Between 5% and 21% of patients with PND were also diagnosed with breast cancer [4, 5]. Consequently, it is critical to recognize genuine papillary lesions and accurately distinguish between benign and malignant conditions.

The use of mammography, ultrasound (US), galactography, magnetic resonance imaging (MRI), and fiberoductoscopy separately provides distinct and differentiating diagnostic value in cases of PND [6]. Breast US is frequently the preferred method for PND due to its cost-effectiveness, convenience, and noninvasive nature. However, because of the nonspecific ultrasonographic features, malignant papillary lesions are difficult to distinguish from benign ones. Thus, the integration of multiple technologies may be required to improve diagnostic accuracy [7]. As is widely acknowledged, traditional X-ray galactography is capable of accurately locating and identifying intraductal lesions [8]. Furthermore, research using the contrast agent SonoVue in experimental rabbit mammary glands has been conducted, with a focus on investigating intraductal drug delivery in breast cancer [9]. Drawing on these findings, we propose administering the contrast agent SonoVue into the lactiferous duct via the discharge nipple, a novel technique we call ultrasound galactography (USG), to achieve precise diagnostic localization. Furthermore, contrast-enhanced ultrasound (CEUS) has emerged as a valuable imaging modality capable of effectively visualizing microcirculation perfusion within papillary lesions, thereby increasing diagnostic specificity [10]. Hence, it is reasonable to expect that combining USG and CEUS for PND can meet both localization and qualitative diagnostic value requirements [11]. This innovative combination is known as dual CEUS (D-CEUS). There has been no prior study on the diagnostic utility of D-CEUS in PND with breast ductal lesions, making it a promising area for future research.

Materials and methods

Patients and design

This prospective multicenter study included clinical diagnosis and treatment activities for eligible patients between January 2020 and December 2022. Participants were recruited through the US departments of three comprehensive medical centers: Fujian Provincial Hospital, The Second Affiliated Hospital of Fujian Medical University, and The First Affiliated Hospital of Fujian Medical University. The current study was approved by the scientific and ethical committee of Fujian Provincial Hospital (No. K2020-03-128). Furthermore, all participating patients gave written informed consent.

Patients were selected based on the definition of PND: Women with unilateral, spontaneous, and bloody or serous discharge, usually arising from a single duct orifice of the nipple [1]; aged ≥ 18 years old; conventional US revealing ductal lesions or suspicious duct-related findings. Exclusion criteria included patients within one-year post-pregnancy or breastfeeding, those with milky or green discharge, and conditions such as nipple inversion, intolerable pain, ductal narrowing, or blockage near the nipple due to a lesion.

D-CEUS image acquisition and analysis

All participants underwent bilateral breast US examinations, including a thorough examination of the nipple-areolar complex area [12]. The study documented ductal dilation, the type of discharge, and the presence of papillary lesions. In cases of multiple unilateral breast lesions, the largest one was chosen for the study. Lesions < 3 cm from the nipple were classified as central, while those ≥ 3 cm from the nipple were considered peripheral. Breast lesions were classified using the analytical criteria of the ACR Breast Imaging-Reporting and Data System (BI-RADS) [13].

Both conventional US and D-CEUS were performed on Philips EPIQ5 and Philips EPIQ7 color Doppler ultrasonography machines (Philips Healthcare, Bothell, USA) equipped with L18-5 (5–18 MHz) and L9-3 (3–9 MHz) linear transducers. For CEUS, the mechanical index was set to 0.06–0.08, gain to 100–120 dB, single focus, and image depth of about 3–4 cm. Real-time dual imaging was used in contrast mode.

For D-CEUS, the application involved diluted SonoVue (Bracco Suisse SA). At the start of the procedure, 5 mL of normal saline was mixed thoroughly with SonoVue lyophilized powder and shaken for 20 s before being set aside. Initially, USG was performed with the patient in a supine position, and the area around the nipple and areola was disinfected twice with povidone-iodine. Gentle pressure applied from the periphery to the nipple around the areola caused discharge, which was then wiped away with a cotton swab. The procedure involved injecting a solution of SonoVue suspension, diluted at a 1:30 ratio with saline, into the discharging nipple. A 27G blunt needle attached to a 5-mL syringe was inserted into the discharge hole, and contrast medium (0.5–1 mL) was gradually injected until the patient experienced slight

discomfort or resistance. Following needle withdrawal, the nipple was covered with a disposable patch and US imaging was performed. Ten minutes later, CEUS was performed, involving an intravenous injection of 4 mL of SonoVue suspension through the elbow vein. The entire USG and CEUS procedures were recorded in 3-minute video clips for later review.

Based on previous clinical experience and research, we chose the most clinically significant US features to observe in D-CEUS [10, 14, 15]. The procedure entailed documenting the position of the ductal system using the clock method, observing the smoothness of the duct wall, ductal continuity, nodular growth direction, the boundary between nodule and duct, and the shape of the nodule. CEUS observations included peak intensity, vascularity signs, enhancement scope, and a perfusion defect.

The proposed BI-RADS classification standard for D-CEUS was presented as follows: Category 1: no ductal dilation before galactography; imaging revealed smooth and continuous ductal walls with no papillary lesions; Category 2: ductal dilation before galactography; after imaging, smooth and continuous ductal walls were observed, with no papillary lesions; or there was filling material in the mammary duct but no enhancement; Category 3: the duct wall was thickened, rough, twisted, and devoid of papillary lesions, or the duct wall was smooth and continuous with papillary lesions (maximum diameter ≤ 10 mm and patient's age ≤ 50 years old), showing homogeneous or heterogeneous hypoenhancement, isoenhancement, and lacks malignant enhancement features. Category 4: an indeterminate type between Categories 3 and 5, was classified according to the number of high-risk factors and malignant signs combined with papillary lesions. Papillary lesions combined with one item were classified into Category 4a, with two items into Category 4b, and with three items into Category 4c. Category 5: ductal papillary lesions combined with at least one high-risk factor and three malignant signs or has ≥ 4 malignant signs. Malignant signs included interrupted and twisted mammary ducts, longitudinal growth of nodules, unclear boundaries between nodules and ducts in USG, heterogeneous hyper-enhancement or isoenhancement in CEUS, enlarged enhancement scope, the presence of perfusion defects, internal vascularity signs, or peripheral "crab-claw-like" enhancement. High-risk factors included a lesion with a maximum diameter > 10 mm, age > 50 years, and bloody discharge.

Participant's management

Patients with PND underwent follow-up, biopsy, or surgical intervention based on the determined risk level during the examination. In the case of surgical intervention, methylene blue dye was intraductally injected to ensure localization before surgery. If follow-up was selected, patients underwent sonography and/or mammographya every 6 months for 1 to 2 years or until the discharge resolved, whichever came first [16]. In cases where the discharge persisted for more than two years, diagnostic surgical excision was recommended.

Reference standard

The final diagnosis for each participant was determined based on pathological results or comprehensive clinical follow-up. All ductal papillary findings from pathology were considered positive, while nonpapillary lesions were classified as negative. According to the ACR BI-RADS 5th Edition [13], the malignant probabilities associated with the various BI-RADS classifications were as follows: Category 2: benign, malignancy possibility 0%; Category 3: possibly benign, malignancy possibility < 2%; Category 4a: low suspicious malignancy, malignancy possibility > 2% but ≤ 10%; Category 4b: moderately suspicious of malignancy, malignancy possibility > 10% but ≤ 50%; Category 4c: highly suspicious of malignancy, malignancy possibility > 50% but < 95%; Category 5: highly suggestive of malignancy, malignancy possibility ≥ 95%. Using pathological results as the gold standard, the true malignant incidence rate of each subcategory of the D-CEUS BI-RADS classification was determined.

Statistical analysis

All statistical analyses were conducted using SPSS software (version 23.0), and receiver operating characteristic (ROC) curves were created with MedCalc 19.5.6 statistical software. Normally distributed quantitative data were presented as mean ± standard deviation (X ± S). Intergroup comparisons were made using independent sample t-tests. Categorical data were expressed as frequency (%) and analyzed using chi-square tests or Fisher's exact test. D-CEUS feature parameters that were significant in univariate logistic regressions were included in multivariate logistic regression models to create ROC curves. A significance level of $P < 0.05$ was considered statistically significant.

Results

Study participants

The study initially enrolled 102 eligible female participants, aged 29–80 years (average 47.6 ± 9.4). Throughout the study, eight participants dropped out due to duct needle failure, three continued to have serous discharge for at least a year and declined further examination or surgery, and four were lost to follow-up. Ultimately, 87 participants successfully completed the study. None of the participants experienced significant pain, allergic reactions, bleeding, infection, or increased discharge. Pathological results were obtained for 76 cases, which

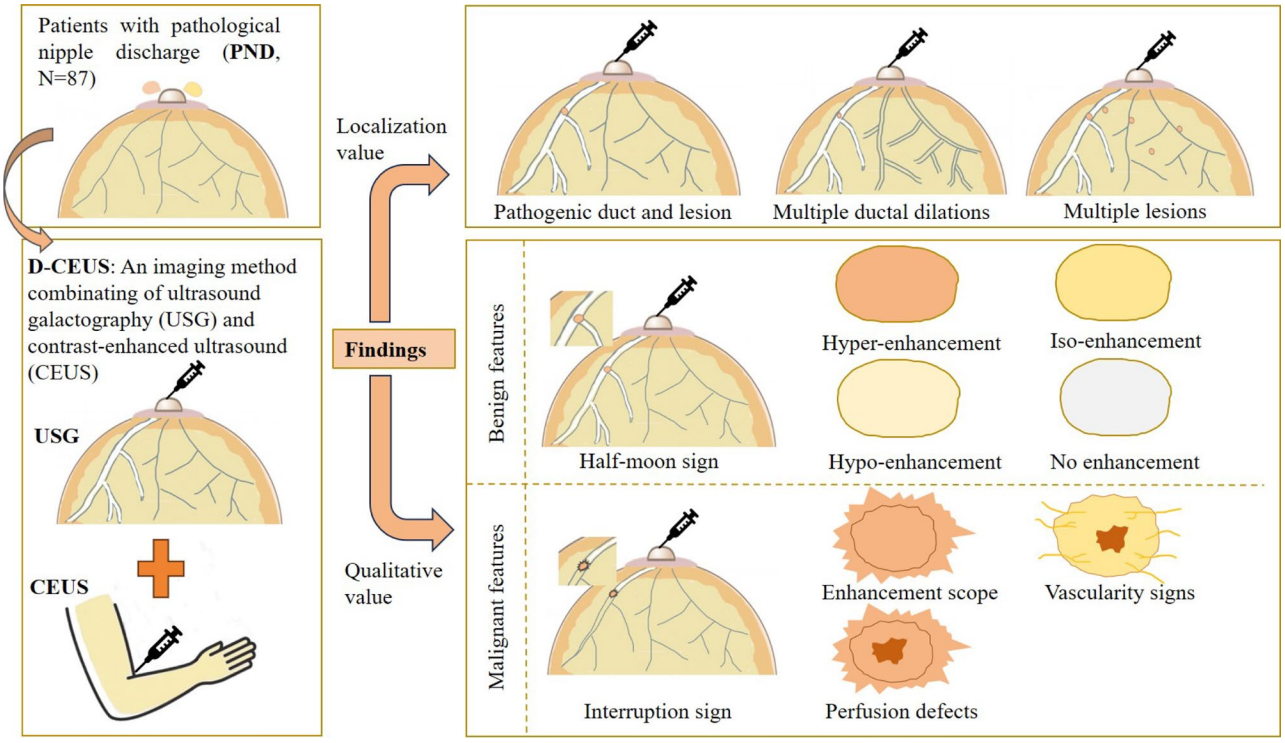

Fig. 1 The graphical abstract of this study

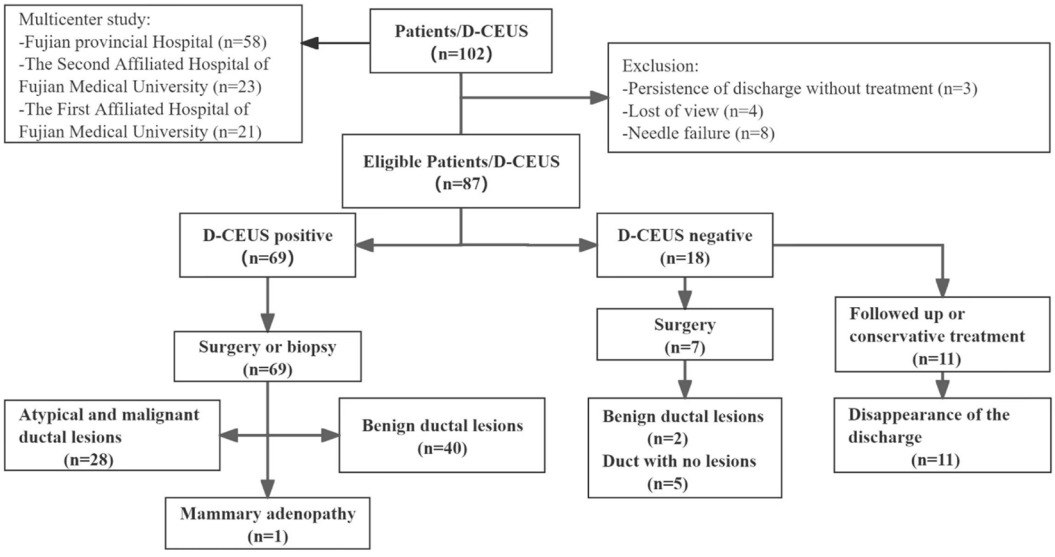

Fig. 2 A flow chart of the study process

included 43 benign papillary lesions (such as benign papillomas, nipple adenomatosis, and inflammatory granuloma), 6 atypical lesions (atypical papilloma, atypical ductal hyperplasia), and 22 malignant lesions (including papillary carcinoma, ductal carcinoma in situ, invasive ductal carcinoma). Furthermore, five cases had no ductal papillary lesions. Eleven participants who did not have surgery were followed up for 12–26 months (median 15.7 months), with nipple discharge spontaneously resolving in some cases (Figs. 1 and 2). The study included atypical lesions in the malignant group to acknowledge their high risk of cancer progression [17].

Baseline data comparison between D-CEUS and conventional US

Conventional US revealed ductal ectasia in addition to ductal lesions in 31 cases, with multiple ductal dilations seen in 12 of these cases. Furthermore, 57 cases showed

Table 1 Baseline features of patients with PND

Characteristics *N* = 87	Benign *N* = 59 (%)	Atypical or Malignant *N* = 28 (%)	χ^2	*P*-Value
Age, y, M (Q25, Q75)	50.0 (36.0, 53.0)	51.5 (47.5, 59.0)	2.56	0.011
≤ 50	40 (67.8)	13 (46.4)	3.64	0.046
> 50	19 (32.2)	15 (53.6)		
Location				
Central	38 (64.4)	15 (53.6)	1.65	0.199
Peripheral	21 (35.6)	13 (46.4)		
Size, mm, M (Q25,Q75)	8.6 (7.6, 11.0)	11.7 (8.8, 15.5)	2.90	0.004
≤ 10	39 (66.1)	10 (35.7)	7.13	0.008
> 10	20 (33.9)	18 (64.3)		
Discharge color				
Bloody	10 (16.9)	11 (39.3)	5.17	0.023
Non-bloody	49 (83.1)	17 (60.7)		
Ductal ectasia				
Present	24 (40.7)	7 (25.0)	2.04	0.154
Absent	35 (59.3)	21 (75.0)		
Lactation history				
Yes	53 (89.8)	24 (85.7)	0.32	0.574
No	6 (10.2)	4 (14.3)		

suspicious duct-related lesions (single or multiple) in the conventional US (Table 1).

Detection accuracy of papillary lesions between conventional US and D-CEUS

In the study, USG precisely localized the pathogenic duct in 85 cases, while conventional US accurately localized 71 cases, indicating a statistically significant difference in localization capabilities between the two methods ($P < 0.001$). Particularly in cases with multiple lesions, USG effectively identified the target lesion. Pathological results confirmed that 70 of the 87 patients with PND had ductal lesions. The accuracy of conventional US in detecting whether PND was associated with papillary lesions was 73.5% (64/87), whereas D-CEUS was 96.6% (84/87). The accuracy difference between the two methods for identifying the presence or absence of ductal lesions in patients with PND was statistically significant ($P < 0.001$). D-CEUS accurately detected papillary lesions in 68 cases of patients with PND, with 2 cases remaining undetected (1 case of intraductal papilloma and 1 case of adenoma, both with a diameter ≤ 5 mm). Additionally, one case was misdiagnosed as an intraductal lesion when it was actually sclerosing adenosis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of D-CEUS in detecting papillary lesions were 97.1%, 94.1%, 98.6%, and 88.9%, respectively.

Comparison of BI-RADS classification results between conventional US and D-CEUS

Based on sonographic findings, the BI-RADS classification results for conventional US and D-CEUS are shown in Table 2. Following D-CEUS examination, 69 cases showed varying degrees of enhancement in ductal lesions (BI-RADS 3 to 5), with 15 cases having multiple lesions within the involved ductal systems (≥ 2 lesions) and the largest diameter between 3.7 and 23 mm (average 10.8 ± 3.6 mm). In ten cases, intraductal fillings were found without enhancement (BI-RADS 2); six cases showed normal glandular hyperplasia compressing the duct or glandular lesions within adjacent ducts after ductal contrast that were not ductal papillary lesions (BI-RADS 2); and two cases showed ductal distortion and wall thickening without focal occupancy after USG (BI-RADS 3).

Analysis of imaging features for benign and atypical or malignant papillary lesions

The correlation between sonographic features and the benign or malignant nature of 68 papillary lesions was outlined in Table 3. Five imaging features observed on USG (smoothness of the duct wall, ductal continuity, nodular growth direction, nodule-duct boundary and nodule shape) and four enhancement features on CEUS (peak intensity, vascularity signs, perfusion defect, and enhancement scope) showed significant differences between benign and atypical or malignant papillary lesions ($P < 0.05$). The imaging features of benign papillary lesions on D-CEUS were depicted in Fig. 3, demonstrating that the contrast agent can form a semi-circular pattern around the lesion, resulting in a "half-moon sign."

Table 2 Comparison of BI-RADS classification results between conventional US and D-CEUS in PND patients

BI-RADS	Conventional US			D-CEUS		
	Benign (*N* = 59)	Atypical or malignant (*N* = 28)	Malignancy risk	Benign (*N* = 59)	Atypical or malignant (*N* = 28)	Malignancy risk
2	0	0	/	16	0	0%
3	8	0	0%	15	0	0%
4a	26	7	21.2%	20	2	9.1%
4b	21	10	32.3%	6	5	45.5%
4c	4	8	66.7%	2	10	83.3%
5	0	3	100%	0	11	100%

Table 3 Sonographic features on D-CEUS between benign and atypical or malignant papillary lesions

Sonographic features	Benign *N* = 40 (%)	Atypical or Malignant *N* = 28 (%)	χ^2	*P*-Value
Duct wall				
Smooth	35 (87.5)	16 (57.1)	8.10	0.004
Thickened/rough	5 (12.5)	12 (42.9)		
Ductal continuity				
Continuous	37 (92.5)	9 (32.1)	27.42	< 0.001
Interrupted	3 (7.5)	19 (67.9)		
Growth direction				
Paralleled	39 (97.5)	20 (71.4)	9.75	0.002
Longitudinal	1 (2.5)	8 (28.6)		
Nodule-duct boundary				
Clear	37 (92.5)	10 (35.7)	24.88	< 0.001
Blurred	3 (7.5)	18 (64.3)		
Nodule shape				
Regular	27 (67.5)	11 (39.3)	5.32	0.021
Irregular	13 (32.5)	17 (60.7)		
Enhancement mode				
Hypo-enhancement	17 (42.5)	2 (7.1)	14.80	0.001
Iso-enhancement	12 (30.0)	6 (21.4)		
Hyper-enhancement	11 (27.5)	20 (71.4)		
Vascularity signs				
Present	2 (5.0)	10 (35.7)	13.13	< 0.001
Absent	38 (95.0)	18 (64.3)		
Perfusion defects				
Present	5 (12.5)	17 (60.7)	17.49	< 0.001
Absent	35 (87.5)	11 (39.3)		
Enhancement scope				
Enlarged	1 (2.5)	16 (57.1)	26.23	< 0.001
Not enlarged	39 (97.5)	12 (42.9)		

In contrast, malignant lesions may present with signs such as thickened duct walls, disruption of duct continuity, and distortion (Fig. 4).

The imaging features with statistically significant differences between the benign and malignant groups were analyzed using multivariate logistic regressions. Table 4 summarizes the variable assignments for each feature parameter. Multiple collinearity tests were performed on these variables, and the variance inflation factor for all variables was less than 3, indicating that there was no multicollinearity between the variables. The multivariate logistic regression analysis identified three independent risk factors for malignancy: duct continuity, the boundary between nodule and duct, and peak intensity. These three variables, chosen using stepwise regression, were used to build a new multivariate logistic regression model (Table 5).

Evaluating the ability of D-CEUS feature parameters to predict the benign or malignant nature of PND

To further assess the predictive capability of ductal continuity, the nodule-duct boundary, and peak intensity (including hyper-enhancement and isoenhancement) for malignant papillary lesions, we created ROC curves for each of these feature parameters, both individually and in combination. We evaluated the diagnostic value of these parameters using ROC curves (Fig. 5). As a result, the areas under the curves (AUC) for these features were 0.801, 0.784, and 0.754, respectively. The multivariate logistic regression model, simplified to "ductal continuity + boundary + peak intensity" (AUC_{ROC} = 0.937, 95% CI: 88.54–98.87%), outperformed univariate logistic regression models and had a higher area under the ROC curve.

Discussion

By leveraging insights from galactography and fiberoptic ductoscopy techniques [1, 18], our study improves standardized operational procedures. First, we refined the injection needle. A 27G blunt-tip needle with a finer inner diameter (0.4 mm) was chosen for easier entry into the mammary duct. This modification significantly improved patient comfort, simplified the procedure, and eliminated the need for anesthesia and warming lamp irradiation. The success rate of USG was 78.4%, which exceeded the reported success rate of 70.2% for ductoscopic examinations [1]. Second, the study used diluted SonoVue as the contrast agent for USG, which enabled real-time dual imaging in contrast mode. This method allowed for better differentiation between ductal lesions and surrounding glandular tissues, especially in cases without concurrent ductal dilation or multiple ductal lesions. Compared to existing imaging methods, such as traditional X-ray galactography with low specificity, technical challenges, contrast agent allergies, and radiation exposure [19, 20], and ductoscopy with invasive issues, blind spots, susceptibility to damage, and low applicability rates [21–23], D-CEUS does not have such shortcomings. It provides economical simplicity, safety, non-invasive characteristics, freedom from radiation, and real-time imaging capabilities.

In our successful imaging cases, 97.7% (85/87) correctly identified the pathogenic duct. Notably, the accuracy of locating the pathogenic duct significantly exceeded that of conventional US by 81.6% (71/87), indicating a statistically significant difference ($P < 0.001$). Among the 70 pathologically confirmed ductal lesions, D-CEUS correctly identified 68 cases and ruled out 16 suspected ductal lesions initially diagnosed by conventional US, resulting in an impressive diagnostic accuracy of 96.6% (84/87). When compared to conventional US, D-CEUS significantly enhances diagnostic efficacy in detecting

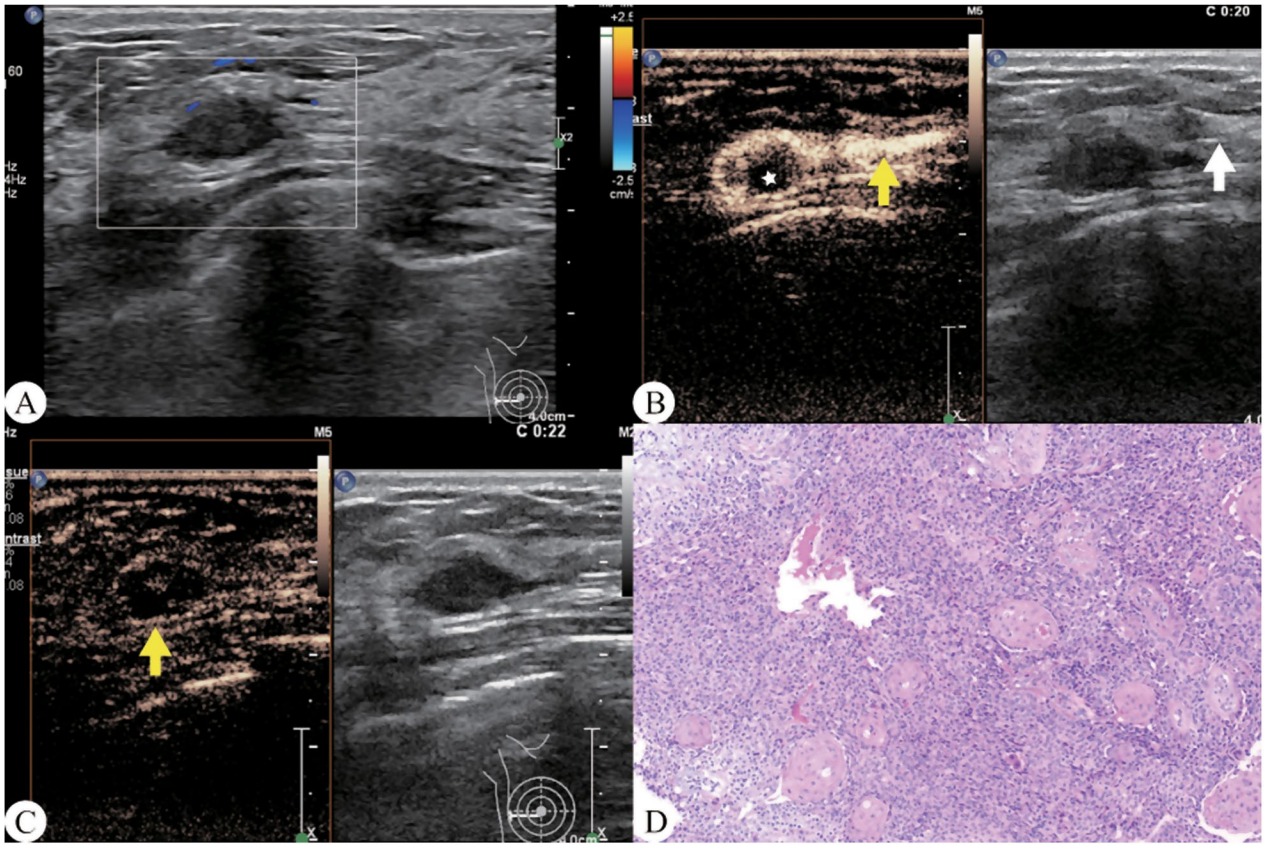

Fig. 3 A patient presented with serous discharge from the right breast for one month. A Breast ultrasound revealed a hypoechoic nodule at 9 o'clock of the right breast, 30 mm from the nipple. The relationship between this nodule and the duct and discharge was unclear. B Ultrasound galactography clearly showed a continuous duct communicating with the nodule (yellow arrow), with the contrast agent surrounding half of the nodule (star). However, visualizing the discharge duct in two-dimensional mode remained challenging (white arrow). C CEUS showed the hypoechoic nodule exhibiting heterogeneous hypo-enhancement (arrow). D Pathology identified the lesion as an intraductal papilloma

active papillary lesions ($P < 0.001$), with sensitivity, specificity, PPV, and NPV of 97.1%, 94.1%, 98.6%, and 88.9%, respectively. Moreover, our previous study on using contrast-enhanced MRI for identifying active intraductal lesions in PND found diagnostic sensitivity and specificity of 96% and 85%, respectively [15]. Our findings indicate that D-CEUS, with its increased sensitivity and specificity, is comparable to the diagnostic capabilities of contrast-enhanced MRI, making it an important tool for screening papillary lesions in the context of lactiferous duct imaging.

The classification of breast lesions using BI-RADS has become an important step in clinical practice. This systematic categorization not only helps to predict malignancy risk but also guides appropriate management strategies. Noteworthy observations from classification results highlight a potential flaw in the conventional US, especially in the BI-RADS 4a category, where the actual malignancy rate (21.2%) exceeds the expected ACR BI-RADS range (>2% and ≤10%). This discrepancy may result in the underestimation of some malignant lesions, emphasizing the need for more accurate classification tools. In contrast, the malignancy probabilities for all categories classified by D-CEUS fall within the expected ACR BI-RADS ranges, making it a more reliable classification tool than conventional US. This accurate classification not only helps to make appropriate treatment decisions but also helps to avoid unnecessary interventions. D-CEUS classified 52.5% (31/59) of benign lesions as BI-RADS 2 or 3. We believe that for lesions classified as BI-RADS 1, 2, or 3 by D-CEUS, short-term lumpectomy may be unnecessary. Imaging follow-up for 1 year or longer could be a safe alternative, as suggested by ACR BI-RADS guidelines. Lesions classified as ≤3 can be observed over time, while those categorized as ≥4a require biopsy or surgery [13]. In patients with PND caused by benign lesions, around 80% of cases resolve spontaneously within two years [16]. In this study, 11 cases were discharged either conservatively or during follow-up, highlighting the potential of D-CEUS in facilitating a more nuanced and less invasive approach to managing benign lesions associated with PND. This

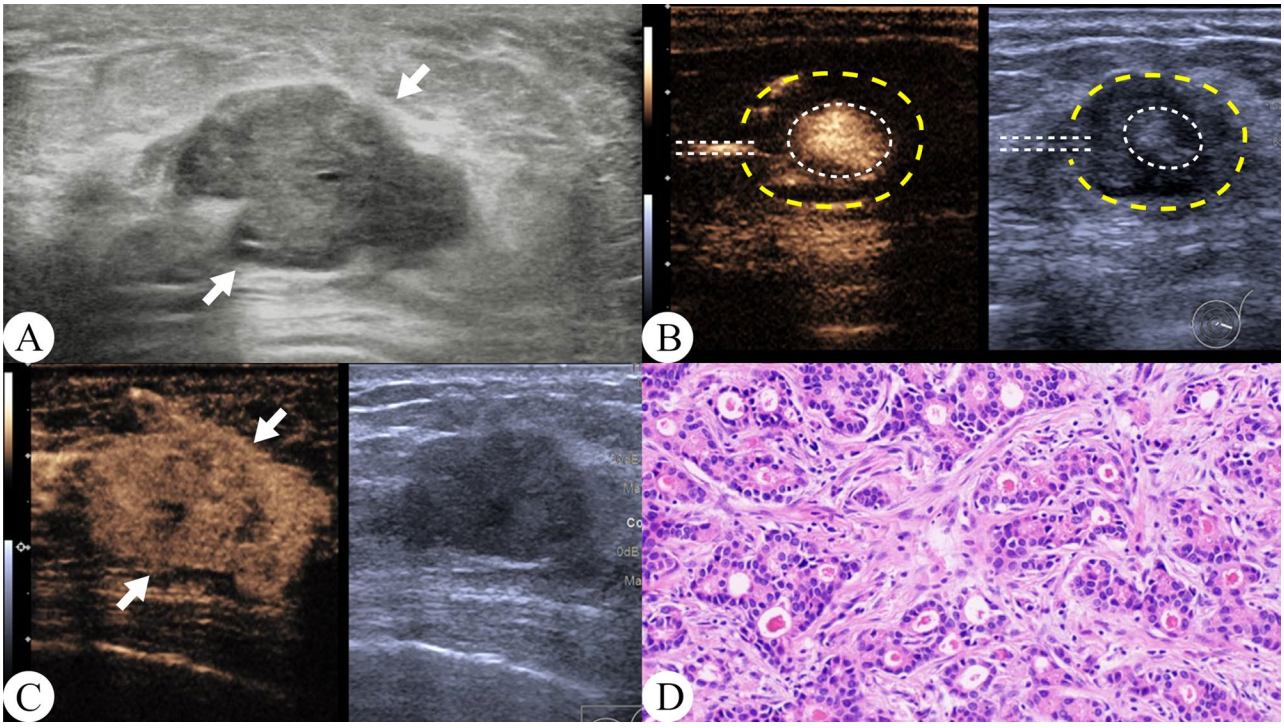

Fig. 4 A patient presented with serous discharge from the left breast for two days. A Breast ultrasound revealed a hypoechoic nodule at the 3 o'clock position of the left breast. The relationship between this nodule and the duct was unclear. B USG revealed twisted ductal structures with lesions infiltrating outward along the ducts. C CEUS showed the nodule exhibiting heterogeneous hyper-enhancement and an enlarged enhancement scope (arrow). D Pathology identified the lesion as an invasive ductal carcinoma

Table 4 Assignment of variables and results of multicollinearity diagnosis in multifactorial binary logistic regression analysis

D-CEUS feature parameters	Variable assignments description	VIF
Smoothness of duct wall	0 = smooth;1 = thickened/rough	1.65
Ductal continuity	0 = continuous;1 = interrupted	2.44
Nodular growth direction	0 = paralleled;1 = longitudinal	1.54
Nodule-duct boundary	0 = clear;1 = blurred	2.17
Nodule shape	0 = irregular;1 = regular	1.68
Peak intensity	0 = hypo-enhancement; 1 = iso-enhancement;2 = hyper-enhancement	1.23
Vascularity signs	0 = absent;1 = present	1.60
Perfusion defects	0 = absent;1 = present	1.73
Enhancement scope	0 = not enlarged;1 = enlarged	2.86

suggests that for lesions with negative results, a short-term lumpectomy may be unnecessary, and imaging follow-up for a year or more may be a safe alternative [24].

Furthermore, our study discovered statistically significant factors—patient age > 50 years and lesion size exceeding 10 mm—that distinguish between benign from atypical or malignant ductal lesions. This finding is consistent with reports in the existing literature [25, 26]. Furthermore, the bloody discharge lesions have a strong association with malignancy, a conclusion which is supported by the research of Ahn et al. as well [17, 27]. Our findings also showed that ductal continuity, the nodule-duct boundary, and peak intensity are independent risk factors for malignancy. The combined diagnostic efficacy of these three features, as measured by an AUC of 0.937, demonstrated high diagnostic efficiency. The pathological basis for these malignant signs may be angiogenic factor-driven infiltration into surrounding tissues in malignant tumors [28]. Conversely, in benign lesions, the contrast agent formed a semi-circular pattern around the lesion, resulting in a distinct "half-moon sign". This finding is one of the most distinguishing features, providing important information about the separation between the lesion and the duct.

Limitations

This multicenter prospective study represents a pioneering effort in combining USG and CEUS for the comprehensive evaluation of patients with PND, enhancing diagnostic specificity through microvascular imaging features. However, our study has some limitations. Firstly,

Table 5 Multivariate logistic regression analysis

Variable	β	SE	Wald	*P*-Value	OR	95%CI
Ductal continuity	2.71	0.93	8.36	0.004	15.12	2.40-95.25
Nodule-duct boundary	3.03	1.16	6.79	0.009	20.66	2.12-201.46
Peak intensity (hyper-enhancement)	4.20	1.60	6.93	0.008	66.73	2.92-1522.62
Peak intensity (iso-enhancement)	3.23	1.63	3.93	0.047	25.32	1.04-618.34

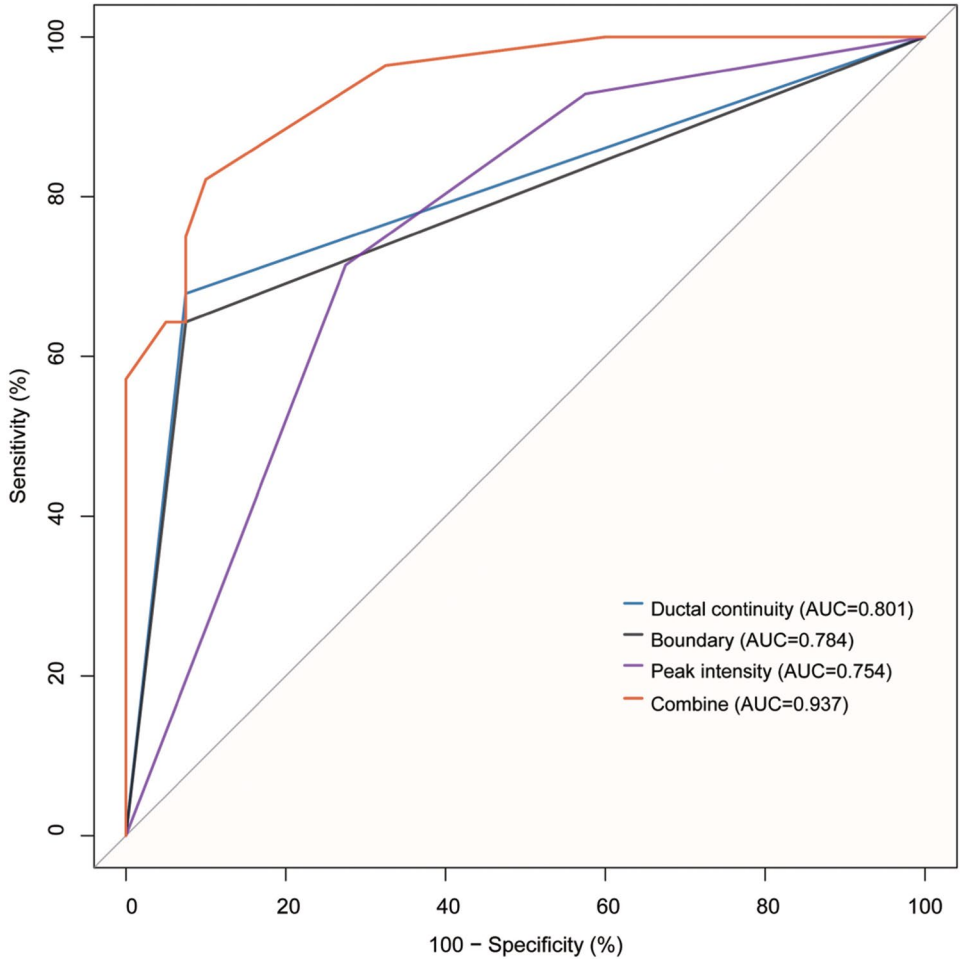

Fig. 5 ROC curve analysis of the diagnostic value of 4 models in papillary lesions

D-CEUS is only applicable in cases where conventional US reveals ductal lesions or suspicious duct-related findings, for patients without detectable lesions, additional imaging modalities are required. Furthermore, the complexity of lesion morphology and individual variability has hindered the establishment of a unified quantitative standard, a common challenge in the field. In future studies, we plan to explore artificial intelligence-based quantitative analysis methods to improve the objectivity and reproducibility of our assessments. Ultimately, as an exploratory study, the current research may have some degree of selection bias in the study population. In the future, we plan to expand the sample size to validate the findings.

Conclusions

This study emphasizes the clinical value of D-CEUS in elucidating the etiology of PND and distinguishing benign, atypical, and malignant papillary lesions. A multifactorial analysis identified three parameters associated with malignancy, and a prediction model based on these features demonstrated superior diagnostic accuracy compared to any single D-CEUS parameter. We also look forward to conducting further comparative studies with the currently authoritative diagnostic method, fiberoptic

ductoscopy, to explore its potential advantages and clinical value.

Abbreviations

D CEUS	Dual contrast-enhanced ultrasound
CEUS	Contrast enhanced ultrasound
PND	Pathological nipple discharge
ROC	Receiver operating characteristic
AUC	Area under the curve
NPV	Negative predictive value
PPV	Positive predictive value

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Author contributions
Yanchun Zhao and Songsong Wu conceived the study, collected the data, and drafted the manuscript. Yucheng Lin and Ziwei Xu designed the study, edited the manuscript and pictures. Zhongtao Bao and Lingpeng Tang processed data and contributed to drafting the manuscript. Guorong Lyu provided critical revisions for important intellectual content in the manuscript. Xing Chen assisted with data collection. All authors contributed to the article and approved the submitted version.

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Data availability
The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request. Please contact the corresponding author (lgr_feus@sina.com).

Declarations

Ethics approval and consent to participate
The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Fujian Provincial Hospital. Written informed consent was obtained from individual or guardian participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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