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Original Article

Ultrasonography in granulomatous mastitis: diagnostic differentiation, treatment response, and prognostic value

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Abstract: Objective: This study aimed to evaluate the diagnostic value of ultrasonography in distinguishing granulomatous mastitis (GM) from ductal carcinoma in situ (DCIS), and to assess its prognostic relevance in monitoring treatment response and predicting recurrence. Methods: In this retrospective study, we analyzed conventional B-mode ultrasound and contrast-enhanced ultrasound (CEUS) features in 146 patients with histologically confirmed GM and 140 with DCIS. Key comparisons included: (1) B-mode characteristics (lesion morphology, posterior acoustic features, microcalcifications, vascular patterns, etc.); (2) CEUS quantitative parameters [mean transit time (mTTI), time to peak, rise time, etc.]. Clinical treatment responses and recurrence data were also collected for GM patients. Results: GM exhibited distinct ultrasound characteristics compared to DCIS, including more frequent posterior acoustic enhancement (58.90% vs. 12.14%), absence of microcalcifications (82.19% vs. 49.29%), and a higher prevalence of marginal or mixed vascular patterns (83.02% vs. 73.34%) (all $P < 0.001$). On CEUS, GM demonstrated shorter mTTI but higher peak enhancement, wash-in, and wash-out rates than DCIS (all $P < 0.001$). Among the GM cohort, 121 of 146 patients achieved clinical cure. These cured patients had significantly lower pretreatment mTTI values ($P < 0.001$), and mTTI demonstrated predictive value for treatment response (area under the ROC curve = 0.765; sensitivity: 68.0%, specificity: 86.0%). During one-year follow-up, 15 of the 121 cured patients experienced recurrence (12.40%). The presence of ductal dilatation on ultrasound was associated with a higher recurrence rate. Conclusion: Ultrasound, particularly when combined with CEUS parameters, not only facilitates the differentiation of GM from DCIS but also serves as a valuable tool for evaluating treatment response and predicting recurrence in GM patients.

Keywords: Granulomatous mastitis, ductal carcinoma in situ, ultrasound examination, differential diagnosis, evaluation of curative effect, prognosis assessment

Introduction

Granulomatous mastitis (GM) is a chronic inflammatory condition that predominantly affects the lobules of the breast and is often characterized by granuloma formation [1]. The incidence of GM varies by ethnicity and geographic region, with higher prevalence reported in the Mediterranean and certain developing Asian countries [2]. It is widely accepted that GM is driven by immune mechanisms involving both humoral and cell-mediated responses [3]. Studies have identified abundant cluster of differentiation 3 (CD3), CD4, and CD8 lymphocytes in GM lesions, underscoring the pivotal role of cell-mediated immunity in its pathogenesis [4]. The presence of CD79a-positive lymphocytes further suggests a contributory role of humoral immunity [4]. GM is considered a localized autoimmune disease, and the favorable response to corticosteroids and immunosuppressive agents provides additional support for the immunological hypothesis [5].

Due to the clinical and imaging similarities between GM and ductal carcinoma in situ (DCIS), accurate differentiation based solely on clinical judgment or suboptimal imaging techniques remains challenging, often resulting in diagnostic uncertainty or misdiagnosis [6]. With recent advancements, ultrasonography has significantly improved diagnostic accuracy by providing detailed information on lesion morphology, vascularity, and echogenic features, thus aiding in distinguishing GM from DCIS [7, 8].

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Although ultrasound plays a well-established role in the differential diagnosis of GM, its utility in evaluating treatment response and monitoring disease recurrence has not been fully elucidated. The potential of ultrasonography for treatment assessment and early relapse detection represents an emerging area of clinical interest and research focus. Therefore, we conducted a retrospective study to investigate the clinical value of ultrasound, including both conventional and contrast-enhanced techniques in the differential diagnosis of GM, evaluation of treatment efficacy, and prediction of disease recurrence.

Materials and methods

Case selection

This retrospective study was approved by the Ethics Committee of The Sixth People's Hospital of Hengshui. Clinical data from 146 GM patients (GM group) and 140 DCIS patients (DCIS group) admitted to The Sixth People's Hospital of Hengshui from March 2022 to December 2023, were reviewed.

Inclusion criteria: GM group: (1) Diagnosis of GM based on established criteria [9], and confirmed by pathology; (2) Female patients with unilateral, solitary lesions; (3) Complete clinical data, including imaging, treatment, and follow-up; (4) Treatment with corticosteroids combined with surgery and follow-up duration ≥ 1 year. DCIS group: (1) Diagnosis of DCIS based on established criteria [10], and confirmed by pathology; (2) Unilateral, solitary lesions; (3) Complete imaging records.

Exclusion criteria (both groups): (1) Severe heart, liver, kidney, or other major organ dysfunction; (2) Significant consciousness disorders; (3) Severe hematologic or autoimmune diseases; (4) History of breast surgery; (5) Pregnancy or lactation.

Ultrasonic examination method

Serial ultrasound evaluations were performed at standardized timepoints: (1) baseline (pre-treatment), (2) preoperatively, and (3) during follow-up at 1, 3, 6, and 12 months post-treatment. Each session included conventional B-mode and contrast-enhanced ultrasound (CEUS) to assess treatment response and detect recurrence.

Examinations were performed using a Siemens Acuson Sequoia 512 color Doppler system equipped with a high-frequency linear array probe (2.9-9.9 MHz). Patients were placed in a supine position with both breasts and axillae exposed. A coupling agent was applied, and fan-shaped scans were conducted centered on the nipple, including transverse and longitudinal views to visualize lesion morphology and its relationship to surrounding tissue. The following features were recorded: lesion size, shape, location, margins, echogenicity, calcifications, vascularity, and ipsilateral axillary lymph nodes.

For CEUS, the imaging software was activated, and 2.4 mL of SonoVue (Bracco, Italy) was administered intravenously via the antecubital vein, followed by a 5.0 mL saline flush. The enhancement process was observed for no less than 3 minutes, and dynamic video recordings were saved in DICOM format for quantitative analysis using VueBox software.

The region of interest (ROI) was manually delineated in the largest cross-sectional area of the lesion, including: the entire lesion (red), lesion interior (purple), and a reference area (yellow) at the same depth, with a circular ROI diameter of approximately 7 mm.

Quality control was ensured with a factor of > 75%. The time-intensity curve was fitted automatically, and CEUS parameters were extracted, including: time to peak (TTP), mean transit time local (mTTl), rise time (RT), fall time (FT), peak enhancement (PE), wash in rate (WiR), and wash out rate (WoR).

GM treatment (glucocorticoid + surgical treatment)

Patients received oral methylprednisolone (Pfizer Italia S.r.l.) before surgery at an initial dose of 0.5 mg/kg/day, taken once daily in the morning. Breast ultrasound was performed every two weeks to monitor treatment response. Dosage was tapered by 2 mg every two weeks. If significant lesion shrinkage was observed, the dose was reduced by 2 mg weekly until a maintenance dose of 16 mg/day was reached. Surgery was scheduled once the mass had regressed and inflammation had subsided.

Surgical procedure: Under general anesthesia with endotracheal intubation, the patient was placed in the supine position. After routine disinfection and draping, preoperative ultrasound was used to localize the lesion. An appropriate incision was chosen based on lesion location. The surgeon performed layered dissection of skin and subcutaneous tissue, resecting the mass along with a 1 cm margin of surrounding tissue. Intraoperative frozen section analysis was used to assess residual disease.

If necessary, additional tissue was excised to ensure complete removal of the lesion and inflamed surrounding tissue. The cavity was irrigated with saline, and hemostasis was achieved using electrocautery. Drainage was placed, and the incision was closed with absorbable sutures in a subcuticular fashion. A sterile dressing was applied postoperatively. After surgery, the patient was transferred to the post-anesthesia care unit and later returned to the ward for further monitoring.

Data collection

All ultrasound images were retrieved from the hospital system in original DICOM format for re-evaluation. Two physicians, each with over five years of experience in breast ultrasonography, independently reviewed the images in a double-blinded manner. Lesion characteristics were documented using standardized BI-RADS terminology, including shape, margins, posterior acoustic features, microcalcifications, and other parameters. For each patient, key CEUS parameters (RT, mTTI, TTP, etc.) were measured three times, and the average value was used for analysis to ensure data accuracy. A quality control team randomly audited 20% of the cases, with measurement errors maintained within 5%.

Evaluation index and criterion

Differential diagnosis of GM and DCIS: (1) Comparison of conventional ultrasound features between the GM and DCIS groups, including lesion morphology, margins, posterior echoes, and microcalcifications. (2) Comparison of CEUS quantitative parameters between both groups, including RT, mTTI, TTP, FT, PE, WiR, and WoR.

Evaluation of treatment efficacy in GM: According to the 2021 International Multidisciplinary Consensus on the Management of Granulomatous Lobular Mastitis [11], treatment outcomes were categorized into three levels based on symptom resolution, local inflammation, and ultrasound findings.

Clinical cure: Complete resolution of symptoms, no palpable lesions, and disappearance of the lesion on ultrasound. On physical examination, no hard masses are detected, and there is no discernible boundary between the lesion and surrounding glandular tissue.

Improvement: Partial symptom relief with occasional, mild, non-disruptive pain. No obvious palpable masses; ultrasound may show post-operative changes or mild residual inflammation, but the original lesion is no longer visible.

Ineffective: Poor wound healing, persistent symptoms, local bleeding or exudation, significant pain, palpable masses, and ultrasound evidence of ongoing inflammation.

Patients classified as “clinical cure” were included in the cured group (n = 121), while those classified as “improvement” or “ineffective” were included in the non-cured group (n = 25). Ultrasound features and CEUS parameters were compared between the two groups.

Evaluation of short-term recurrence in GM: Recurrence was defined as the reappearance of clinical signs - such as redness, swelling, warmth, pain, abscess, or ulceration - within one year following clinical cure. Recurrence could also be indicated by the appearance of a new lesion on ultrasound, confirmed by fine-needle aspiration cytology or histopathology. GM patients were divided into a recurrence group (n = 15) and a non-recurrence group (n = 106).

Ultrasound features and CEUS parameters were compared between the two groups to assess the role of ultrasonography in predicting short-term recurrence.

The overall study flow is illustrated in **Figure 1**.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 (IBM Corp., USA). Continuous vari-

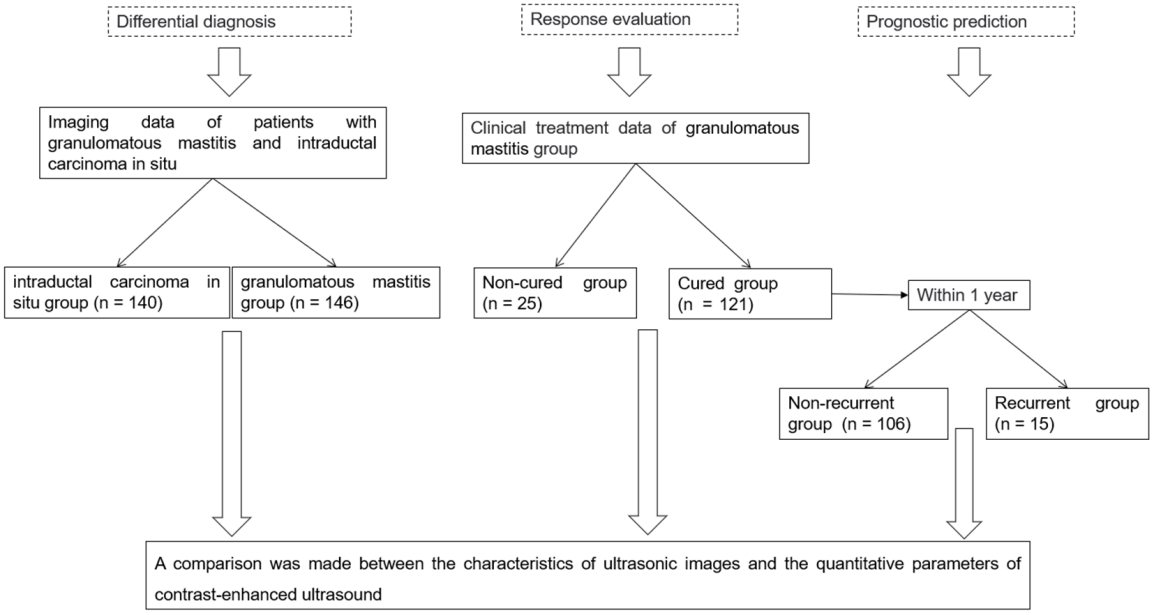

Figure 1. Research process.

Table 1. Comparison of baseline data between the GM and DCIS groups (*M* ± *SD, n%*)

Variables		GM group (n = 146)	DCIS group (n = 140)	t/χ^2	P
Age (years)		50.99 ± 5.82	51.75 ± 5.82	1.099	0.273
Duration of disease (month)		12.42 ± 2.04	12.34 ± 2.38	0.285	0.776
Smoking history	Yes	48 (32.88)	57 (10.71)	1.890	0.169
Drinking history	Yes	59 (40.41)	63 (10.00)	0.615	0.433
Working condition	Brainwork	42 (28.77)	35 (10.00)	2.331	0.507
	Manual labour	58 (39.73)	68 (10.57)		
	Unemployed	20 (13.70)	17 (10.14)		
	Else	26 (17.81)	20 (10.29)		
Residence	City	34 (23.29)	28 (10.00)	0.752	0.687
	Town	43 (29.45)	47 (10.57)		
	Countryside	69 (47.26)	65 (10.43)		

Notes: GM, granulomatous mastitis; DCIS, ductal carcinoma in situ.

ables were expressed as mean ± standard deviation (M ± SD), and independent-samples t-tests were used for between-group comparisons. Categorical variables were presented as counts and percentages [n (%)], and chi-square (χ^2) tests were used for comparison. Receiver Operating Characteristic (ROC) curves were constructed, and the Area Under the Curve (AUC), sensitivity, and specificity were calculated to evaluate the diagnostic performance of ultrasound in assessing treatment response and predicting recurrence. A calibration curve was also generated to validate model performance. A two-sided *P* value < 0.05 was considered statistically significant.

Results

Comparison of baseline data between GM and DCIS groups

There were no significant differences in baseline variables such as age, disease duration, smoking status, alcohol use, occupation, or place of residence between the GM and DCIS groups (all P > 0.05, **Table 1**).

Table 2. Comparison of conventional ultrasonic characteristics between the GM and DCIS groups [*n* (%)]

Ultrasound features	GM group (n = 146)	DCIS group (n = 140)	χ^2	P
Lesion morphology			1.036	0.309
Regular	16 (10.96)	21 (15.00)		
Irregularity	130 (89.04)	119 (85.00)		
Edge of the lesion			0.001	0.976
Smooth	67 (45.89)	64 (45.71)		
Irregular (blurred/angled/spiked)	79 (54.11)	76 (54.29)		
Echo behind the lesion			147.244	< 0.001
No change	8 (5.48)	10 (7.14)		
Enhanced	86 (58.90)	17 (12.14)		
Reduced	13 (8.90)	108 (77.14)		
Mixed change	39 (26.71)	5 (3.57)		
Ductal dilation			0.455	0.500
Yes	34 (23.29)	28 (20.00)		
No	112 (76.71)	112 (80.00)		
Microcalcifications			34.528	< 0.001
Yes	26 (17.81)	71 (50.71)		
No	120 (82.19)	69 (49.29)		
Increased echogenicity of surrounding tissues			63.085	< 0.001
Yes	104 (71.23)	34 (24.29)		
No	42 (28.77)	106 (75.71)		
Vascular supply pattern			155.440	< 0.001
No	20 (13.70)	54 (38.57)		
Internal vascularity	3 (2.05)	67 (47.86)		
Peripheral vascularity	75 (51.37)	19 (13.57)		
Combined vascularity	48 (32.88)	0 (0.00)		
Axillary lymph node enlargement			144.782	< 0.001
Yes	108 (73.97)	6 (4.29)		
No	38 (26.03)	134 (95.71)		

Notes: GM, granulomatous mastitis; DCIS, ductal carcinoma in situ.

Comparison of conventional ultrasonic characteristics between GM and DCIS groups

The GM group more frequently exhibited posterior acoustic enhancement or mixed changes, whereas the DCIS group tended to show posterior attenuation. The incidence of microcalcifications was significantly lower in the GM group. Peripheral tissue enhancement - particularly at lesion margins - was more commonly observed in the GM group. Vascular patterns also differed: GM lesions primarily exhibited peripheral or mixed blood supply, while DCIS lesions tended to have internal or no detectable vascularization. Axillary lymph node enlargement was more common in the GM group ($P < 0.05$, **Table 2**).

Comparison of CEUS quantitative parameters between the GM and DCIS groups

Quantitative parameters: Compared to the DCIS group, the GM group had significantly lower mTTI and significantly higher PE, WiR, and WoR (all $P < 0.05$, **Table 3**).

Comparison of conventional ultrasonic features between the cured and non-cured groups

There were no significant differences in conventional ultrasound features-such as lesion morphology, margin, posterior acoustic features, ductal dilation, or microcalcifications-between the cured and non-cured groups (all $P > 0.05$, **Table 4**).

Table 3. Comparison of quantitative parameters of contrast-enhanced ultrasound between the GM and DCIS groups (*M* ± *SD*)

Parameters	GM group (n = 146)	DCIS group (n = 140)	*t*	*P*
RT (s)	8.06 ± 2.24	8.26 ± 1.74	0.827	0.409
mTTI (s)	45.68 ± 5.36	52.41 ± 5.62	10.349	< 0.001
TTP (s)	12.74 ± 3.65	13.20 ± 2.94	1.177	0.240
FT (s)	16.45 ± 3.78	17.04 ± 3.52	1.367	0.173
PE (a.u)	2716.54 ± 245.32	1745.24 ± 214.23	35.604	< 0.001
WiR (a.u)	412.28 ± 53.21	268.36 ± 44.12	24.941	< 0.001
WoR (a.u)	214.53 ± 26.75	136.54 ± 22.87	26.541	< 0.001

Notes: RT, rise time; mTTI, mean transit time local; TTP, time to peak; FT, fall time; PE, peak enhancement; WiR, wash in rate; WoR, wash out rate; GM, granulomatous mastitis; DCIS, ductal carcinoma in situ.

Comparison of CEUS quantitative parameters between the cured and non-cured groups

In contrast, mTTI was significantly lower in the cured group than in the non-cured group (P < 0.05, **Table 5**). ROC analysis demonstrated an AUC of 0.765 (95% CI: 0.664-0.886), with a sensitivity of 0.680 and specificity of 0.860 (**Figure 2A**). Calibration curve analysis using bootstrap validation revealed a mean absolute error of 0.072, indicating good agreement between predicted and actual treatment outcomes (**Figure 2B**).

Ultrasound features and short-term prognosis in GM

Among the 121 patients classified as cured, 15 experienced recurrence within one year, resulting in a recurrence rate of 12.40%. Ductal dilation was significantly more common in the recurrence group than in the non-recurrence group (P < 0.05, **Table 6**).

Comparison of CEUS quantitative parameters between the recurrence and non-recurrence groups

There were no statistically significant differences in CEUS parameters-including RT, mTTI, TTP, FT, PE, WiR, and WoR-between the recurrence and non-recurrence groups (all P > 0.05, **Table 7**).

Discussion

When analyzing the ultrasound characteristics of GM and DCIS, we found that most GM lesions exhibited posterior acoustic enhancement, likely due to localized inflammation or abscess formation. Typically, GM lesions appear confluent, with inflammatory cell infiltration observed in the lobules, interlobular ducts, and periductal areas. In some cases, abscesses are also present within the lobules.

Alikhassi et al. [12] reported that the most common sonographic finding in GM is an irregular, heterogeneous, poorly defined hypoechoic mass or pseudocyst. Similarly, Kiyak et al. [13] identified heterogeneous parenchyma, irregular hypoechoic masses, and abscess formation as typical features. GM generally presents on ultrasound as an ill-defined, hypoechoic region with associated inflammatory changes or abscess formation.

Our findings also show that microcalcifications are rare in GM but common in DCIS. Both conditions may be associated with neovascularization, which increases vascular permeability and promotes calcium salt deposition, contributing to the formation of microcalcifications. Jiang et al. [14] reported that 65.2% of DCIS patients had calcifications detectable by ultrasound. Gosling et al. [15] studied the morphology of microcalcifications across different histopathological subtypes, revealing structural differences in calcification crystals between benign lesions, DCIS, and invasive malignancies. They suggested that alterations in the local microenvironment, such as angiogenesis, cell death, and immune responses, may influence crystal formation, contributing to the observed differences among lesion types.

In summary, GM and DCIS display distinct sonographic features. GM typically presents as an irregular hypoechoic mass with abscess formation, whereas DCIS more often manifests with microcalcifications. These differences can provide important diagnostic clues in clinical practice.

In addition, our study found that GM often presents with peri-lesional edema and increased echogenicity. Vascular patterns also differ: GM lesions tend to exhibit peripheral or mixed vas-

Table 4. Comparison of conventional ultrasonic features between the cured and non-cured groups [*n* (%)]

Ultrasound features	Cure group (n = 121)	Non-cured group (n = 25)	χ^2	P
Lesion morphology			0.034	0.855
Regular	13 (10.74)	3 (12.00)		
Irregularity	108 (89.26)	22 (88.00)		
Edge of the lesion			0.043	0.835
Smooth	56 (46.28)	11 (44.00)		
Irregular (blurred/angled/spiked)	65 (53.72)	14 (56.00)		
Echo behind the lesion			0.364	0.948
No change	7 (5.79)	1 (4.00)		
Enhanced	10 (8.26)	16 (64.00)		
Reduced	11 (9.09)	2 (8.00)		
Mixed change	33 (27.27)	6 (24.00)		
Ductal dilation			0.183	0.669
Yes	29 (23.97)	5 (20.00)		
No	92 (76.03)	20 (80.00)		
Microcalcifications			2.141	0.143
Yes	19 (15.70)	7 (28.00)		
No	102 (84.30)	18 (72.00)		
Increased echogenicity of surrounding tissues			0.770	0.380
Yes	88 (72.73)	16 (64.00)		
No	33 (27.27)	9 (36.00)		
Vascular supply pattern			2.343	0.504
No	17 (14.05)	3 (12.00)		
Internal vascularity	3 (2.48)	0 (0.00)		
Peripheral vascularity	59 (48.76)	16 (64.00)		
Combined vascularity	42 (34.71)	6 (24.00)		
Axillary lymph node enlargement			0.064	0.800
Yes	89 (73.55)	19 (76.00)		
No	32 (26.45)	6 (24.00)		

Table 5. Comparison of quantitative parameters of contrast-enhanced ultrasound between the cured and non-cured groups (*M* ± *SD*)

Parameters	Cure group (n = 121)	Non-cured group (n = 25)	*t*	*P*
RT (s)	7.98 ± 2.29	8.44 ± 1.92	0.929	0.354
mTTI (s)	44.93 ± 4.96	49.32 ± 5.84	3.904	< 0.001
TTP (s)	12.87 ± 3.66	12.12 ± 3.61	0.932	0.353
FT (s)	16.36 ± 3.74	16.92 ± 4.04	0.678	0.499
PE (a.u)	2725.58 ± 238.93	2672.80 ± 275.25	0.979	0.329
WiR (a.u)	415.37 ± 53.62	397.32 ± 49.46	1.552	0.123
WoR (a.u)	214.83 ± 26.90	213.08 ± 26.46	0.298	0.766

Notes: RT, rise time; mTTI, mean transit time local; TTP, time to peak; FT, fall time; PE, peak enhancement; WiR, wash in rate; WoR, wash out rate.

cularity, while DCIS lesions typically show absent or purely internal vascular flow. These findings are consistent with the underlying pathology. GM is characterized by granuloma formation and inflammation centered around the terminal ductal lobular units, often manifesting as multifocal lesions, abscesses, or sinus tracts [16]. Alikhassi et al. [12] noted that about 50% of GM cases show tubular extensions, connecting bands, and tunnel-like structures on ultrasound, all closely associated with inflammation. Inflammatory changes contribute to breast tissue congestion, resulting in perilesional edema, enhanced echogenicity, and

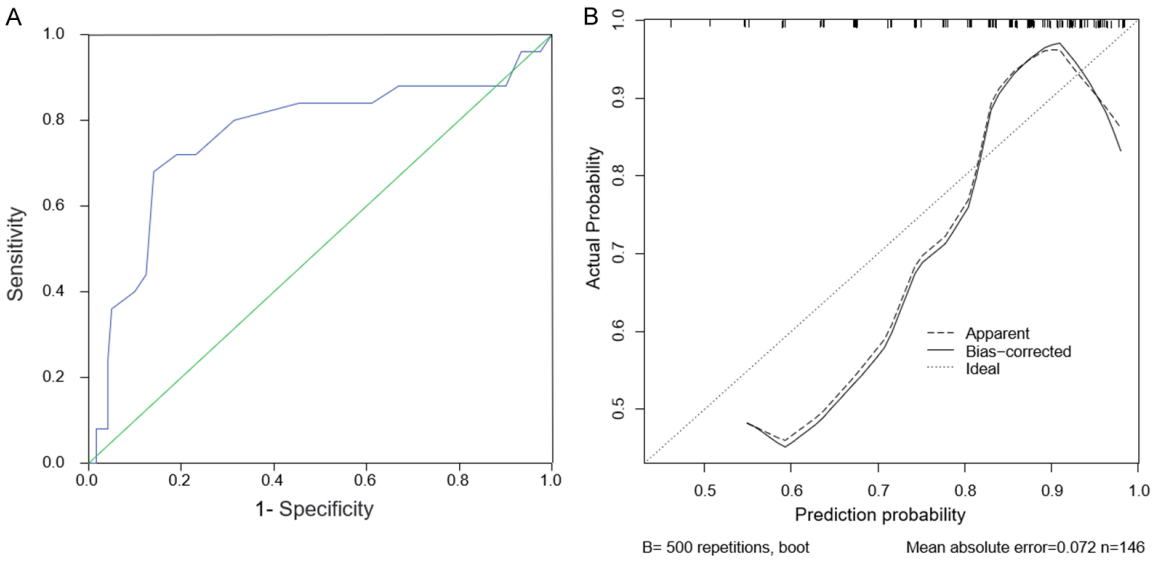

Figure 2. Mean transit time local (mTTI) evaluation of therapeutic efficacy. A. Receiver operating characteristic curve; B. Calibration curve.

Table 6. Ultrasound features and short-term prognosis in GM [*n* (%)]

Ultrasound features	Non-recurrence group (n = 106)	Recurrence group (n = 15)	X^2	*P*
Lesion morphology			0.120	0.729
Regular	11 (10.38)	2 (13.33)		
Irregularity	95 (89.62)	13 (86.67)		
Edge of the lesion			0.884	0.347
Smooth	49 (46.23)	5 (33.33)		
Irregular (blurred/angled/spiked)	57 (53.77)	10 (66.67)		
Echo behind the lesion			3.071	0.381
No change	6 (5.66)	1 (6.67)		
Enhanced	64 (60.38)	8 (53.33)		
Reduced	11 (10.38)	0 (0.00)		
Mixed change	25 (23.58)	6 (40.00)		
Ductal dilation			36.939	< 0.001
Yes	16 (15.09)	13 (86.67)		
No	90 (84.91)	2 (13.33)		
Microcalcifications			2.642	0.104
Yes	17 (16.04)	5 (33.33)		
No	89 (83.96)	10 (66.67)		
Increased echogenicity of surrounding tissues			0.664	0.415
Yes	74 (69.81)	12 (80.00)		
No	32 (30.19)	3 (20.00)		
Vascular supply pattern			1.681	0.641
No	16 (15.09)	3 (20.00)		
Internal vascularity	2 (1.89)	1 (6.67)		
Peripheral vascularity	51 (48.11)	7 (46.67)		
Combined vascularity	37 (34.91)	4 (26.67)		
Axillary lymph node enlargement			3.017	0.082
Yes	29 (27.36)	1 (6.67)		
No	77 (72.64)	14 (93.33)		

Table 7. Comparison of quantitative parameters of contrast-enhanced ultrasound between the recurrence and non-recurrence groups (*M* ± *SD*)

Parameters	Non-recurrence group (n = 106)	Recurrence group (n = 15)	*t*	*P*
RT (s)	7.99 ± 2.34	7.93 ± 2.02	0.090	0.928
mTTI (s)	45.21 ± 5.08	43.00 ± 3.53	1.625	0.107
TTP (s)	12.68 ± 3.69	14.20 ± 3.21	1.514	0.133
FT (s)	16.27 ± 3.76	16.93 ± 3.67	0.638	0.525
PE (a.u)	2715.05 ± 235.35	2800.00 ± 259.07	1.292	0.199
WiR (a.u)	411.91 ± 52.72	439.87 ± 55.35	1.911	0.058
WoR (a.u)	213.71 ± 27.06	222.80 ± 25.21	1.228	0.222

Notes: RT, rise time; mTTI, mean transit time local; TTP, time to peak; FT, fall time; PE, peak enhancement; WiR, wash in rate; WoR, wash out rate.

posterior acoustic enhancement, along with increased peripheral vascularity. Boufettal et al. [17] similarly observed vascular proliferation in the surrounding tissues of GM lesions on ultrasound.

By contrast, DCIS usually lacks significant inflammatory response and exhibits minimal vascularity, typically limited to internal flow or no detectable flow. Additionally, we observed axillary lymph node enlargement in 73.97% of GM cases, compared to only 4.29% in DCIS. Alper et al. [18] reported that GM may be associated with ultrasound features such as skin thickening, subcutaneous edema, and reactive axillary lymphadenopathy. Although axillary lymph node metastasis in DCIS is generally low-reported to range between 0% and 14% [19, 20], its presence should not be dismissed. Axillary lymph node enlargement alone is insufficient for differentiating between GM and DCIS; comprehensive clinical and imaging evaluation remains essential for accurate diagnosis.

Our study identified significant differences in CEUS parameters between GM and DCIS. Specifically, GM exhibited lower mTTI and higher PE, WiR, and WoR compared to DCIS. These variations likely reflect differences in pathological features, hemodynamics, and tissue architecture. GM, as a chronic inflammatory disease, is characterized by granuloma formation. This process involves local vascular proliferation, increased capillary permeability, and reduced intravascular resistance, collectively leading to enhanced perfusion and faster blood flow [16, 21]. Consequently, PE increases while mTTI decreases.

In contrast, the infiltrative growth pattern of DCIS can disrupt existing microvasculature, resulting in vessel narrowing, occlusion, or functional loss [16]. As a result, WiR and WoR values tend to be lower in DCIS. These CEUS parameter differences, rooted in vascular dynamics and structural pathology, offer critical insight into the imaging characteristics of these two diseases and may enhance diagnostic accuracy in clinical practice.

Although surgery remains the mainstay of GM treatment, recurrence after surgery is a well-documented clinical challenge [22]. Therefore, multimodal treatment strategies combining surgery with corticosteroids, antibiotics, methotrexate, or traditional Chinese medicine have been proposed. Martinez-Ramos et al. [2] reported improved long-term outcomes with combined medical and surgical therapy.

In our study, among 146 GM patients treated with corticosteroids and surgery, 121 achieved clinical cure while 25 did not. We explored the predictive value of pre-treatment ultrasound parameters in evaluating therapeutic response. Notably, mTTI was significantly lower in the cured group than in the non-cured group. ROC curve analysis demonstrated that mTTI had moderate predictive value for treatment response. mTTI reflects the time required for contrast enhancement to reach its peak and then decline to half-maximum intensity, serving as an indirect measure of perfusion. A prolonged mTTI suggests enhanced vascular activity, often linked to active inflammation or pathological angiogenesis, such as in tumors. Conversely, the lower mTTI in the cured group may reflect reduced perfusion and fewer pathological vessels, implying that effective treatment suppresses angiogenesis and inflammatory activity, ultimately improving outcomes. Therefore, mTTI holds potential as a noninvasive imaging biomarker for assessing GM therapeutic response.

Despite favorable outcomes with combined therapy, recurrence remains a concern. In our cohort, 15 out of 121 cured patients (12.40%)

experienced relapse within one year. Pretreatment ductal dilation on ultrasound was significantly associated with recurrence. This may be due to altered local microenvironments, which can facilitate microbial colonization and increase the risk of recurrent inflammation. Moreover, ductal dilation may serve as a proxy for the severity of the inflammatory response, with more pronounced ductal changes reflecting higher inflammatory burden and subsequent relapse risk. Accumulated secretions in dilated ducts may also promote bacterial growth, perpetuating inflammation.

Other potential recurrence-related factors include extent of disease, smoking, hyperprolactinemia, and inverted nipple history [23-25]. Therefore, comprehensive evaluation of these risk factors is essential to guide personalized treatment strategies and improve long-term prognosis.

This study has several limitations. First, as a single-center retrospective analysis, it is subject to selection bias and limited control of confounding factors. Second, although the study included 286 patients, the sample size remains modest for rare conditions like GM and DCIS, which may limit statistical power for subgroup analyses. Third, ultrasound interpretation is inherently operator dependent. Despite efforts to reduce inter-observer variability through double-blind review and quality control, some measurement discrepancies may persist. Lastly, the follow-up period of one year may be insufficient to capture long-term recurrence, particularly in a condition like GM with delayed relapse potential.

Future research should address these limitations. First, multicenter prospective cohort studies are needed to expand sample size and validate key diagnostic indicators, particularly CEUS-derived parameters such as mTTI cutoff values under standardized protocols. Second, development of AI-based ultrasound analysis tools using deep learning algorithms may facilitate automated lesion recognition and parameter quantification, reducing subjectivity and enhancing diagnostic consistency. Third, extending the follow-up period to 3-5 years and establishing a structured recurrence monitoring system are critical for better outcome assessment. Lastly, integrating molecular pathology to investigate associations between imaging features and specific biomarkers could offer new avenues for precision diagnosis and personalized therapy in GM.

In conclusion, a diagnostic model integrating CEUS parameters with conventional ultrasound features holds clinical value in distinguishing granulomatous mastitis from ductal carcinoma in situ, helping to reduce both misdiagnosis of GM and missed detection of DCIS. Furthermore, CEUS parameters, especially mTTI, may serve as useful indicators for evaluating treatment efficacy and predicting recurrence in GM. Continued innovation in ultrasound imaging and its clinical application is essential to advancing the diagnosis, monitoring, and management of GM.

Disclosure of conflict of interest

None.

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