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ORIGINAL RESEARCH

Ultrasonic Parameters as Biomarkers for Tumor Staging and Aggressiveness in Breast Cancer: Correlation with GP73 and miR-27a

Zi-Yu Tao[1,*], Rong Rong[2,*], Lei-Ping Zhou[3]

[1]Obstetrics and Gynecology Hospital Fudan University, Shanghai, 200233, People's Republic of China; [2]Department of Clinical Laboratory, The Second People's Hospital of Hefei, Hefei Hospital Affiliated to Anhui Medical University, Hefei, 230000, People's Republic of China; [3]Department of Ultrasound, International Peace Maternity and Child Health Hospital, Shaghai, 200063, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lei-Ping Zhou, Department of Ultrasound, International Peace Maternity and Child Health Hospital, Shaghai, 200063, People's Republic of China, Tel +86-13761708810, Email Zhouleiping68@163.com

Objective: To investigate correlations between CEUS parameters and serum GP73/miR-27a in breast cancer.

Methods: In the study, 117 highly suspected breast cancer diagnosed and treated in our hospital during March 2022 to April 2024 were included. Meanwhile, pathologic examination was used as the gold standard for diagnosis in this study. The 117 subjects were divided into breast cancer group (69 cases) and non-breast cancer group (48 cases). Both groups underwent contrast-enhanced ultrasound (CEUS), and the parameters of peak intensity (PI), time to peak (TTP), wash-inslope (WIS), gradient (Grad) were recorded. The levels of GP73 and miR-27 in serum of both groups were examined. The relationship between ultrasonography parameters and serum GP73 and miR-27a expression levels was evaluated by correlation analysis.

Results: CEUS parameters (PI, WIS, Grad) in cancer patients were significantly higher than benign group ($P<0.05$), while TTP was lower. GP73 and miR-27a levels were elevated in cancer patients ($P<0.05$), with stage III–IV showing higher values than stage I–II ($P<0.05$). GP73 correlated positively with Grad ($r=0.330$, $P=0.006$), while miR-27a correlated with WIS ($r=0.311$, $P=0.009$) and Grad ($r=0.424$, $P<0.001$). ROC analysis revealed AUCs of 0.771–0.776 for individual parameters and 0.945 for combined markers.

Conclusion: CEUS parameters and serum GP73/miR-27a levels correlate with breast cancer severity, demonstrating synergistic diagnostic value (AUC=0.945), supporting their combined use for early detection and progression assessment.

Keywords: breast cancer, ultrasonic parameters, GP73, miR-27a, correlation analysis

Introduction

As one of the most common malignant tumors today, breast cancer predominantly affects female while male cases are rare. Recent epidemiological studies show that the global incidence of breast cancer is rising annually.[1,2] The incidence and mortality of this type of cancer are high and often insidious. As a result, patients may not have specific symptoms in the early stages and may be diagnosed in the mid-term or late stages.[3] Therefore, timely and accurate diagnosis is crucial for reducing mortality and improving their prognosis.[4] With advancements in modern medical diagnostic and therapeutic technologies, ultrasound has emerged as an important tool for diagnosing breast diseases in clinical practice. Contrast-enhanced ultrasound (CEUS), which involves injecting contrast agents to enhance scattered echoes, allows for the observation and analysis of microcirculation, thereby significantly improving the sensitivity, specificity, and accuracy of clinical diagnosis. This enables more precise early detection of malignant diseases.[5,6]

The selection of GP73 and miR-27a as biomarkers in this study is grounded in their distinct roles in tumor biology and their potential interplay with ultrasound imaging features is a type II transmembrane glycoprotein positioning in the Golgi apparatus. It exhibits high expression levels in the colon, small intestine, and stomach tissues, while its expression is relatively low in other tissues.[7] According to recent studies, GP73 expression is abnormally elevated in various

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malignant tumors. GP73 may contribute to tumor initiation, progression, invasion, and metastasis through mechanisms involving the regulation of inflammatory factors and oxidative stress responses.[8,9] Notably, GP73 overexpression has been linked to angiogenesis and extracellular matrix remodeling in breast cancer,[10] processes that may directly influence CEUS parameters such as perfusion patterns and vascular heterogeneity. This biological relevance makes GP73 a compelling candidate for correlative analysis with ultrasound-derived microcirculation metrics.

MicroRNAs (miRNAs) are non-coding single-stranded RNA molecules that bind to target genes and regulate physiological processes such as protein translation. Many studies have confirmed that aberrant miRNA expression is closely associated with differentiation and local infiltration of breast cancer. miR-27a was specifically chosen due to its dual role in tumor progression: it promotes epithelial-mesenchymal transition (EMT) through targeting tumor suppressor genes,[11] while also modulating vascular endothelial growth factor (VEGF) pathways.[12] These mechanisms suggest that miR-27a levels may correlate with ultrasound features of tumor aggressiveness, such as irregular margins on B-mode imaging or rapid wash-in/wash-out kinetics on CEUS. In addition, miRNA is expected to be a biomarker for diagnosis and prediction of breast cancer prognosis due to its stability in serum and body fluids.[13,14] miR-27a, a member of the miR-27 family, negatively regulates gene expression and plays a role in the progression of various cancers such as liver, lung, and breast cancer. The highly-expressed miR-27a is linked to tumor cell metastasis and chemotherapy resistance.[15,16] Recent work by Yuan et al[17] demonstrated that serum miR-27a levels correlate with dynamic contrast-enhanced MRI parameters in liver cancer, providing precedent for investigating its relationship with functional ultrasound markers.

To enhance the clinical diagnostic efficiency of breast cancer and elucidate the relationship between ultrasound parameters and patient biological indicators, this study investigates the correlation between ultrasound parameters and GP73 and miR-27a level in breast cancer.

Data and Methods

Clinical Data

117 suspected breast cancer patients that treated in our institution from March 2022 to April 2024 were included in this study. Pathologic examination was used as the gold standard for diagnosis in this study. The patients were categorized into breast cancer group (n=69) and non-breast cancer group (n=48). This study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital, Fudan University, and complies with the Declaration of Helsinki. Informed consent was obtained from all study participants.

Inclusion Criteria and Exclusion Criteria

Inclusion Criteria

① All cases were confirmed as breast cancer or benign breast lesions through pathological sections; ② Female cases; ③ Single tumor; ④ Patients voluntarily accepted contrast-enhanced ultrasound examination; ⑤ Patients' clinical data were complete.

Exclusion Criteria

① Intolerance to the contrast agent used in the study; ② Severe heart, liver, kidney failure and cerebrovascular disease.③ Patient had surgery, chemotherapy or antitumor therapy prior to this study.④ Patients with other primary malignant tumors.

Ultrasound Examination

The examination was performed by a LOGIQ-S7 diagnostic ultrasound system (General electric) with a high-resolution real-time linear array transducer. The parameters were set to the probe frequency of 8–14 MHz, the volume width of 1.0 mm, and the angle between the acoustic beam and the blood flow < 60°. During the examination, the patient completely exposed her breasts and armpits in a supine position. A routine ultrasound was first performed to assess the patient's bilateral breast status and to determine the location of the lesion. Subsequently, an optimal imaging plane was selected for contrast-enhanced ultrasound. The contrast agent was rapidly injected into the patient's anterior elbow vein and flushed with 5.0 mL of 0.9% saline after administration of 2.5 mL of contrast agent. Dynamic observation and recording of the breast lesion were conducted. When the lesion reached peak enhancement, regions of interest (ROIs)

were selected, and time-intensity curves were generated using QLAB analysis software. Curve fitting was performed to obtain relevant parameters, including peak intensity (PI), time to peak (TTP), wash-inslope (WIS), and gradient (Grad).

Detection of Serum GP73 and miR-27a

Venous blood samples were collected from both groups during early morning fasting. The serum was separated by centrifugation of the venous blood drawn. The GP73 expression level in serum of the two groups was detected by ELISA (The assay kit was purchased from Abcam, USA).

The expression level of miR-27a in serum of the two groups were detected by RT-qPCR. Total RNA was extracted from the serum using TRizol reagent, and the concentration and purity of total RNA were detected by ultraviolet spectrophotometry. The primer sequences were designed and synthesized by Shanghai Sangon Biotechnology Company. miR-27a: forward primer 5′-ACAGCCTCCATGGGAA-3′, reverse primer 5′-TGGAGTGTGGCGTTCG-3′; U6: forward primer 5′-CTCGCGCAGCCTTGACA-3′, reverse primer 5′-AACTTCGGAATTGCAC-3′. RNA was reverse transcribed into cDNA using a reverse transcription kit, and quantitative PCR was performed using the miScript SYBR Green kit. The reaction condition was carried out at 95°C for 30 min, 94°C for 15s, 60°C for 30s then 72°C for 30s, with a total of 45 rounds. U6 was used as the internal reference gene, and the relative expression level of miR-27a was detected by the $2^{-\Delta\Delta}$Ct method.

Statistical Analysis

The statistical analysis of the study was by SPSS 29.0. The comparison of count data was performed by *t*-test, and that of measurement data was by chi-square test. Results were considered statistically significant at $P<0.05$.

Results

Clinical Data

The average age of breast cancer group was (57.39 ± 8.32) years, with an average BMI of (22.73 ± 2.16) kg/m². Fifty-one of the patients were menopausal, 15 had hypertension, and 8 had diabetes. The average age of non-breast cancer group was (59.10 ± 11.46) years, with an average BMI of (23.05 ± 2.73) kg/m². There were 42 cases of menopause, 12 hypertension, and 7 diabetes. The comparison of clinical data between two groups showed no statistically significant difference ($P>0.05$) (Table 1).

Changes of Contrast-Enhanced Ultrasound Parameters

The contrast-enhanced ultrasound parameters PI, WIS and Grad of breast cancer group were higher than those of non-breast cancer group ($P<0.05$), and the TTP of breast cancer group was lower than that of non-breast cancer group ($P<0.05$), as shown in Table 2.

Table 1 Comparison of Clinical Data

Clinical Data	Breast Cancer Group (n=69)	Non-Breast Cancer Group (n=48)	t/χ^2	P
Age (years, mean±SD)	57.39±8.32	59.10±11.46	0.935	>0.05
BMI (kg/m2, mean±SD)	22.73±2.16	23.05±2.73	0.707	>0.05
Menopause [n(%)]				
Yes	51 (73.91)	32 (66.67)	0.721	>0.05
No	18 (26.09)	16 (33.33)		
Hypertension [n(%)]				
Yes	15 (21.74)	12 (25.00)	0.170	>0.05
No	54 (78.26)	36 (75.00)		
Diabetes [n(%)]				
Yes	8 (11.59)	7 (14.58)	0.226	>0.05
No	61 (88.41)	41 (85.42)		

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Table 2 Comparison of Contrast-Enhanced Ultrasound Parameters (mean±SD)

Group	Number of Cases	PI (dB)	WIS (dB/s)	TTP (s)	Grad (dB)
Breast cancer group	69	7.95±2.03	8.11±2.17	18.50±5.12	1.08±0.26
Non-breast cancer group	48	5.18±1.42	6.38±1.35	24.18±6.43	0.51±0.14
t	-	8.162	4.900	5.309	13.845
P	-	<0.001	<0.001	<0.001	<0.001

Table 3 Comparison of GP73 and miR-27a Level (mean±SD)

Group	Number of Cases	GP73 (ng/L)	miR-27a
Breast cancer group	69	118.42±31.58	1.642±0.239
Non-breast cancer group	48	50.37±15.10	0.973±0.152
t	-	13.855	17.122
P	-	<0.001	<0.001

Comparison of GP73 and miR-27a Level

The relative expression level of GP73 and miR-27a in breast cancer group were higher than those in non-breast cancer group ($P<0.05$), as shown in Table 3.

Comparison of Contrast-Enhanced Ultrasound Parameters by Different Courses

The PI, WIS and Grad of patients with stage III–IV were apparently higher than those at stage I–II ($P<0.05$), while the TTP was obviously lower than that at stage III–IV ($P<0.05$), as shown in Table 4.

Comparison of GP73 and miR-27a of Patients with Different Stages

The relative expression level of GP73 and miR-27a in patients with stage III–IV was remarkably higher than those with stage I–II ($P<0.05$), as shown in Table 5.

Correlation Analysis of Contrast-Enhanced Ultrasound Parameters and GP73, miR-27a

The correlation analysis illustrated that GP73 in breast cancer patients was positively correlated with Grad (r=0.330, P=0.006), while miR-27a showed positive correlations with WIS (r=0.311, P=0.009) and Grad (r=0.424, P=0.001). No significant correlations were observed between GP73 and PI/WIS/TTP or between miR-27a and PI/TTP (all P>0.05) (Figure 1 and Table 6).

Table 4 Comparison of Contrast-Enhanced Ultrasound Parameters by Different Stages (mean±SD)

Group	Number of Cases	PI (dB)	WIS (dB/s)	TTP (s)	Grad (dB)
Stage I–II	43	7.21±1.79	7.05±2.35	19.99±5.26	0.91±0.21
Stage III–IV	26	9.17±2.65	9.85±1.78	16.03±4.23	1.36±0.30
t	–	3.667	5.230	3.252	7.321
P	–	<0.001	<0.001	0.002	<0.001

Table 5 Comparison of GP73 and miR-27a in Patients with Different Stages (mean±SD)

Group	Number of Cases	GP73 (ng/L)	miR-27a
Stage I–II	43	104.47±29.38	1.540±0.211
Stage III–IV	26	141.49±46.23	1.810±0.301
t	-	4.073	4.375
P	-	<0.001	<0.001

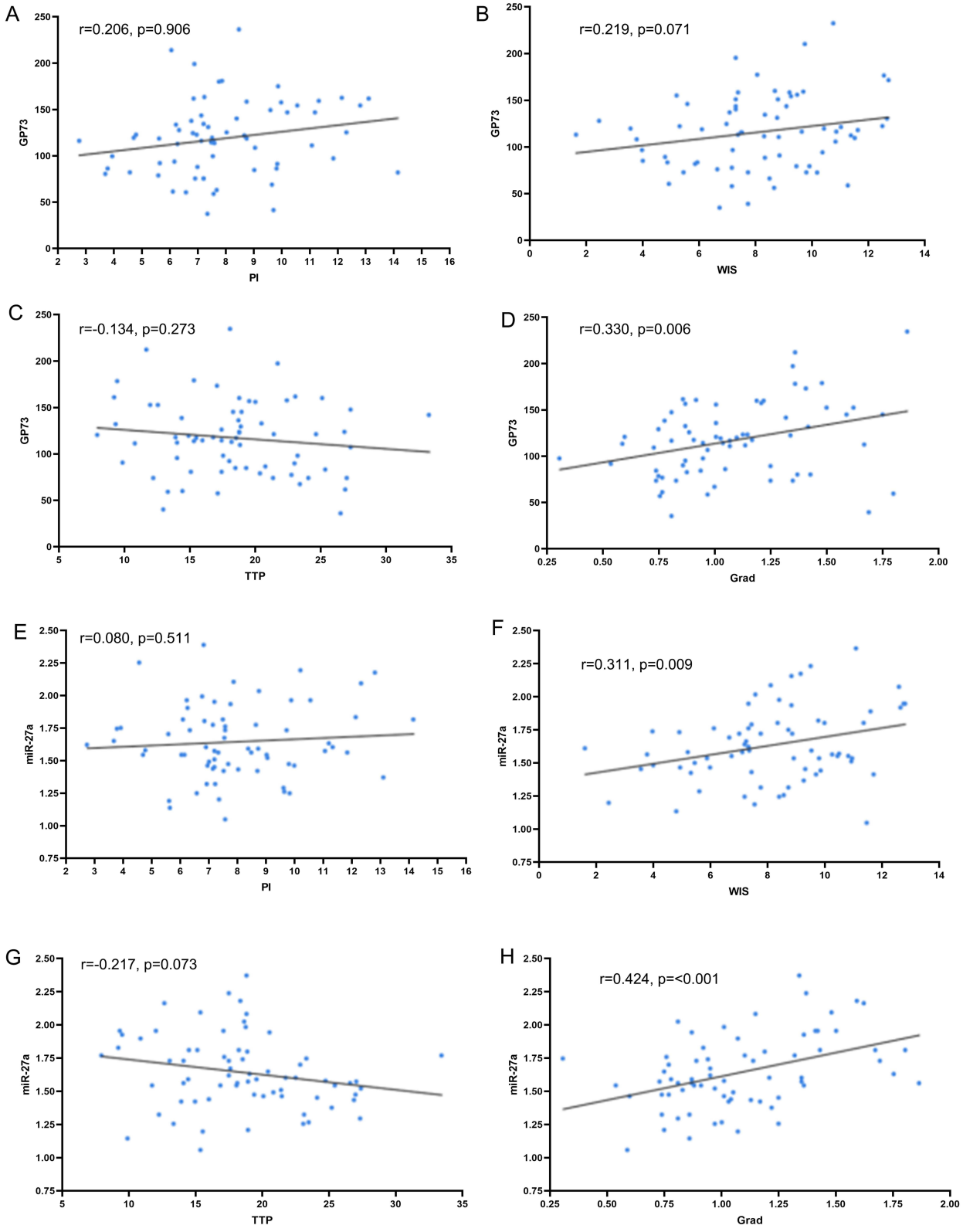

Figure 1 Correlation of ultrasonographic parameters with GP73 and miR-27a. (**A**) GP73 and PI (P=0.090); (**B**) GP73 and WIS (P=0.071); (**C**) GP73 and TTP (P=0.273); (**D**) GP73 and Grad (P=0.006); (**E**) miR-27a and PI (P=0.511); (**F**) miR-27a and WIS (P=0.009); (**G**) miR-27a and TTP (P=0.073); (**H**) miR-27a and Grad (P<0.001).

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Table 6 Correlation Coefficients of Contrast-Enhanced Ultrasound Parameters and Serum GP73, miR-27a in Patients with Breast Cancer

Indicator	Statistical Value	PI	WIS	TTP	Grad
GP73	r	0.206	0.219	−0.134	0.330
	P	0.090	0.071	0.273	0.006
miR-27a	r	0.080	0.311	−0.217	0.424
	P	0.511	0.009	0.073	<0.001

ROC Curve Analysis of Diagnostic Value of Contrast-Enhanced Ultrasound Parameters and GP73, miR-27a

The diagnostic value of contrast-enhanced ultrasound parameters and serum GP73/miR-27a for breast cancer was analyzed by ROC curves. The areas under the curve (AUC) for PI, WIS, TTP, Grad, GP73, and miR-27a were 0.771, 0.760, 0.776, 0.768, 0.776, and 0.727, respectively. The composite indicator (combined parameters) achieved an AUC of 0.945 (95% CI: 0.904–0.985), with 88.4% sensitivity and 89.6% specificity (Figure 2 and Table 7).

Discussion

Most breast cancers occur as tumors of the epithelial tissue of the breast and are more likely to have lymph node metastases. It has been found that most patients experience symptoms such as breast lumps, nipple retraction or bloody nipple discharge when seeking medical assistance.[18] As people's lifestyles and environments change, the incidence of cancer is increasing every year and is affecting the younger population.[19] The current clinical diagnosis of breast cancer is based on imaging and histopathologic examination. The imaging diagnostic methods include CT, ultrasound, and MRI, among which ultrasound includes two-dimensional gray-scale, color Doppler ultrasound, real-time tissue elastography, and contrast-enhanced ultrasound. It is widely used in breast screening and preoperative diagnosis of breast cancer. It's simple to operate and inexpensive, which is highly accepted by most patients.[20] Compared with mammography X-ray, MRI and other techniques, ultrasound examination can display the contour of breast lesion areas, tissue layers, and the

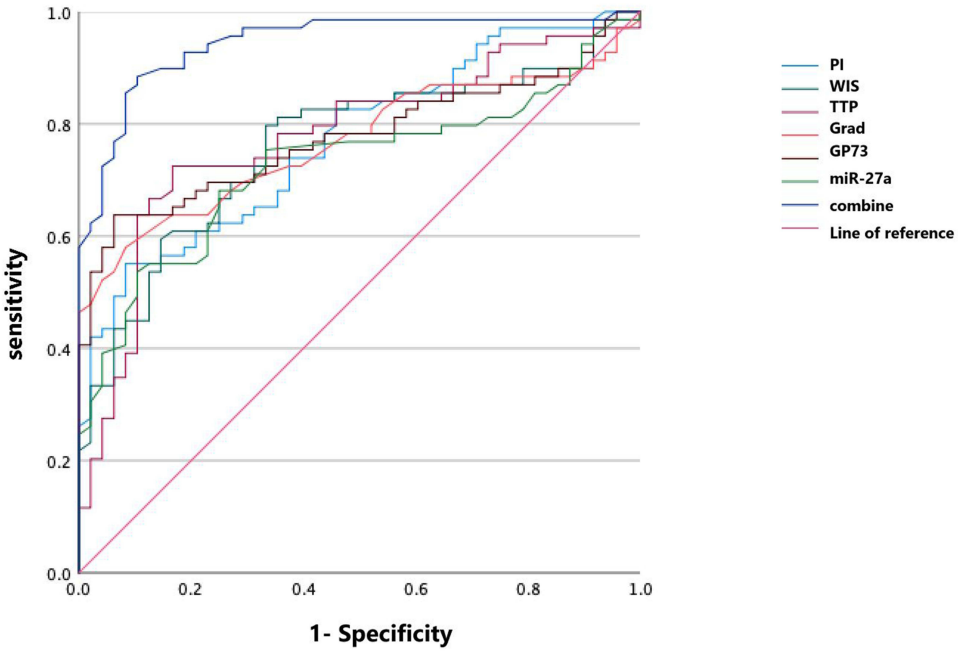

Figure 2 ROC curve analysis of the diagnostic value of contrast-enhanced ultrasound parameters and serum GP73, miR-27a for breast cancer.

Table 7 Parameters of ROC Curves for Contrast-Enhanced Ultrasound Parameters and Serum GP73, miR-27a in the Diagnosis of Breast Cancer

Indicator	Area under the Curve	Sensitivity	Specificity	P	95% CI
PI	0.771	55.10%	91.70%	<0.001	0.688~0.854
WIS	0.760	79.70%	66.70%	<0.001	0.673~0.847
TTP	0.776	72.50%	83.30%	<0.001	0.690~0.863
Grad	0.768	58.00%	91.70%	<0.001	0.682~0.853
GP73	0.776	63.80%	93.70%	<0.001	0.692~0.861
miR-27a	0.727	53.60%	89.60%	<0.001	0.635~0.819
Union	0.945	88.40%	89.60%	<0.001	0.904~0.985

condition of bilateral axillary lymph nodes, which has high application value in distinguishing benign and malignant lesions.[21] Conventional ultrasound for breast cancer examination is to observe the condition inside the patient's blood vessels through the echo performance during the examination process, and judge the nature of the tumor according to different echoes. However, the diameter of tumor tissue is difficult to clearly show through conventional ultrasound.[22] Contrast-enhanced ultrasound, on the other hand, directly injects contrast agents into the blood vessels, presenting the morphology and stenosis of the vessels at a faster speed and with clearer images.[23] The emergence of contrast-enhanced ultrasound has made it possible to diagnose malignant tumors at an early stage without cost. It can not only accurately reflect the microvascular perfusion within the lesion tissue, but also detect the low-flow and low-velocity microcirculation within and around the tumor.[24,25] According to this study, the contrast-enhanced ultrasound parameters PI, WIS, and Grad of breast cancer group were notably higher than those in non-breast cancer group, while TTP was significantly lower. At the same time, the PI, WIS, and Grad of stage III–IV breast cancer were higher than those at stage I–II, and TTP was significantly lower than that at stage III–IV. Significant differences were observed in malignant lesions compared to ultrasonographic parameters in benign breast lesions. Meanwhile, the changes in contrast-enhanced ultrasound parameters are closely related to the disease progression. Contrast-enhanced ultrasound not only helps in diagnosing breast cancer clinically but also assessing patients' cancer condition. At present, the pathogenesis of breast cancer has not been completely elucidated, and it may be related to factors such as immune disorder, activation of oncogenes, and inactivation of tumor suppressor genes.[26,27] GP73 exists on the surface of Golgi apparatus. It activates the extracellular factor Wnt/β-catenin signaling pathway, enhances tumor cell proliferation, regulates the expression of proto-oncogene C-myc, promotes the malignant transformation of normal cells, induces epithelial-mesenchymal transition (EMT), and enhances the metastatic ability of tumor cells.[28,29] miR-27a activates the Wnt/β-catenin signaling pathway and promotes proliferation and invasion of breast cancer cells. Down-regulated expression of miR-27a can inhibit the expression of vascular endothelial growth factor, block the formation of new blood vessels, and promote tumor metastasis.[30,31] Additionally, the highly-expressed miR-27a can upregulate expression of tumor necrosis factor-α, promote the proliferation of cancer cells, and enhance invasive and metastatic ability of tumor cells, thereby promoting the malignant progression of tumors.[32–34] As this research indicated, the relative expression level of GP73 and miR-27a in breast cancer was apparently higher than those in non-breast cancer group. Meanwhile, the relative expression level of GP73 and miR-27a in breast cancer at stage III–IV was higher than those at stage I–II. This is consistent with the conclusion reported by other scholars,[35,36] which suggests that there is an abnormally high expression of GP73 and miR-27a in breast cancer patients, and such high expression status is associated with the progression of patients' disease.

According to the correlation analysis results of this study, there were significant positive correlations between GP73 levels and Grad parameters (r=0.330, P=0.006) and between miR-27a levels and WIS (r=0.311, P=0.009) and Grad parameters (r=0.424, P<0.001). These findings suggest that contrast-enhanced ultrasound parameters are closely associated with the expression of GP73 and miR-27a, which may reflect their involvement in tumor progression through shared biological pathways. However, the observed correlations do not necessarily imply direct causality. The mechanistic link between GP73 and Grad (a parameter reflecting perfusion intensity change rate) could be explained by GP73's role in promoting angiogenesis through Wnt/β-catenin signaling.[37,38] Enhanced vascularization may lead to steeper

contrast uptake gradients (higher Grad values), as seen in malignant lesions. Similarly, miR-27a's correlation with WIS (wash-in slope) and Grad aligns with its known function in regulating VEGF-driven vascular permeability, potentially accelerating contrast agent influx.[39]

Nevertheless, three critical limitations must be acknowledged: First, as a cross-sectional study, our data cannot establish temporal or causal relationships between biomarker levels and ultrasound parameters. Second, the correlations, though statistically significant, showed moderate effect sizes (r=0.311–0.424), suggesting additional unmeasured factors contribute to ultrasound parameter variability. Third, the lack of in vitro experiments prevents direct verification of whether GP73/miR-27a overexpression mechanistically alters vascular phenotypes detectable by CEUS.

Furthermore, an evaluation of the diagnostic value of combining contrast-enhanced ultrasound parameters with GP73 and miR-27a for breast cancer diagnosis yielded an area under the curve (AUC) of 0.945. This indicates that the integration of these markers holds substantial clinical utility for diagnosing breast cancer. Importantly, the superior diagnostic performance of the combined model supports the hypothesis that GP73/miR-27a and CEUS parameters capture complementary aspects of tumor biology – molecular drivers (biomarkers) and their functional consequences (perfusion dynamics).

Conclusion

In conclusion, the contrast-enhanced ultrasound parameters, GP73 level, and miR-27a expression are closely associated with the severity of breast cancer. Ultrasonographic parameters of breast cancer patients exhibit a significant correlation with the expression ofGP73 and miR-27a. The integration of contrast-enhanced ultrasound parameters with GP73 and miR-27a demonstrates high diagnostic accuracy for breast cancer, thereby enhancing the clinical utility of these markers in disease assessment.

Disclosure

Zi-Yu Tao and Rong Rong are co-first authors for this study. The authors declare no competing interests in this work.

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