Clinical utility of quantitative ultrasonography parameters combined with serum cancer antigen 15-3, human epidermal growth factor receptor 2 and soluble E-cadherin in diagnosing mass-type breast cancer

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Abstract. Contrast-enhanced ultrasonography (CEUS), a newly developed imaging technique, holds certain value in differentiating benign from malignant tumors. Additionally, serum tumor markers also exhibit significant clinical importance in the diagnosis and monitoring of malignant tumors. Reports have indicated abnormal expression of HER-2, CA153 and sE-cad in breast cancer. Early diagnosis of breast cancer facilitates early clinical intervention and enhances the overall quality of life for patients. Therefore, this study aims to explore the clinical value of quantitative CEUS parameters combined with serum levels of CA153, HER-2 and sE-cad in diagnosing mass-type breast cancer. In total, 49 patients with breast cancer (breast cancer group) and 56 patients with benign breast tumors (benign group) were selected as the study participants, while 50 healthy women served as the control group. Ultrasonography was performed on the patients in the breast cancer and benign groups using diagnostic color Doppler ultrasonography. The serum CA15-3, HER-2 and sE-cad levels in all three study groups were measured using a fully automated electrochemiluminescence immunoassay. Pearson's correlation test was used to analyze the correlation between the quantitative ultrasonography parameters and serum CA15-3, HER-2 and sE-cad levels. Logistic multivariate regression analysis was performed to analyze the independent risk factors, and a receiver operating characteristic curve was plotted to assess the diagnostic value of these factors. The peak intensity (PI), wash-in slope (WIS), gradient (Grad) and local mean transit time (mTTI), along with the CA15-3, HER-2 and sE-cad levels in the breast cancer group were significantly higher, and the time to peak (TTP) was significantly lower, compared with those values in the benign and control groups. CA15-3, HER-2 and sE-cad were negatively correlated with TTP in the breast cancer group (all $P<0.05$) and positively correlated with PI, WIS, Grad and mTTI (all $P<0.05$). The area under the curve (AUC) values for CA15-3, HER-2, sE-cad, PI, WIS, Grad, mTTI and TTP for the diagnosis of malignant breast cancer were 0.640, 0.730, 0.687, 0.683, 0.692, 0.737, 0.697 and 0.671, respectively. The AUC for the combined diagnosis was 0.919, with a sensitivity of 0.857 and a specificity of 0.911, outperforming each index alone for a single diagnosis. Logistic multivariate regression analysis revealed that HER-2, TTP, PI, WI and Grad were independent risk factors for malignant breast cancer. In conclusion, combining the quantitative ultrasonography parameters with the CA15-3, HER-2 and sE-cad levels facilitated the differential diagnosis of benign and malignant breast lesions, and may provide a reference for clinical treatment in the future.

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Introduction

Breast cancer, a common malignancy worldwide, remains a global public health problem. The Global Cancer Burden data estimates that in 2020 there were 2.26 million new cases of breast cancer (1). Mass-type breast cancer is a typical feature of breast cancer (2). However, owing to negligence in breast self-examination and clinical examination, patients continue to be diagnosed at an advanced stage of disease (3). Previous and ongoing research has had significant implications for improving the clinical outcomes of breast cancer owing to the progress achieved in the fields of screening, diagnosis and therapeutic strategies for breast cancer management (4). Lifestyle and environmental factors (lack of physical exercise, alcohol consumption and high-fat diet) affect the development of breast cancer, the appropriate management of which could result in a reduction in morbidity and mortality. Other diagnostic tests, such as mammography, ultrasonography, breast self-examination and magnetic resonance imaging, aid in the early detection of tumors (5). Recently, there has been significant improvement in the speed and resolution of image acquisition; however, imaging-based diagnosis is restricted by subjective factors, such as the experience and ability of clinicians, and their capability to reproduce results and promote screening (6).

The formation of new blood vessels, reduction in blood flow resistance and elevation of blood flow in breast cancer lesions form the basis of cancer cell growth. Thus, an accurate estimation of blood flow status in tumor lesions can provide a basis for determining malignancy (7). In breast imaging examinations, ultrasound has become the first choice for physicians and patients owing to its simplicity, economy, effectiveness, convenience and safety (8). Doppler ultrasound is a common approach for evaluating blood flow status in clinical practice, and the evaluation of blood flow parameters can quantify blood flow in local tissues (9). Color Doppler ultrasound is a promising alternative for assessing tumor responses in breast cancer due to its availability, reproducibility and cost-effectiveness (10).

Additionally, with increases in healthcare costs and the introduction of novel targeted therapies, the application of biomarkers has become an approach to assist in cancer diagnosis, prognosis, treatment response prediction, and disease monitoring during and after treatment (11). Cancer antigen 15-3 (CA15-3) is a tumor protein in a variety of cancer types, particularly breast cancer (12). CA15-3 levels in breast secretions can differentiate between malignant and benign breast tumors, serving as a valuable parameter for diagnosing breast cancer (13). Human epidermal growth factor receptor 2 (HER-2; also known as erbB-2) is a receptor tyrosine-protein kinase that is commonly implicated in breast cancer proliferation and division (14). Testing for the HER-2 oncogene has increased in breast cancer owing to its function as both a prognostic and predictive factor (15). E-cadherin can be removed from the cell surface through proteolytic cleavage, resulting in an 80-kDa fragment known as soluble E-cadherin (sE-cad) (16). sE-cad, a paracrine/autocrine signaling molecule, activates or suppresses diverse signaling pathways and functions in the progression of multiple types of cancer, including breast cancer (17). The aforementioned studies have emphasized the diagnostic efficacy of color Doppler ultrasound, serum CA15-3, HER-2 and sE-cad levels in diagnosing breast cancer. Additionally, certain studies have examined the diagnostic utility of Doppler ultrasound parameters combined with other serum indicators in breast cancer. For instance, Ren *et al* (18) reported that the combination of Doppler ultrasound parameters with matrix metalloproteinase-11 demonstrated a high diagnostic accuracy rate for breast cancer. The independent prognostic significance of increased preoperative serum CA15-3 and carcinoembryonic antigen (CEA) levels has also been confirmed in luminal B breast cancer (19). Another study revealed that serum nucleosomes were more sensitive and less specific markers than CEA and CA15-3 for the diagnosis of early stage breast cancer (20). Meanwhile, *HER-2* gene amplification is a potential prognostic parameter for advanced-stage breast cancer (20). Nevertheless, to the best of our knowledge, no study has addressed the combination of quantitative ultrasonography parameters with the serum levels of CA15-3, HER-2 and sE-cad in diagnosing mass-type breast cancer. Therefore, the present study assessed the clinical utility of combining these factors in diagnosing this disease.

Materials and methods

Participants. Data from 49 patients with single-lesion mass-type breast cancer (breast cancer group) and 56 patients with benign breast tumors (benign group), all of whom were female and had single lesions, who were diagnosed according to postoperative pathology between July 2019 and September 2021 at Beihua University Affiliated Hospital (Jilin, China), were retrospectively collected and analyzed. Patients in the breast cancer group were aged 42-68 years, with a median age of 52 years, and patients in the benign group were aged 40-64 years, with a median age of 51 years. The inclusion criteria were as follows: i) Fulfilled the diagnostic criteria for mass-type breast cancer according to the criteria for breast cancer classification based on pathologic confirmation (21); ii) Breast Imaging Reporting and Data System classification (≥3 categories) (21); and iii) completed follow-up treatment in Beihua University Affiliated Hospital with complete clinical data available. Patients who underwent breast surgery and hormone therapy, individuals intolerant to ultrasound contrast agents, those whose diagnoses were not confirmed by postoperative pathology or for whom clinical data were incomplete, those with other diffuse breast lesions, who had been treated with surgery, chemotherapy or medication before consultation, and those with serious cardiac, hepatic and renal dysfunctions were excluded from the present study. Another 50 healthy women were selected as the control group, with an age range of 39-66 years and a median age of 51 years.

Ultrasound examination. Patients were examined using a color Doppler ultrasound system (Resona 7; Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) equipped with an ML6-15 probe set to a frequency of 12 MHz. First, the patient underwent routine ultrasound examination, which was designed to generate high-quality, two-dimensional images of the breasts to obtain a good understanding of the breasts bilaterally and determine the location of the lesions. Second, a more optimal cut surface was selected to enter into the imaging stage, and 2.5 ml contrast agent (SonoVue; Bracco) was rapidly injected into the elbow vein of the patient, followed by washing with 5.0 ml of 0.9% saline. The dynamics of the breast lesion were then observed in detail and recorded. The region of interest was selected when the breast lesion reached peak enhancement. The region of interest was selected in the internal region of the lesion as well as at the edges at five points, and the value of the selected region of interest was measured to calculate the mean value. The normal breast tissue at the same depth from healthy individuals in the control group was selected as the control area (22). Finally, time-intensity curves were obtained using QLAB analysis software (version 9.0; Philips Healthcare) and subsequently curve-fitted to derive the specific higher values of the following corresponding contrast parameters: Time to peak (TTP), peak intensity (PI), wash-in slope (WIS), gradient (Grad) and local mean transit time (mTTI).

Table I. Comparison of the general characteristics among the three groups.

Characteristic	Control group (n=50)	Benign group (n=56)	Breast cancer group (n=49)	P-value
Age, years	51.78±5.76	51.13±5.11	52.08±5.74	0.661
Body mass index, kg/m^2	23.06±2.35	23.63±2.26	23.49±2.41	0.433
Smoking history, n (%)				0.751
Yes	10 (20.00)	10 (17.86)	7 (14.29)	
No	40 (80.00)	46 (82.14)	42 (85.71)	
Drinking history, n (%)				0.320
Yes	8 (16.00)	22 (39.29)	18 (36.73)	
No	42 (84.00)	34 (60.71)	31 (63.27)	

Table II. Comparison of the ultrasonographic parameters among the three groups.

Group	TTP, sec	PI, dB	WIS, dB/sec	Grad, dB	mTTI, sec
Control (n=50)	31.87±7.80	3.69±0.94	5.18±1.88	0.51±0.15	42.31±5.77
Benign (n=56)	25.13±5.27[a]	4.76±1.13[a]	6.03±2.12[a]	0.73±0.20[a]	52.24±8.27[a]
Breast cancer (n=49)	22.44±4.26[a,b]	6.09±2.28[a,b]	8.08±3.39[a,b]	0.95±0.32[a,b]	59.61±10.89[a,b]

[a]P<0.05 vs. control group. [b]P<0.05 vs. benign group. PI, peak intensity; WIS, wash-in slope; Grad, gradient; mTTI, local mean transit time; TTP, time to peak.

Determination of serum CA15-3, HER-2 and sE-cad levels. The results from these tests were collected from the medical records. Briefly, 5 ml of blood was collected from patients in the morning after fasting. After spontaneous coagulation at 25˚C, the blood samples were centrifuged at 2,264 x g for 20 min at 25˚C, and the upper layer of serum was collected. The serum levels of CA15-3, HER-2 and sE-cad were determined using an automated electrochemiluminescence immunoassay system (MODULAR E170; Roche Diagnostics), following the manufacturer's instructions. The reagent kits used were CA153 (Roche; cat. no. 03045838122), HER-2 (Shanghai Yaji Biotechnology Co., Ltd.; cat. no. CL04956), and sE-Cad (Hubei Huabang Biotechnology Co., Ltd.; cat. no. HBP35511R). Operations were strictly conducted according to the instrument's operating procedures and the reagent kit manuals.

Statistical analysis. Statistical analysis was performed using SPSS version 26.0 (IBM Corp.). Enumeration data are presented as n (%), with comparative analysis performed using the χ^2 test or Fisher's exact test. Measurement data are presented as the mean ± standard deviation. For comparisons among multiple groups, one-way ANOVA was adopted and post hoc pairwise comparisons were conducted using the LSD method. Correlations between quantitative ultrasonography parameters and the CA15-3, HER-2 and sE-cad levels were analyzed using Pearson's correlation coefficient. Logistic multivariate regression was used to analyze the independent risk factors. The receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) for individual and combined detections of ultrasound parameters along with serum levels of CA15-3, HER-2, and sE-cad was calculated. A cut-off value was selected, and the diagnostic performance of the observational indicators was analyzed at this cut-off point. Based on the coordinates of the curve, a series of sensitivity and 1-specificity values were obtained. By subtracting 1-specificity from sensitivity and sorting the results, the maximum value of the Youden Index was determined as the aforementioned cut-off value. P<0.05 was considered to indicate a statistically significant difference.

Results

General information. No statistical differences were observed in the general characteristics of the patients, such as age, body mass index, smoking history and alcohol consumption history, among the three groups (all P>0.05; Table I).

Ultrasonographic parameters. The PI, WIS, Grad and mTTI values were significantly higher and the TTP was significantly lower in the breast cancer group compared with those in the benign and control groups. Significantly higher PI, WIS, Grad and mTTI values and a lower TTP value were also observed in the benign group compared with those in the control group (all P<0.05; Table II).

Serum CA15-3, HER-2 and sE-cad levels. The CA15-3, HER-2 and sE-cad levels were significantly higher in the breast cancer group compared with those in the benign and control groups, and the CA15-3, HER-2 and sE-cad levels were significantly higher in the benign group compared with those in the control group (all P<0.05; Table III). This suggests that the levels of CA153, HER-2 and sE-cad are elevated in both benign breast diseases and breast cancer.

Table III. Comparison of serum CA15-3, HER-2 and sE-cad levels among the three groups.

Group	CA15-3, U/ml	HER-2, U/ml	sE-cad, ng/ml
Control (n=50)	13.54±2.26	7.44±1.45	1,732.54±289.64
Benign (n=56)	29.97±8.36[a]	15.30±2.29[a]	1,968.46±392.02[a]
Breast cancer (n=49)	34.59±9.11[a,b]	18.64±4.46[a,b]	2,257.89±478.11[a,b]

[a]P<0.05 vs. control group. [b]P<0.05 vs. benign group. CA15-3, cancer antigen 15-3; HER-2, human epidermal growth factor receptor 2; sE-cad, soluble E-cadherin.

Table IV. Correlation analysis of quantitative ultrasonography parameters with CA15-3, HER-2 and sE-cad levels in the breast cancer group.

	CA15-3		HER-2		sE-cad	
Variable	r	P-value	r	P-value	r	P-value
TTP	-0.452	0.001	-0.525	<0.001	-0.526	<0.001
PI	0.530	<0.001	0.436	0.006	0.596	<0.001
WIS	0.327	0.022	0.425	0.007	0.420	0.003
Grad	0.564	<0.001	0.397	0.005	0.462	<0.001
mTTI	0.402	0.004	0.512	0.002	0.591	<0.001

CA15-3, cancer antigen 15-3; HER-2, human epidermal growth factor receptor 2; sE-cad, soluble E-cadherin; PI, peak intensity; WIS, wash-in slope; Grad, gradient; mTTI, local mean transit time; TTP, time to peak.

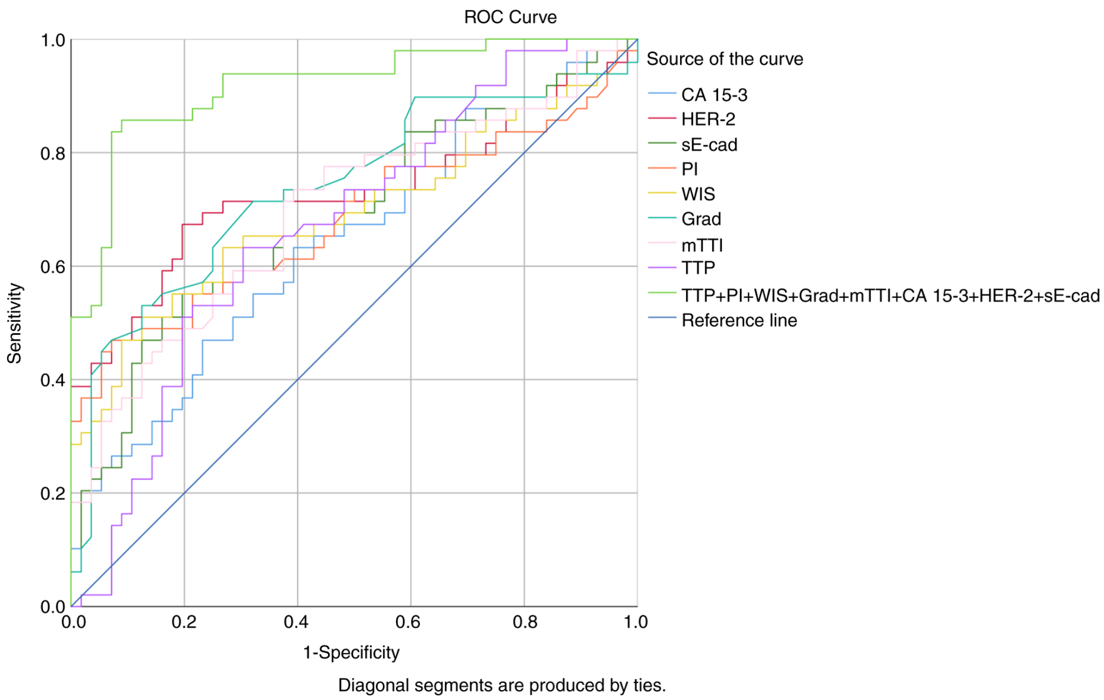

Figure 1. ROC curves of the quantitative parameters of ultrasonography combined with the serum CA15-3, HER-2 and sE-cad levels in the diagnosis of malignant breast cancer. ROC, receiver operating characteristic; CA15-3, cancer antigen 15-3; HER-2, human epidermal growth factor receptor 2; sE-cad, soluble E-cadherin; PI, peak intensity; WIS, wash-in slope; Grad, gradient; mTTI, local mean transit time; TTP, time to peak.

Correlation analysis of the quantitative ultrasonography parameters with the CA15-3, HER-2 and sE-cad levels in the breast cancer group. Correlation analysis revealed that the CA15-3, HER-2 and sE-cad levels were negatively correlated with TTP in the breast cancer group (all P<0.05) and positively correlated with PI, WIS Grad and mTTI (all P<0.05) (Table IV).

Table V. Receiver operating characteristic analysis.

						Asymptotic 95% confidence interval	
Variable	AUC	Cut-off value	Sensitivity	Specificity	P-value	Lower	Upper
CA15-3	0.640	32.430	0.633	0.607	0.014	0.533	0.746
HER-2	0.730	17.295	0.673	0.804	0.000	0.627	0.833
sE-cad	0.687	2246.325	0.551	0.804	0.001	0.584	0.790
PI	0.683	6.280	0.469	0.071	0.001	0.575	0.790
WIS	0.692	8.425	0.510	0.875	0.001	0.586	0.798
Grad	0.737	0.935	0.531	0.875	0.000	0.638	0.836
mTTI	0.697	53.205	0.735	0.607	0.001	0.595	0.799
TTP	0.671	0.042	0.633	0.696	0.003	0.567	0.774
Combination[a]	0.919	-	0.857	0.911	0.000	0.865	0.972

[a]Combination: TTP + PI + WIS + Grad + mTTI + CA15-3 + HER-2 + sE-cad. CA15-3, cancer antigen 15-3; HER-2, human epidermal growth factor receptor 2; sE-cad, soluble E-cadherin; PI, peak intensity; WIS, wash-in slope; Grad, gradient; mTTI, local mean transit time; TTP, time to peak.

Diagnostic value of the ultrasound parameters combined with the serum CA15-3, HER-2 and sE-cad levels in benign and malignant breast cancer. The diagnostic value of the ultrasound parameters combined with the serum CA15-3, HER-2 and sE-cad levels for benign breast tumors and malignant breast cancer were analyzed using ROC curves. ROC curve analysis yielded the following AUC values in the diagnosis of malignant breast cancer: CA15-3, 0.640 [95% confidence interval (CI), 0.533-0.746]; HER-2, 0.730 (95% CI, 0.627-0.833); sE-cad, 0.687 (95% CI, 0.584-0.790); PI, 0.683 (95% CI, 0.575-0.790); WIS, 0.692 (95% CI, 0.586-0.798); Grad, 0.737 (95% CI, 0.638-0.836); mTTI, 0.697 (95% CI, 0.595-0.799); and TTP, 0.671 (95% CI, 0.567-0.774). The respective sensitivities were 0.633, 0.673, 0.551, 0.469, 0.510, 0.531, 0.735 and 0.633, and the respective specificities were 0.607, 0.804, 0.804, 0.071, 0.875, 0.875, 0.607 and 0.696. The AUC for the combined diagnosis in the diagnosis of malignant breast cancer was 0.919 (95% CI, 0.865-0.972), with a sensitivity of 0.857 and a specificity of 0.911, outperforming each index alone for a single diagnosis (Table V and Fig. 1). When considering whether malignant breast cancer was the dependent variable (0=benign breast tumor, 1=malignant breast cancer) and CA15-3, HER-2, sE-cad, PI, WIS, Grad, mTTI and TTP were the independent variables, the logistic multifactorial regression analysis showed that HER-2 ≥17.295, TTP <0.042, PI ≥6.28, WIS ≥8.425 and Grad ≥0.935 were independent factors for malignant breast cancer detection (all P<0.05; Tables VI and VII).

Table VI. Assignment table.

Factor	Assignment[a]
CA15-3	<32.43=0, ≥32.43=1
HER-2	<17.295=0, ≥17.295=1
sE-cad	<2246.325=0, ≥2246.325=1
PI	<6.28=0, ≥6.28=1
WIS	<8.425=0, ≥8.425=1
Grad	<0.935=0, ≥0.935=1
mTTI	<53.205=0, ≥53.205=1
TTP	≥0.042=0, <0.042=1
Malignant breast cancer	No=0, Yes=1

[a]Values assigned based on the cut-off value. CA15-3, cancer antigen 15-3; HER-2, human epidermal growth factor receptor 2; sE-cad, soluble E-cadherin; PI, peak intensity; WIS, wash-in slope; Grad, gradient; mTTI, local mean transit time; TTP, time to peak.

Discussion

Early diagnosis is a vital aspect of breast cancer therapy. Among the diverse diagnostic platforms available, imaging modalities are the primary tool that yields valuable data for patients with breast cancer (23). Additionally, advances and developments in molecular biology technologies have resulted in the identification of cancer-related tumor molecular markers. Evaluating the serum levels of these biomarkers can provide valuable information regarding the occurrence, invasion and metastasis of breast cancer (24). In the present study, the clinical utility of quantitative ultrasonography parameters combined with the serum CA15-3, HER-2 and sE-cad levels in diagnosing mass-type breast cancer were assessed.

Ultrasound examination, particularly Doppler ultrasound, yields highly detailed resolution and can clearly identify the location, size, shape, boundary, echo, calcification, internal structure and other lesion conditions. Moreover, Doppler ultrasound can display the surrounding tissues that determine invasion (25). Furthermore, high-frequency Doppler ultrasound can clearly reflect hemodynamic information by examining tumor angiogenesis together with peripheral blood flow characteristics of lesions, thereby further identifying benign and malignant breast masses (26). In the present study, the breast cancer group exhibited significant differences in ultrasound

Table VII. Logistic multivariate regression analysis.

						95% CI for EXP(B)	
Factor	B	S.E.	Wald	P-value	Exp(B)	Lower	Upper
HER-2 ≥17.295	1.806	0.722	6.245	0.012	6.083	1.476	25.068
TTP <0.042	-3.190	1.149	7.711	0.005	0.041	0.004	0.391
PI ≥6.28	4.034	1.346	8.980	0.003	56.467	4.037	789.847
WIS ≥8.425	2.252	0.997	5.103	0.024	9.502	1.347	67.017
Grad ≥0.935	2.200	0.822	7.173	0.007	9.028	1.804	45.177
CA15-3 ≥32.43	0.373	0.832	0.201	0.654	1.452	0.284	7.424
sE-cad ≥2246.325	-0.011	0.929	0.000	0.990	0.989	0.160	6.104
TTP <0.042	1.070	0.726	2.174	0.140	2.915	0.703	12.084

HER-2, human epidermal growth factor receptor 2; PI, peak intensity; WIS, wash-in slope; Grad, gradient; TTP, time to peak; S.E. standard error; CI, confidence interval.

parameters compared with the benign and control groups. Specifically, the breast cancer group had significantly higher PI, WIS, Grad and mTTI values and a significantly lower TTP value. In addition, the benign group also exhibited higher PI, WIS, Grad and mTTI values and a lower TTP value compared with the control group, but the magnitude of variation was less than that of the breast cancer group. This confirmed the value of the quantitative ultrasonography parameters in the diagnosis of malignant breast cancer. However, ultrasound examination has some limitations, including low sensitivity to calcification and a restricted ability to accurately recognize calcification in the early stages of breast cancer (27). Therefore, when using Doppler ultrasound alone, there is always the possibility of a missed diagnosis or misdiagnosis.

Serum markers are used as prognostic risk factors in addition to therapeutic effectiveness in a number of malignant tumors (28). For instance, CA15-3 may be a promising parameter for the early diagnosis of breast cancer, and its detection is safe and accessible (13). HER-2 is highly expressed or amplified in 20-30% of primary invasive breast cancer cases, and upregulation of HER-2 is associated with a poor prognosis, as HER-2 can modulate cell proliferation, adhesion and differentiation (29). HER-2 serves a notable role as a diagnostic marker (or at least a screening marker) for the early selection of treatments for patients with breast cancer. Therefore, in the present study, the serum levels of HER-2 and other factors in combination with quantitative ultrasonography parameters for the diagnosis of breast cancer were investigated. sE-cad levels are associated with poor survival in patients with metastatic breast cancer and, since sE-cad reflects tumor angiogenesis, it may have therapeutic significance in anti-angiogenic treatment (30). In the present study, it was observed that the serum CA15-3, HER-2 and sE-cad levels were significantly higher in the breast cancer group compared with those in the benign and control groups. Additionally, the levels of these serum markers were also higher in the benign group compared with those in the control group, but the degree of elevation was not as high as in the breast cancer group. This suggests that the CA15-3, HER-2 and sE-cad levels are significantly higher in patients with malignant breast cancer.

Lee *et al* (31) reported that patients with metastatic breast cancer exhibit higher levels of tumor markers than those with primary breast cancer, and that those with higher levels of tumor markers before surgery are more likely to relapse. Owing to the relatively easy measurement and the low cost of biomarker assays, regular measurement of serum tumor marker levels can provide useful information for the early detection of recurrence (32,33). To improve the diagnosis of breast tumors, the combined application of multiple technologies has gained significant attention (34). These diagnoses, combined with new surgical techniques and radiotherapy, form a multidisciplinary collaborative approach to minimize recurrence and reduce treatment-related incidence rates (35). Similarly, color Doppler ultrasound, in combination with the serum marker CA15-3, could improve the diagnosis of breast cancer, demonstrating that combined detection may serve as an effective tool for early diagnosis and clinical intervention (36). The combined measurement of HER-2 and CA15-3 can also enhance the sensitivity and overall accuracy of breast cancer diagnosis (37). Moreover, targeted therapy against sE-cad combined with other therapies could potentially provide a new therapeutic strategy for the treatment of breast cancer (38). In the present study, the correlations between the quantitative ultrasonography parameters and the serum CA15-3, HER-2 and sE-cad levels were probed and the results demonstrated that the levels of CA15-3, HER-2 and sE-cad in the breast cancer group were negatively correlated with TTP and positively correlated with PI, WIS, Grad and mTTI. This finding revealed an association between ultrasound parameters and serum markers and provided a theoretical basis for the combined use in diagnosis. Subsequently, the diagnostic value of ultrasound parameters combined with serum CA15-3, HER-2 and sE-cad for benign and malignant breast cancer were ascertained. ROC curve analysis showed that the AUC for the combination of ultrasound parameters with serum CA15-3, HER-2 and sE-cad levels was 0.919, with the sensitivity and specificity also reaching a higher level than that of each individual index tested alone. This result was superior to the diagnostic performance of any single index, further confirming the advantages of combined use in diagnosis for the detection of malignant breast cancer. In addition, the logistic multivariate regression analysis showed that HER-2 ≥17.295, TTP <0.042, PI ≥6.28, WIS ≥8.425 and Grad ≥0.935 were independent factors in malignant breast cancer detection.

The utility of contrast-enhanced ultrasound (CEUS) in distinguishing malignant from benign breast lesions using general ultrasound equipment has been demonstrated, and it has certain diagnostic and prognostic value in breast cancer (39,40). However, a previous study evaluated HER-2 upregulated breast cancer and other types of breast cancer based on CEUS column line drawings and clinical features, and the results showed that the prediction model based on these features could not differentiate HER-2 upregulated breast cancer from other breast cancer types (41). CEUS mainly relies on the observation and analysis of ultrasonography images, and the choice of parameters is relatively limited. In the present study, by analyzing the AUC values of the aforementioned combined tests, it was demonstrated that quantitative ultrasonography parameters (such as PI, WIS, Grad, mTTI and TTP) in combination with serum CA15-3, HER-2 and sE-cad values may improve the accuracy of diagnosing malignant breast cancer. Moreover, HER-2 expression is positively correlated with vascular endothelial growth factor (VEGF), which is upregulated in 20-30% of human breast cancer cases (42-44). Similarly, quantitative ultrasonography parameters (such as PI, WIS, Grad, mTTI and TTP) in combination with serum CA15-3, HER-2 and sE-cad levels may provide more comprehensive coverage of breast cancer biology than HER-2 and VEGF and may provide more information regarding the biological behavior of the tumor, since CA15-3 and sE-cad are also important tumor markers for breast cancer, thus increasing the diagnostic accuracy and reliability. Therefore, the present study observed the expression levels of HER-2, CA15-3 and sE-cad between benign and malignant tumors, and adopted HER-2, CA15-3 and sE-cad combined with quantitative ultrasonography parameters to diagnose malignant breast cancer. The results of the present study indicated that the combination of the HER-2, CA15-3 and sE-cad levels with the quantitative ultrasonography parameters was beneficial for the diagnosis of benign and malignant tumors.

In conclusion, the combination of quantitative ultrasonography parameters with the CA15-3, HER-2 and sE-cad levels facilitated the differential diagnosis of benign and malignant breast lesions and may provide a reference for clinical treatment. As such, different diagnostic methods in combination with clinical features of patients can improve diagnostic accuracy, which provides a reference and informs future clinical practice. However, the number of patients recruited in the present study was relatively small, and more in-depth studies with larger sample sizes should be conducted in the future.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KH contributed to conception and design. YW contributed to manuscript editing and the acquisition of data. YM and KH contributed to the experimental studies and the analysis and interpretation of data. CX contributed to revising the manuscript (for intellectual content) and the analysis and interpretation of data. All authors read and approved the final version of the manuscript. KH, YW, YM and CX confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted under the approval of the Ethics Committee of Beihua University Affiliated Hospital (Jilin, China; approval no. 2019-038). Written informed consent was acquired from all subjects.

Patient consent for publication

Written informed consent was acquired from all subjects.

Competing interests

The authors declare that they have no competing interests.

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