

Development and evaluation of clinical models based on ultrasound, serum CA153 and molecular subtype in predicting the efficacy of neoadjuvant chemotherapy in breast cancer

MING-YUE DU¹ and SHU-E ZENG^{1,2}

¹Department of Medical Ultrasound, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430079, P.R. China; ²Breast Cancer Center, National Key Clinical Specialty Discipline Construction Program, Hubei Provincial Clinical Research Center for Breast Cancer, Hubei Cancer Hospital, Wuhan, Hubei 430079, P.R. China

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Abstract. Breast cancer is a threat to health, and reliable predictors for neoadjuvant chemotherapy (NAC) efficacy remain limited. The aim of the present study was to develop a clinical model that combines ultrasonography with clinical and pathological characteristics to predict the effectiveness of NAC in patients with breast cancer prior to surgery. The present retrospective study included patients with pathologically confirmed primary breast cancer who underwent NAC followed by surgery based on predefined inclusion and exclusion criteria. Patients were randomly allocated to a test and a validation set in a 7:3 ratio. Clinical data, comprehensive pathological reports and ultrasound imaging features were collected from the Hospital Information System of Hubei Cancer Hospital (Wuhan, China). Univariate and multivariate logistic regression analyses were conducted to identify independent predictive factors, with significance set at a bilateral $P < 0.05$. The receiver operating characteristic curve was used to assess the performance of the model. The present study included 323 female patients with breast cancer. Univariate analysis indicated significant differences in tumor diameter changes, mass margin and posterior echo patterns (classified as shadow, enhancement or no posterior features), change in serum carbohydrate antigen 153 (CA153) levels, clinical N stage (classified as cN0-cN3), hormone receptor expression, Ki-67 levels and molecular type between the pathological complete response (pCR) and pathological incomplete response (non-pCR) group. Multivariate analysis

identified margin, molecular subtype, changes in tumor diameter and serum CA153 levels as significant predictors included in the final model ($P < 0.05$). Furthermore, the present study model was validated in the validation set. The area under the curve for the predictive model in test set was 0.823 (95% confidence interval, 0.765-0.881), while in the validation set, it was 0.884 (95% confidence interval, 0.816-0.953). The integrated model, which incorporated ultrasound, serum CA153 levels and molecular subtypes, demonstrated notable potential for preoperative assessment of NAC efficacy in the future.

Introduction

Breast cancer ranks among the most common prevalent malignant tumors impacting the health of women, with an estimated 2.30 million new cases and 764,000 deaths globally in 2023 (1). Recently, the age of onset has demonstrated a decreasing trend, with China accounting for 12.2% of novel global cases and 9.69% of global mortality annually (2). Neoadjuvant chemotherapy (NAC) is a systemic treatment administered before local interventions such as surgery or radiation therapy, serving a key role in the management of locally advanced breast cancer (3). The primary objectives of NAC include shrinking tumor size, improving clinical staging, preparing for surgical removal and accommodating the preferences of patients who wish to conserve their breasts (4). Furthermore, during the administration of these drugs, the sensitivity of the tumor to chemotherapy can be evaluated, aiding in the development of postoperative treatment strategies. This method can increase the likelihood of breast-conserving surgeries, with reported increases of 20-30% compared with upfront surgery (5), and improve patient survival rates, contributing to its growing use in recent years (4,6,7). Previous studies indicated that patients who achieve a pathological complete response (pCR) following NAC experience markedly improved overall and disease-free survival rates, particularly those with triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive subtypes (8-10). Nonetheless, breast cancer displays notable molecular diversity, and subtypes respond

Correspondence to: Professor Shu-E Zeng, Department of Medical Ultrasound, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, 116 Zhuodaquan South Road, Wuhan, Hubei 430079, P.R. China
E-mail: zengshue7799@sina.com

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differently to treatments (11-13). Thus, accurately assessing the effectiveness of NAC is key to determining appropriate treatment paths, guiding preoperative evaluations and informing postoperative chemotherapy, while also offering notable prognostic insights in the future (14,15).

Ultrasonography is a quick, non-invasive imaging method that does not involve radiation and is extensively used in diagnosing breast conditions. Ultrasonography allows for accurate measurement of tumor dimensions, morphology and blood flow characteristics (16). In comparison with mammography and physical examinations, ultrasound (US) provides more precise measurements of the changes in breast mass sizes. Ultrasonographic characteristics of breast cancer are associated with pathological classifications and molecular biological markers (17-19). However, the accuracy of US assessment is dependent on the skill of the operator. In cases where tumor size does not markedly decrease, the number of cancer cells can diminish after NAC, making it inadequate in predicting the true response to treatment. Certain studies have proposed that integrating patient-specific factors such as clinical stage, grade and subtype, could enhance diagnostic precision of breast cancer (20,21).

Biomarkers such as the estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki-67 serve a notable role in the treatment and prognosis of breast cancer. Breast cancer is categorized into four molecular subtypes (namely, luminal A, luminal B, triple-negative and HER2⁺) based on these biomarkers. Patients with these different subtypes respond differently to chemotherapy (21). It is widely accepted that the effectiveness of NAC varies among these molecular classifications (22-24). In addition to these pathological markers, serum tumor markers (TM) are substances identified in malignant cells or on their membranes, resulting from abnormal expression of genes or proteins driven by neoplastic transformation. Serum TM serve as indicators in evaluating how tumors respond to treatment (25). Tracking TM levels provide insights into tumor development and progression, making them key to clinical monitoring of patients with cancer. For instance, carbohydrate antigen 153 (CA153) is a key serum TM monitored in the early diagnosis of breast cancer. The abnormal levels of serum TM are often associated with clinical staging and lymph node metastasis in patients with breast cancer (26). This marker can aid in the initial evaluation of treatment responses for patients with tumors (27-29).

It is possible to predict the response to NAC (7,14,16,30). Although there is ongoing exploration of different imaging metrics and clinical TM to assess the effectiveness of NAC, no singular measure has proven to be reliably predictive, to the best of our knowledge. The present study aims to develop a clinical model that combines US imaging with clinical characteristics to predict response to NAC in breast cancer. Furthermore, the present study model aims to offer a more precise, safe and effective strategy in enhancing the accuracy of predicting pCR, identifying early reaction to NAC and supplying dependable data for future treatment modifications. Therefore, the present study aims to improve survival rates and the overall quality of life of patients in the future.

Patients and methods

Study design and patients. The present retrospective cohort study was approved by the Ethics Committee of Hubei Cancer

Hospital (approval no. 2020-KYLL-S08; Wuhan, China). The present study included a total of 883 patients diagnosed with breast cancer who underwent surgical procedures after NAC at the Hubei Cancer Hospital (Wuhan, China) from January 2021 to December 2022. Of these, 529 patients initially met the inclusion criteria. All data were derived from archived electronic medical records. The present study performed retrospective data extraction in early 2023, after all included patients had completed their full treatment courses and their electronic medical records were fully archived. No prospective patient enrollment or real-time data collection was conducted during the clinical treatment period. The decision to administer NAC was based on the guidelines set forth by the National Comprehensive Cancer Network guidelines (31). The inclusion criteria were as follows: i) Patients with a confirmed diagnosis for breast cancer via core needle biopsy at Hubei Cancer Hospital prior to NAC; ii) patients with complete pathological and immunohistochemical evaluations of both pre-NAC biopsies and post-operative samples; and iii) patients with US examinations and comprehensive reports before and after NAC, along with serum CA153 levels measured at both time points. A total of 206 patients were excluded from the analysis due to various reasons, including secondary breast cancer, inflammatory breast cancer or bilateral breast cancer, ambiguous clinical staging or molecular subtype, incomplete clinical and pathological data, subpar US images that hindered the extraction of ultrasonic characteristics and notable dysfunction of the heart, liver, kidneys or other organs (Fig. 1). It should be noted that the initial protocol preliminarily estimated a sample size of 200 cases based on historical admission data. However, the expansion of the Breast Cancer Center led to a marked rise in patient volume starting in 2021. The present study ultimately included all consecutive eligible patients within the predefined study period, yielding a total of 323 included cases.

US protocol. US evaluations were performed by specialists with ≥ 5 years of professional experience. Each patient underwent standard brightness-mode US at the beginning (pre-NAC) and again within 1 week before surgery after completing NAC. Patients received 6-8 cycles of NAC. The timing of the last preoperative US was determined by the clinical team based on factors such as treatment response, side effects and surgical scheduling, occurring after the 6th, 7th or 8th cycle. All participants in the present study were examined using different US scanners and transducer probes, positioned supine with their arms raised to allow complete visibility of the breast. These assessments focused on various parameters, including morphological characteristics, margins, location (indicated by clock-point numbers and distance from the skin), maximum tumor diameter, posterior echo pattern, interaction with adjacent tissues, internal calcifications and blood flow. If elastography or contrast-enhanced US (CEUS) examinations were performed, those findings were documented concurrently. These examinations were conducted at the discretion of the senior ultrasound physician when additional assessment of tumor vascularity (CEUS) or stiffness (elastography) was considered necessary to aid in classification.

Histopathology. All pathological specimens obtained after surgery were analyzed by two experienced pathologists from

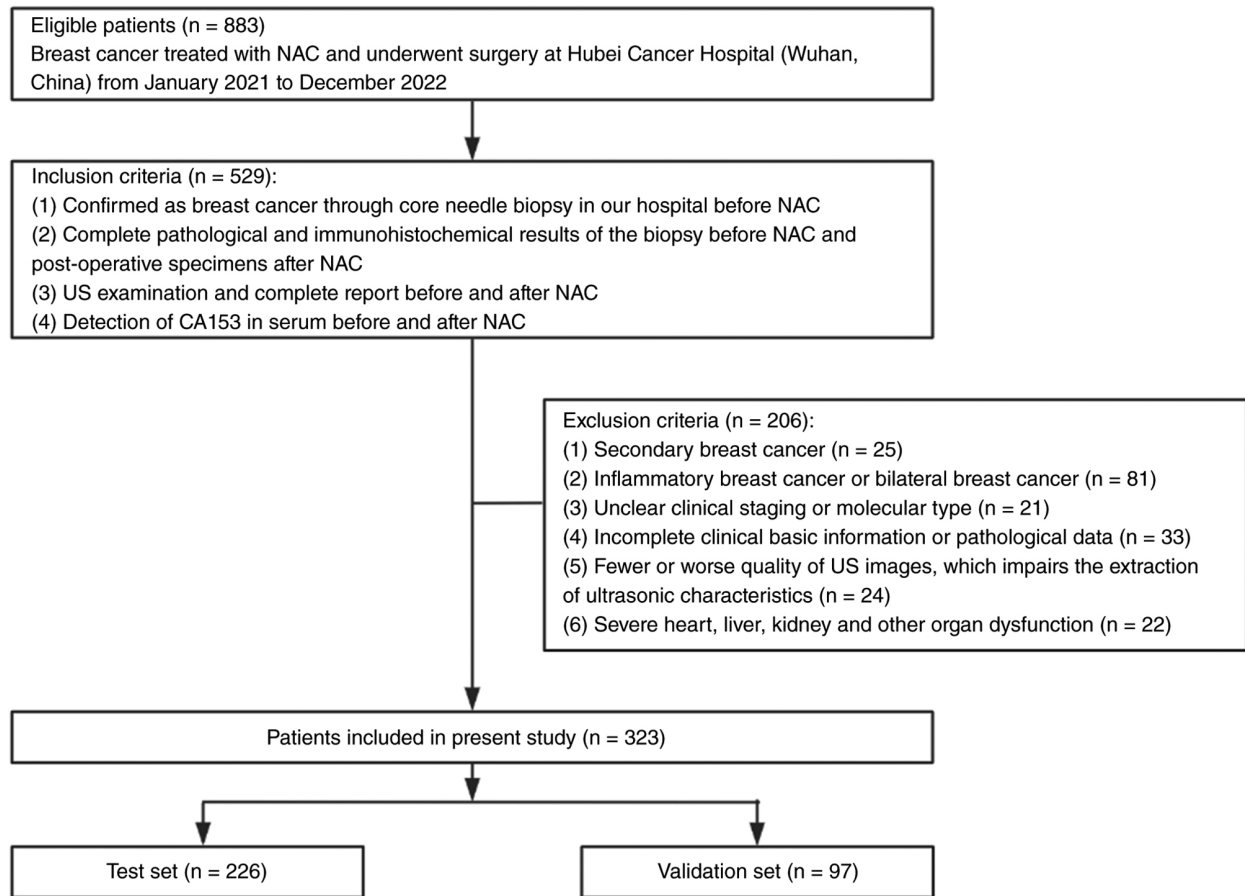


Figure 1. Flowchart of the criteria for case collection, inclusion and exclusion in the present study. NAC, neoadjuvant chemotherapy; US, ultrasound; CA153, carbohydrate antigen 153.

Hubei Cancer Hospital, each with >5 years of experience in the field. The evaluation utilized the Miller and Payne (MP) method, comparing core needle biopsy samples taken before chemotherapy and those collected post-treatment. The assessment of residual tumor cells following NAC was categorized into five grades: i) G1, no tumor cell loss; ii) G2, loss <30%; iii) G3, 30-90% reduction; iv) G4, loss of >90%; and v) G5, absence of malignant cells. According to the MP grading system (32), a pathological incomplete response (non-pCR) is characterized by G1-G4, where tumor cells remain in the tumor bed. A pCR is classified as G5, indicating no invasive cancer cells are present at the tumor bed, although ductal carcinoma *in situ* may still be identified. Tumor cells were classified as ER⁺/PR⁺ if staining was ≥1%; otherwise, the tumor cells were considered negative. Immunohistochemistry results were interpreted as HER2 negative for scores of (-) and (+) (22,24), while (+++) indicated HER2 positivity. For scores of (++) , additional fluorescence *in situ* hybridization (FISH) test was performed, with a FISH result of (+) considered positive and (-) negative. Tissue samples were retrieved from archived formalin-fixed paraffin-embedded (FFPE) blocks. Specimens were fixed in 10% neutral-buffered formalin at room temperature for 24 h. Sections (4 μm) were mounted on glass slides and subjected to routine hematoxylin-eosin (H&E) staining at room temperature (hematoxylin for 5 min, eosin for 1 min). FISH was performed on 4 μm-FFPE sections using the HER2/CEP17 dual-color FISH probe kit (Cat. No. F.01359-01; Guangzhou

LBP Medicine Science & Technology Co., Ltd.), according to the manufacturer's instructions. Enzymatic permeabilization was performed with kit-supplied pepsin at 37°C for 6-10 min, with the incubation duration optimized according to tissue conditions, followed by post-fix using 10% neutral buffered formalin at room temperature for 10 min. Briefly, 10 μl of premixed hybridization buffer containing HER2/CEP17 probes was applied to tissue sections. Co-denaturation was conducted at 85°C for 5 min, followed by hybridization at 37°C for 10-18 h in a humidified chamber. Post-hybridization stringent washing was carried out using kit-provided buffers. Nuclei were counterstained with DAPI at room temperature for 5 min. Fluorescence signals were visualized and captured using an Olympus BX51 fluorescence microscope. Hormone receptor (HR) positivity was defined as positivity for ER and/or PR. A Ki-67 index indicating ≥20% positive cells was classified as high expression, while <20% was classified as low expression (33). According to the 2023 St. Gallen consensus (34), breast cancer was categorized into four subtypes: i) Luminal A (ER⁺ and/or PR⁺, HER2⁻ and Ki-67 <14%); ii) luminal B (ER⁺ and/or PR⁺, HER2⁻ and Ki-67 ≥14% or ER⁺ and/or PR⁺, HER2⁺ and any Ki-67); iii) HER2 upregulation (ER⁻/PR⁻, HER2⁺ and any Ki-67); and iv) TNBC (ER⁻/PR⁻, HER2⁻ and any Ki-67).

Biopsy and NAC. Patients underwent a core needle biopsy at Hubei Cancer Hospital, which pathology confirmed as primary invasive breast cancer. An immunohistochemical

analysis was carried out to establish the molecular subtype. IHC was performed on 4 μm FFPE sections. Tissue specimens were fixed in 10% neutral buffered formalin at room temperature for 24 h and embedded in paraffin. Antigen retrieval was performed in pre-boiled 0.01 M citrate buffer (pH 6.0) with a pressure cooker at 121°C; slides were heated for 3 min, cooled for 20 min and rinsed under running tap water, followed by rehydration in a descending ethanol series. Endogenous peroxidase activity was blocked with 3% H_2O_2 for 10 min at room temperature. Sections were incubated overnight at 4°C with primary antibodies against ER (cat. No. 790-4324; 1:100), PR (cat. No. 790-2223; 1:100), HER2 (all Ventana, Cat. No. 790-4493; 1:200), and Ki-67 (Dako, Cat. No. M7240; 1:100). HRP-labelled secondary antibody from the EliVision™ plus kit (KIT-9902; Fuzhou Maxim Biotech, China) was applied for 1 h at room temperature. Immunoreactivity was visualized with DAB, and sections were counterstained with Mayer's hematoxylin at room temperature for 1-3 min prior to examination under a light microscope. In cases where there was notable enlargement of the axillary lymph nodes, a lymph node aspiration was performed concurrently to assess if it was due to breast cancer metastasis. All patients included in the present study received 6-8 cycles of standard NAC, with the specific regimen tailored by the medical team based on the immunohistochemical molecular subtype results, following the Chinese Society of Clinical Oncology guidelines for breast cancer management (35). Comprehensive information on regimens, drugs, cycles and distribution of molecular subtype are provided in Table SI. The most frequently utilized regimens were doxorubicin + cyclophosphamide followed by docetaxel (AC-T; 8 cycles) and epirubicin + cyclophosphamide followed by docetaxel (EC-T; 8 cycles), accounting for 240 patients or 74.3%. For patients with HER2 positivity, regimens containing trastuzumab and/or pertuzumab (such as EC-TH, AC-THP, TCHP, TCbHP and TCH/TCbH) were administered in accordance with the Chinese Society of Clinical Oncology Breast Cancer guidelines [2021 edition (36) and 2022 edition (35)] available at the time of treatment.

Clinical data collection from patients. The present study collected clinical, US and pathological information, which included age. While the frequency of monitoring was determined by the judgment of the physician, the present study documented the maximum tumor diameter and serum CA153 levels during both the initial (baseline) and final (preoperative) assessments for the present analysis. The present study also noted US characteristics before NAC, the surgical approach adopted post-NAC and the initial clinical T and N stages based on the 2017 American Joint Committee on Cancer 8th edition breast cancer TNM staging criteria (37). Furthermore, the present study evaluated biopsy pathological data before NAC, including ER and PR status, HER2 expression, Ki-67 index and the presence of axillary lymph node metastasis. Post-surgery, the present study recorded pathological data such as occurrence of vascular or nerve invasion and whether a pCR was achieved (Fig. 1).

Statistical analysis. For model development and internal validation, the dataset was divided randomly into a test set (70%) and a validation set (30%) using a straightforward random

allocation technique [utilizing the SPSS random number generator (version 26.0, IBM Corp.)] (38). The percentage reduction in maximum tumor diameter was determined using the formula: (Initial diameter-preoperative diameter)/initial diameter $\times 100\%$. Receiver operating characteristic (ROC) curve analysis was utilized to ascertain the ideal cut-off point in predicting pCR, based on the Youden index (sensitivity + specificity-1). Measurement data are presented as mean $\pm$ standard deviation, while categorical data are indicated as frequencies (%). Normality assessments were conducted on the measurement data from both the test and validation set. The unpaired Student's t-test was used for comparisons of continuous variables between groups. Categorical data were compared between groups using either the χ^2 or Fisher's exact test. $P < 0.05$ was considered to indicate a statistically significant difference.

Variable selection. In the test set, the data was categorized according to the achievement of pCR. A univariate logistic regression analysis was conducted to investigate the factors associated with pCR, and variables demonstrating $P < 0.05$ were included into a multivariate logistic regression analysis. The present analysis used a forward stepwise selection approach, using the likelihood ratio method, using an entry threshold of $\alpha = 0.05$ and a removal threshold of $\alpha = 0.10$; IBM SPSS Statistics (version 26.0; IBM Corp.). The main variables, including US characteristics, CA153 levels, molecular subtype and pCR results, had no missing data. However, elastography and CEUS data, which were only available for certain subsets, were excluded from the primary model and thus, no imputation was performed.

Interaction testing. The logistic regression model [using the 'Enter' method; IBM SPSS Statistics (version 26.0; IBM Corp.)] was used to examine two predetermined interactions by incorporating product terms: i) Molecular subtype in conjunction with US margin; and ii) the variation in CA153 alongside the variation in tumor diameter. An interaction of $P < 0.05$ was considered to indicate a statistically significant difference.

Model evaluation. An odds ratio (OR) > 1 suggests an increased probability of achieving pCR. The assessment of the model was performed in both the test and validation sets. For the validation process, the calibration and discrimination were evaluated using the Hosmer-Lemeshow goodness-of-fit test and the area under the ROC curve (AUC) (39). To examine possible confounding effects associated with age and tumor size, a sensitivity analysis was conducted using forced entry ('Enter' method) logistic regression, incorporating these two factors alongside the initial predictors. In all evaluations, a two-sided $P < 0.05$ was considered to indicate a statistically significant difference. Variance inflation factor (VIF) was calculated to assess multicollinearity between selected variables. All statistical analyses were carried out using the commercially available SPSS software (version 26.0; IBM Corp.).

Results

Clinical data of patients. A total of 323 patients were included in the present study (mean age $\pm$ standard deviation,

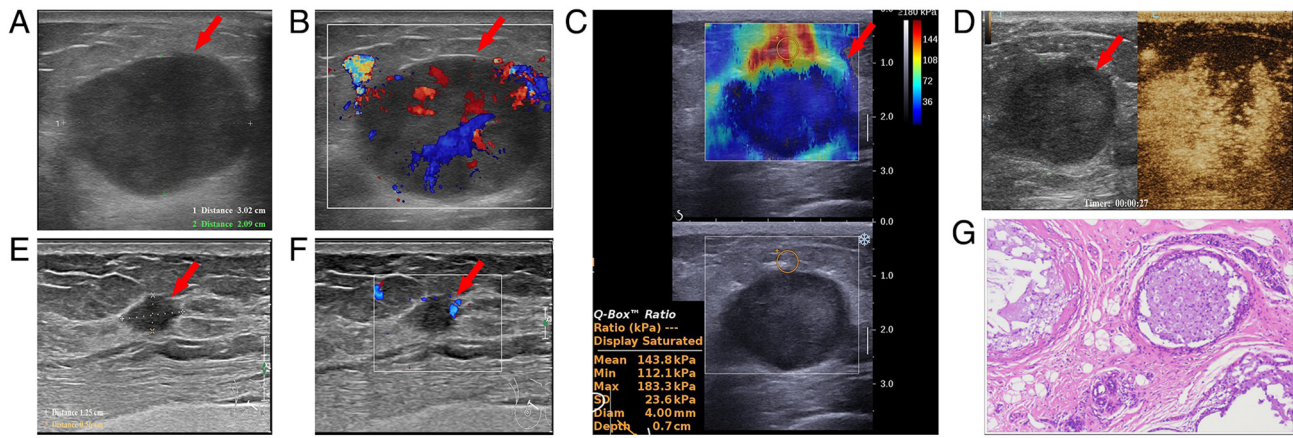


Figure 2. A 69-year-old female patient with invasive breast cancer, clinical T2N0M0. The biopsy pathology indicated: Estrogen receptor (-), progesterone receptor (-), human epidermal growth factor receptor 2 (-) and a high level of Ki-67. The corresponding immunohistochemistry supporting evidence for this patient is presented in Fig. S2. US examination before treatment: In the right breast at 1 o'clock, 2.96x2.1 cm-mass with circumscribed margin and regular shape and post-echo attenuation. (A and B) Internal rough perforating vessels were observed. (C) Representative SWE image of breast lesion presenting a 'hard ring' sign. (D) Contrast-enhanced US examination with Sonovue: The mass indicated heterogeneous high enhancement at 16 sec and the range after contrast was larger than before. (E) After 8 cycles of EC-T regimen (epirubicin + cyclophosphamide-paclitaxel), the tumor size reduced to 1.25x0.56 cm. (F) CDFI revealed sparse peripheral vascularity. (G) Postoperative pathology after total resection of the right breast indicated a complete response after chemotherapy (the original breast lesion of the Miller-Payne grading system: grade 5). Magnification, x200. The red arrow indicates the lesion. US, ultrasound; SWE, shear-wave elastography.

49.9±10.9 years; range, 21-74 years). Among the present study cohort, 226 patients were assigned to the test set and 97 patients to the validation set. Comprehensive clinical, US and pathological information were collected from all participants (Table I). The mean serum CA153 levels was recorded at 21.7±25.5 U/ml, while the maximum tumor diameter was 3.9±2.1 cm. US analysis revealed that a notable portion of the tumors exhibited irregular shapes (89.8%; 290/323) and the posterior echoes indicated no notable changes (59.1%; 191/323), with 29.1% (94/323) displaying shadowing. The majority of patients in the present study had axillary lymph node metastasis (81.1%; 262/323). The predominant molecular subtype identified was luminal B (49.2%; 159/323), with clinical stages T2 (71.5%; 231/323) and N1 (55.4%; 179/323) being the most prevalent. Of the 323 patients, 292 (90.4%) underwent total mastectomy as part of their radical treatment, while 31 (9.6%) opted for breast-conserving surgery after NAC, with 29.7% (96/323) achieving a pCR. The characteristics of test and validation sets are detailed in Table I, demonstrating no statistically significant differences in the distribution of all the variables between the two groups (all $P>0.05$).

Univariate analysis in test set. In the test set ($n=226$), 30.1% (68/226) of patients achieved a pCR. Table II illustrates the comparisons between patients in the pCR and non-pCR groups. Tumor size reduction and the age of patients were categorized based on the cut-off values derived from the Youden index. The determined optimal cut-off value of tumor size reduction was 48.5% (with sensitivity at 0.892 and specificity at 0.882, yielding a Youden index of 0.774), which was rounded to 50% for practical application (data not shown). Among the pCR group ($n=68$), 22.1% ($n=15$) of them were aged <46 years of age and 91.2% ($n=62$) had tumors ≥ 2.1 cm. By contrast, in the non-pCR group, 33.5% ($n=53/158$) were aged <46 years, with a notable majority (88.6%; 140/158) having tumor diameters >2.1 cm. However, these differences were not statistically

significant (all $P>0.05$). A reduction in maximum diameter by $\geq 50\%$ was more frequently observed in the pCR group (73.5%; 50/68), while the non-pCR group predominantly exhibited diameter changes <50% (72.8%; 115/158), with these differences being statistically significant ($P<0.001$). In the pCR group, the most prevalent US features in the pCR group was a circumscribed margin (82.3%; 56/68; Fig. 2), whereas only 32.9% (52/158) of the non-PCR group displayed this characteristic (Fig. 3), indicating a statistically significant difference ($P<0.001$). Both in the pCR and non-PCR group, the absence of posterior features was common; however, tumors with post-echo attenuation were significantly more frequent in the non-pCR group (34.2%; 54/158) compared with the pCR group (17.6%; 12/68) ($P=0.024$). No significant differences were identified in morphological characteristics, twisted perforating vessels or calcification between the two groups (all $P>0.05$). Clinical N1 status ($P=0.014$ and a reduction in serum CA153 levels post-NAC ($P=0.037$) were significantly more prevalent in the pCR group (both 73.5%; 50/68) than in the non-pCR group (46.8%, 74/158 and 41.2%, 65/158). The pCR group also demonstrated elevated Ki-67 levels (83.8%, 57/68) and higher proportion of negative hormone receptors (ER⁻ and PR⁻; 64.8%, 44/68) ($P=0.035$ and $P=0.006$, respectively; Fig. S1) compared with the non-pCR group (70.2%, 111/158 and 36.1%, 57/158). Luminal B (55.7%, 88/158) and HER2 (21.5%, 34/158) were the most common subtypes in the non-pCR group (Fig. S2), while TNBC (39.7%, 27/68) and luminal B (30.8%, 21/68) subtypes were the most common subtypes in the pCR group. The overall distribution differed significantly ($P=0.021$). No significant differences were noted in clinical T stage or HER2 expression between the two groups (all $P>0.05$).

Multivariate logistic regression analysis in test set. In the present study, variables with $P<0.05$ from the univariate analysis were incorporated into the multivariate logistic regression analysis. The results of the multivariate analysis (Table III)

Table I. Patient and tumor characteristics in the present study.

Characteristics	Total patients (n=323)	Test set (n=226)	Validation set (n=97)	P-value
Age (years), mean $\pm$ SD	49.9 $\pm$ 10.9	50.3 $\pm$ 10.9	49.2 $\pm$ 10.9	0.424
CA153, U/ml, mean $\pm$ SD	21.7 $\pm$ 25.5	22.4 $\pm$ 25.5	19.9 $\pm$ 25.6	0.407
Tumor diameter (cm), mean $\pm$ SD	3.9 $\pm$ 2.1	3.9 $\pm$ 2.1	3.8 $\pm$ 2.0	0.694
Change in tumor diameter (%), n (%)				0.821
<50	188 (58.2)	133 (58.8)	55 (56.7)	
$\geq$ 50	135 (41.8)	93 (41.2)	42 (43.3)	
Margin, n (%)				0.871
Circumscribed	153 (47.4)	108 (47.8)	45 (46.4)	
Not circumscribed	170 (52.6)	118 (52.2)	52 (53.6)	
Morphological characteristics, n (%)				0.715
Regular	33 (10.2)	24 (10.6)	9 (9.3)	
Irregular	290 (89.8)	202 (89.4)	88 (90.7)	
Posterior echo pattern, n (%)				0.985
No posterior features	191 (59.1)	133 (58.8)	58 (59.8)	
Enhancement	38 (11.8)	27 (11.9)	11 (11.3)	
Shadow	94 (29.1)	66 (29.3)	28 (28.9)	
Calcification, n (%)				0.780
Yes	148 (45.8)	104 (46.0)	44 (44.3)	
No	175 (54.2)	122 (54.0)	53 (55.7)	
Twisted perforating vessels, n (%)				0.742
Yes	153 (47.4)	105 (46.4)	48 (49.5)	
No	170 (52.6)	121 (53.6)	49 (50.5)	
Axillary lymph node metastasis, n (%)				0.645
Yes	262 (81.1)	183 (80.9)	79 (81.4)	
No	61 (18.9)	43 (19.1)	18 (18.6)	
Change in CA153 levels, n (%)				0.913
Increase	160 (49.5)	111 (49.1)	49 (50.5)	
Decrease	163 (50.5)	115 (50.9)	48 (49.5)	
Surgical method, n (%)				0.309
Breast-conserving	31 (9.6)	21 (9.3)	10 (10.3)	
Radical	292 (90.4)	205 (90.7)	87 (89.7)	
Clinical T stage (%)				0.793
1	20 (6.2)	12 (5.3)	8 (8.2)	
2	231 (71.5)	163 (72.1)	68 (70.1)	
3	48 (14.9)	35 (15.5)	13 (13.5)	
4	24 (7.4)	16 (7.1)	8 (8.2)	
Clinical N stage (%)				0.839
0	61 (18.9)	43 (19.0)	18 (18.6)	
1	179 (55.4)	124 (54.9)	55 (56.7)	
2	47 (14.6)	33 (14.6)	14 (14.4)	
3	36 (11.1)	26 (11.5)	10 (10.3)	
Vascular/nerve invasion (%)				0.913
No	195 (60.4)	136 (60.2)	59 (60.8)	
Yes	128 (39.6)	90 (39.8)	38 (39.2)	
Hormone receptor, n (%)				0.372
Negative	185 (57.3)	125 (55.3)	60 (61.9)	
Positive	138 (42.7)	101 (44.7)	37 (38.1)	
HER2 (%)				0.101
Negative	251 (77.7)	175 (77.4)	76 (78.4)	
Positive	72 (22.3)	51 (22.6)	21 (21.6)	

Table I. Continued.

Characteristics	Total patients (n=323)	Test set (n=226)	Validation set (n=97)	P-value
Ki-67 levels, n (%)				0.372
Low	80 (24.8)	58 (25.7)	22 (22.7)	
High	243 (75.2)	168 (74.3)	75 (77.3)	
Molecular type, n (%)				0.272
Luminal A	23 (7.1)	16 (7.1)	7 (7.2)	
Luminal B	159 (49.2)	109 (48.2)	50 (51.6)	
HER2	72 (22.3)	51 (22.6)	21 (21.6)	
TNBC	69 (21.4)	50 (22.1)	19 (19.6)	
pCR, n (%)				
Yes	96 (29.7)	68 (30.1)	28 (28.8)	
No	227 (70.3)	158 (69.9)	69 (71.2)	

pCR, pathological complete response; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; CA153, carbohydrate antigen 153.

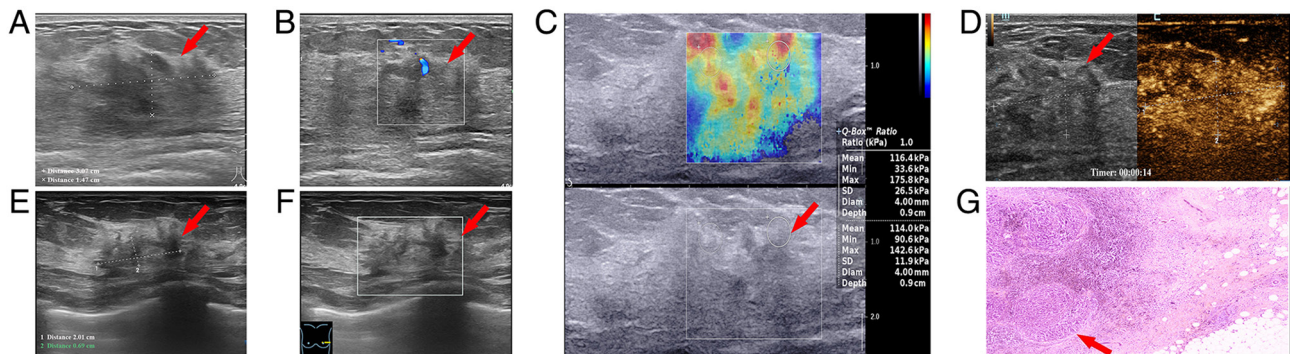


Figure 3. A 40-year-old female patient with invasive breast cancer, clinical T2N2M0, biopsy pathology: Estrogen receptor (+), progesterone receptor (+), human epidermal growth factor receptor 2 (+) and high expression of Ki-67. US examination before treatment: Size of 3.07x1.47 cm, 3 o'clock in the left breast, mass with dis-circumscribed margin and irregular shape. (A and B) Color Doppler flow imaging revealed no perforator vessels. (C) Representative SWE image of breast lesion. The mean stiffness of the mass was 116 kPa, corresponding to the mean Young's modulus, indicating relatively stiff tissue. (D) Contrast-enhanced US examination with Sonovue: The tumors indicated heterogeneous hyperenhancement, and the range did not expand significantly. (E) After 8 cycles of TCbHP regimen (docetaxel + carboplatin + trastuzumab + pertuzumab), the tumor size was 2.01x0.69 cm. (F) No obvious blood flow signals were detected on CDFI. (G) After total left mastectomy and axillary lymph node dissection, H&E staining showed a moderate response (the original breast lesion of the Miller-Payne grading system: grade 3) without neurovascular invasion. Magnification: x200). The red arrow indicates the lesion. SWE, shear-wave elastography.

indicated that, in the US evaluation, a tumor diameter reduction $\geq 50\%$ (adjusted OR, 5.197; 95%CI, 1.635-16.518) and a circumscribed margin (adjusted OR, 9.157; 95%CI, 4.242-19.765) are significantly associated with pCR (Figs. 2 and 3). Additional independent predictors of pCR included molecular subtype, with the TNBC subtype indicating a significant independent association with pCR when compared with luminal A (adjusted OR, 4.262; 95%CI, 1.647-11.028). A reduction in CA153 levels (adjusted OR, 2.227; 95%CI, 1.061-4.675) also demonstrated a significant relationship with pCR (all $P < 0.05$).

Sensitivity analyses that adjusted for age and tumor size categories did not markedly alter the ORs (Table SII) for

the AUC of the present study model (Fig. S3). To further determine whether a circumscribed margin serves only as a substitute for TNBC, stratified and interaction analyses were performed (Table SIII). In the non-TNBC subgroup (Luminal+/HER2+; n=176), the OR for a circumscribed margin was 1.827 [OR=1.827; 95% confidence interval (CI), 1.015-4.389; $P=0.067$]; for the TNBC subgroup (luminal-/HER2+; n=50), the OR was 1.875 (95% CI, 0.482-7.372; $P=0.133$). Interaction tests demonstrated no significant modification effects from molecular subtype x margin ($P=0.667$) or CA153 x tumor diameter reduction ($P=0.42$), suggesting that the influence of margin on pCR did not differ significantly between patients

Table II. Univariate analysis of patients in the test set (n=226) classified into pCR and non-pCR groups.

Characteristics	Total, n (%)	PCR (n=68), n (%)	Non-PCR (n=158), n (%)	B value	OR	95% CI	P-value
Age, years							
≥46	158 (69.9)	53 (77.9)	105 (66.5)		Reference		
<46	68 (30.1)	15 (22.1)	53 (33.5)	-0.579	0.561	0.289-1.087	0.087
Tumor diameter, cm							
≥2.1	202 (89.4)	62 (91.2)	140 (88.6)		Reference		
<2.1	24 (10.6)	6 (8.8)	18 (11.4)	0.284	1.329	0.503-3.509	0.566
Change in tumor diameter, %							
≥50	93 (41.2)	50 (73.5)	43 (27.2)		Reference		
<50	133 (58.8)	18 (26.5)	115 (72.8)	-2.005	0.135	0.071-0.256	<0.001 ^a
Margin							
Not circumscribed	118 (52.2)	12 (17.6)	106 (67.1)		Reference		
Circumscribed	108 (47.8)	56 (82.4)	52 (32.9)	2.253	9.513	4.694-19.277	<0.001 ^a
Morphological characteristics							
Irregular	202 (89.4)	62 (91.2)	140 (88.7)		Reference		
Regular	24 (10.6)	6 (8.8)	18 (11.3)	0.284	1.329	0.503-3.508	0.566
Posterior echo pattern							0.038 ^a
No posterior features	133 (58.8)	45 (66.2)	88 (55.7)		Reference		
Enhancement	27 (11.9)	11 (16.2)	16 (10.1)	0.296	1.344	0.576-3.138	0.494
Shadow	66 (29.3)	12 (17.6)	54 (34.2)	-0.833	0.453	0.211-0.894	0.024 ^a
Twisted perforating vessels							
Yes	105 (46.4)	31 (45.5)	74 (46.8)		Reference		
No	121 (53.6)	37 (54.5)	84 (53.2)	-0.05	0.951	0.538-1.682	0.863
Calcification							
Yes	104 (46.0)	30 (44.1)	74 (46.8)		Reference		
No	122 (54.0)	38 (55.9)	84 (53.2)	-0.110	0.896	0.506-1.587	0.707
Change in CA153 levels							
Increase	111 (49.1)	18 (26.5)	93 (58.8)		Reference		
Decrease	115 (50.9)	50 (73.5)	65 (41.2)	0.663	1.941	1.039-3.627	0.037 ^a
Axillary lymph node metastasis							
Yes	183 (80.9)	60 (88.3)	123 (77.8)		Reference		
No	43 (19.1)	8 (11.7)	35 (22.2)	0.05	1.051	0.509-2.174	0.892
Clinical T stage							0.447
4	16 (7.1)	3 (4.4)	13 (8.2)		Reference		
1	12 (5.3)	3 (4.4)	9 (5.8)	0.368	1.444	0.236-8.844	0.691
2	163 (72.1)	54 (79.4)	109 (68.9)	0.764	2.147	0.587-7.854	0.248
3	35 (15.5)	8 (11.8)	27 (17.1)	0.250	1.284	0.281-5.656	0.741
Clinical N stage							0.016 ^a
3	26 (11.5)	3 (4.4)	23 (14.6)		Reference		
0	43 (19.0)	8 (11.8)	35 (22.2)	0.966	2.629	0.668-10.346	0.167
1	124 (54.9)	50 (73.5)	74 (46.8)	1.583	4.869	0.385-17.123	0.014 ^a
2	33 (14.6)	7 (10.3)	26 (16.4)	0.671	1.769	0.397-7.891	0.455
Ki-67 levels							
High	168 (74.3)	57 (83.8)	111 (70.2)		Reference		
Low	58 (25.7)	11 (16.2)	47 (29.8)	-0.786	0.456	0.220-0.946	0.035 ^a

Table II. Continued.

Characteristics	Total, n (%)	PCR (n=68), n (%)	Non-PCR (n=158), n (%)	B value	OR	95% CI	P-value
HER2							
Negative	175 (77.4)	51 (74.9)	124 (78.5)		Reference		
Positive	51 (22.6)	17 (25.1)	34 (21.5)	0.352	1.422	0.711-2.801	0.308
Hormone receptor							
Negative	125 (55.3)	44 (64.8)	57 (36.1)		Reference		
Positive	101 (44.7)	24 (35.2)	101 (63.9)	-0.808	0.446	0.250-0.795	0.006 ^a
Molecular type							0.021 ^a
Luminal A	16 (7.1)	3 (4.4)	13 (8.2)		Reference		
Luminal B	109 (48.2)	21 (30.8)	88 (55.7)	0.285	1.330	0.353-5.014	0.674
HER2	51 (22.6)	17 (25.1)	34 (21.5)	0.773	2.167	0.543-8.645	0.273
TNBC	50 (22.1)	27 (39.7)	23 (14.6)	1.375	3.957	0.988-15.850	0.052

^aP<0.05. pCR, pathological complete response; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; CA153, carbohydrate antigen 153; CI, confidence interval.

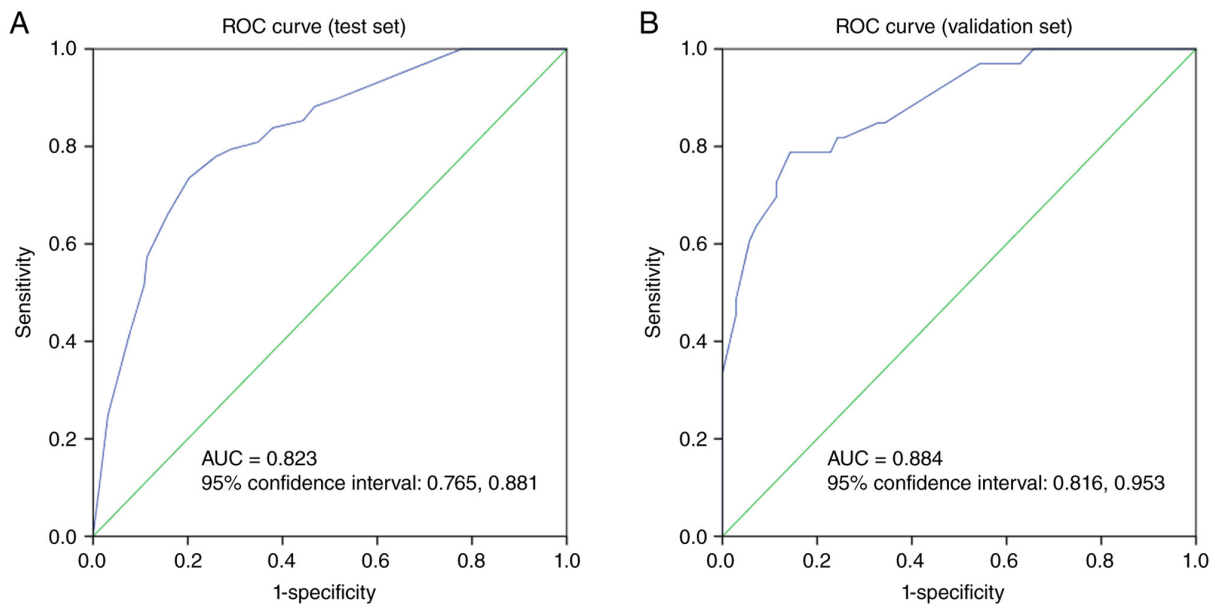


Figure 4. ROC analysis, multivariate combination model in predicting chemotherapy response in (A) test set and (B) validation set. ROC, receiver operating characteristic; AUC, area under the curve.

with TNBC and without TNBC. To evaluate the predictive value of conventional B-mode US, we found that among patients with a $\geq 50\%$ size reduction, 27% had residual disease on pathology, corresponding to a false-positive rate of 27%. To explain the inconsistent significance of cN stage between univariate and multivariate analyses, collinearity testing was performed for cN stage and the ratio of tumor diameter reduction. Moderate multicollinearity was observed (VIF=3.713 for cN stage; VIF=3.554 for $\geq 50\%$ diameter reduction), implying overlapping predictive information for pCR.

Development and validation of the combined model. The integrated multivariate prediction model utilized the adjusted ORs derived from the multivariable analysis (Table III).

The present study model demonstrated notable predictive capability (AUC, 0.823; 95% CI, 0.765-0.881) and effective calibration [Hosmer-Lemeshow goodness-of-fit test: $\chi^2=2.779$; degrees of freedom (df)=7; P=0.905] within the test set. Furthermore, it demonstrated robust predictive performance for pCR (AUC, 0.884; 95% CI, 0.816-0.953) and calibration ability (Hosmer-Lemeshow goodness-of-fit test: $\chi^2=4.298$; df=7; P=0.745) in the validation set (Fig. 4).

Discussion

As breast cancer cases continue to increase globally, NAC has become a key part of treatment plans. Ring *et al* (40) suggested that patients who reach a pCR after NAC may be eligible for

Table III. Multivariate regression analysis in the test set (n=226) and development of predictive model for NAC.

Characteristics	B value	OR	95% CI	P-value
Change in tumor diameter, %				
<50		Reference		
≥50	1.648	5.197	1.635-16.518	0.005 ^a
Change in CA153 levels				
Increase		Reference		
Decrease	0.801	2.227	1.061-4.675	0.034 ^a
Margin				
Not circumscribed		Reference		
Circumscribed	2.214	9.157	4.242-19.765	<0.001 ^a
Molecular type				0.027 ^a
Luminal A		Reference		
Luminal B	0.417	1.518	0.604-3.813	0.374
HER2	0.905	2.472	0.512-11.941	0.260
TNBC	1.450	4.262	1.647-11.028	0.003 ^a

^aP<0.05. OR, odds ratio; TNBC, triple-negative breast cancer; HER2, human epidermal growth factor receptor 2; CA153, carbohydrate antigen 153; CI, confidence interval.

medical management only, sparing them from the discomfort of surgery. Furthermore, understanding the internal bioinformatics of the tumor through treatment responses could lead to improved therapeutic approaches that enhance patient outcomes (8,41). Several studies indicated that achieving pCR is a key indicator of long-term survival for patients undergoing NAC (42,43). However, it is key to ensure the precision of pCR evaluations, as inaccuracies could result in notable risks for patients. Thus, establishing a reliable clinical method to assess the biological responses to NAC before any surgical procedures is key to guiding individualized treatment decisions.

The current progress in US diagnostic technology has markedly enhanced the importance of US assessments in determining the effectiveness of NAC for breast cancer (21). Several US techniques, including two-dimensional US, elastography and CEUS, offer diverse insights into the dimensions, shape, vascularity and stiffness of the tumor (44). US is favored in clinical settings due to its non-ionizing nature and patient-friendly profile. Furthermore, two-dimensional US allows for direct measurement and evaluation of tumor size. However, previous research indicated that changes in tumor size alone provide limited specificity and accuracy in assessing NAC effectiveness. Chemotherapy may eliminate tumor cells without visibly altering the tumor size, and residual cancerous tissue can often appear similar to normal breast tissue on standard US scans (16,45). By contrast, continuous monitoring of the maximum tumor diameter, along with post-echo features and morphology, can effectively predict NAC response (46-48). The present study indicated that a reduction of ≥50% in maximum tumor diameter is a robust independent predictor of pCR, aligning with previous findings (46,49). Furthermore, the present study results indicated that tumor margins and posterior echo characteristics associate with pCR in univariate analysis, while circumscribed margins were a significant independent predictor in multivariate analysis. The

association between tumor margins and pCR has not been explored in recent literature, to the best of our knowledge. The present study suggested that tumors with circumscribed margins are more likely to achieve pCR (P<0.001), potentially due to the varying margins exhibited by different breast cancer molecular subtypes. Previous studies (46,50,51) demonstrated that the majority of TNBC cases display circumscribed margins on US. Furthermore, compared with other molecular subtypes, TNBC is typically associated with a higher histological grade, rapid cell proliferation, increased sensitivity to NAC and a greater likelihood of achieving pCR (30,50,51).

The present study identified circumscribed margins as a significant predictor of pCR. While this characteristic was predominantly observed in TNBC, the interaction tests and stratified evaluations indicated no notable variation in its impact across different molecular subtypes, implying that the predictive significance of circumscribed margins may not be exclusively associated with TNBC. However, the P-values from the stratified evaluations did not achieve statistical significance (both P>0.05); this lack of significance is likely attributed to a small sample size (only 11 patients without circumscribed margins in the TNBC group) and diminished statistical power. Therefore, further extensive prospective research is warranted to validate the present study results.

The univariate analysis in the present study revealed that posterior echo enhancement was a positive indicator in achieving pCR, whereas posterior echo attenuation was associated with a lower likelihood of pCR. The present results indicated that tumors classified as low-grade are more prone to displaying characteristics of posterior echo attenuation. These tumors, characterized by their gradual growth, reduced metastatic potential and clinical stability, tend to respond inadequately to NAC. This finding accounts for the diminished chances of reaching pCR when posterior echo attenuation is observed via US (52). Nonetheless, posterior echo enhancement

was excluded from the final model, indicating a need for validation with a larger sample size in future research. The processes of tumor growth, tumor cell invasion and metastasis in breast cancer are associated with the formation of new blood vessels, particularly microvascular structures (53,54). Alterations in these micro-vessels following NAC often occur before any morphological changes are noted (55-57). The present study findings indicated that the presence of twisted perforating vessels does not markedly impact the effectiveness of NAC. However, color Doppler flow imaging has limited ability to detect micro-vessels due to challenges in visualizing those with slower flow rates and smaller diameters (58). This limitation may result in underestimating the blood supply of the tumor, whereas CEUS effectively visualizes blood flow within tumors. With advancements in elastography technology, previous studies have observed that drug-induced changes in the state of tumors and adjacent tissues can lead to variations in tumor stiffness following NAC (59-61). Furthermore, several studies have reported that higher stiffness values in breast tumors are associated with worse prognoses (62). In the present study, only a limited number of patients underwent elastography and CEUS assessments. However, with the introduction of novel technologies in the Department of Medical Ultrasound, Hubei Cancer Hospital, there has been a notable enhancement in diagnostic accuracy using elastography, CEUS and superb microvascular imaging (SMI). Therefore, data from these innovative technologies may be integrated in future research.

TM serve a key role in indicating the presence and development of tumors. Traditionally, TM have been utilized mainly for the early detection of tumors and assessing prognosis (63-65). Application of TM has expanded to include the evaluation of pathological responses following NAC (27,29,66). Several studies have demonstrated a positive association between CA153 levels and cellular proliferation rates (67,68). Furthermore, elevated serum CA153 levels are associated with advanced stages of breast cancer, and patients exhibiting high CA153 levels are often associated with a worse prognosis. Previous studies reported that CA153 levels are markedly specific indicators of breast cancer recurrence and metastasis (25,26,69). Therefore, healthcare professionals commonly monitor CA153 levels to assess treatment effectiveness and predict outcomes in patients with breast cancer. In line with previous research (25,27,28,66), the present study results indicated that a higher percentage of patients in the pCR group demonstrated a reduction in CA153 levels compared with those in the non-pCR group. Multivariate logistic regression analysis suggested that a decrease in CA153 levels serves as a positive predictor in achieving pCR.

The growth rate of breast cancer cells is a key molecular marker for the disease, and Ki-67 levels are closely associated with its clinicopathological features (70). Several studies indicated that variations in Ki-67 levels before and after NAC are associated with treatment efficacy in patients with breast cancer. Notably, patients with elevated Ki-67 levels prior to NAC demonstrated an improved response to the treatment, leading to enhanced outcomes compared with patients with lower Ki-67 levels (71-73). In the present analysis, a higher percentage of patients with elevated Ki-67 levels were identified in the pCR group compared with those without pCR. These findings are consistent with

a previous study conducted by Wong *et al* (74). However, although Ki-67 levels were entered into the multivariate analysis, it was not retained in the final model. This may be because its predictive information was largely captured by molecular subtype, which are associated with Ki-67 expression and were ultimately selected in the model. Among the biological markers associated with breast cancer, hormone receptors (ER and PR) and HER2 are particularly key to treatment and prognosis assessment (75). Patients with high HER2 levels benefit more from NAC compared with those with lower levels (76,77). Furthermore, Cortazar *et al* (41), reported that the pCR rate in patients lacking hormone receptors was 4.2 times greater compared with that in patients who were hormone receptor-positive, indicating that the luminal subtype, which is hormone receptor-positive, has a less favorable response to NAC compared with HER2-upregulating and TNBC subtypes, making pCR harder to achieve (78). Furthermore, molecular subtypes respond differently to NAC, with triple-negative and HER2⁺ tumors demonstrating a more robust response (79-81). In multivariate logistic regression analysis of the present study, molecular subtype emerged as a key independent predictor of pCR. Specifically, TNBC was significantly associated with a higher likelihood of pCR compared with the luminal subtype.

The present study revealed notable variations in tumor diameter, margin characteristics, posterior echo patterns, CA153 levels, clinical N stage, hormone receptor status, Ki-67 expression and molecular subtypes between the pCR and non-pCR groups. Using multivariate analysis, the present study identified tumor diameter change, margin, CA153 fluctuations and molecular subtypes as key components of the final predictive model, which was subsequently validated on the validation set. These findings suggested a promising clinical framework in predicting the response to NAC prior to surgery. Previous research indicated that earlier N stage is associated with increased benefit from NAC and a higher likelihood of achieving a pCR (82). However, clinical N stage was not retained in the final multivariate model of the present study. Therefore, the present study performed collinearity diagnostics. The results revealed moderate collinearity between clinical node (cN) stage and ratio of tumor diameter reduction. These findings suggested that cN stage and diameter reduction carry notable overlapping predictive information for pCR. Several studies have explored the use of radiomics in predicting pCR in patients with breast cancer, demonstrating promising predictive capabilities (83). Compared with MRI, US has been reported to be more suitable for breast cancer screening because it is simpler to perform, faster and free of ionizing radiation (84). Certain studies have proposed using US images from different periods after treatment to predict pCR (85,86). Nonetheless, accurately capturing and representing tumor images following NAC poses notable challenges. Thus, for patients in the present study, the tumors were marked on the skin prior to treatment.

In summary, the present study developed an integrated model utilizing US, serum CA153 levels and molecular classifications, demonstrating notable potential in assessing the effectiveness of treatment prior to surgery following NAC. However, several limitations should be noted. Firstly, elastography and CEUS were only conducted at the initial

stage (before NAC) to evaluate tumor characteristics and for Breast Imaging Reporting and Data System categorization (87), without being repeated during the pre-surgical evaluation. Therefore, the present study cannot determine the added benefit of these advanced US methods in lowering the false-positive rate compared with standard B-mode US. In the present study, the conventional B-mode US alone had a false-positive rate of 27% in detecting notable responses (>50% reduction in size). This indicated that with a >50% reduction in tumor size observed via US, >25% of patients may still have residual disease. Secondly, the present study model exclusively predicts breast pCR and does not evaluate the status of axillary lymph nodes, thus it should not inform decisions regarding axillary de-escalation. Several studies have demonstrated that alterations in axillary lymph node US characteristics, including cortical thickness, hilar integrity and short-axis reduction rate, are predictive of axillary pCR (88-90). Although the present study did not include this data, the findings provide a rationale for future investigations aimed at optimizing the model by incorporating changes in axillary US features. In the present study, treatment regimens varied; however, no significant pCR differences were identified among NAC regimens within each subtype (all $P>0.05$). This finding suggested that pCR was driven more by tumor biology rather than by regimen choice, consistent with previous meta-analyses (79,91,92). The present study model appeared robust to regimen variation. However, subtle regimen-specific effects (for example, dose or schedule) that affect imaging phenotypes cannot be excluded. Group-level comparisons may still be subject to residual confounding (for example, dose reductions and delays). Future validation in uniformly treated cohorts is warranted. Furthermore, the retrospective nature of the present study may lead to selection bias, and the limited sample size, particularly within the pCR subgroup, could affect the validity of subgroup analysis conclusions. Future prospective studies with larger cohorts are warranted to confirm the clinical applicability of the predictive model in the present study. To mitigate this limitation, a prospective study where all participants will undergo CEUS both at the initial assessment and again after completing NAC but before surgery is currently in progress in Hubei Cancer Hospital. Although data collection and analysis are still ongoing, preliminary observations suggest that CEUS may provide a precise identification of tumor margins and residual viable tissue by evaluating microvascular perfusion (data not published). This prospective study is expected to quantify the advantages of CEUS in decreasing the false-positive rate, thus offering a more dependable imaging foundation in ensuring safe margins in breast-conserving surgeries. With ongoing research, an increasing number of molecular markers associated with breast cancer prognosis are being identified. Future research may incorporate additional tumor molecular markers and US imaging parameters, including CEUS, elastography and SMI, to refine the present study model and enhance predictive accuracy of NAC response, offering clinicians evidence-based guidance for treatment decisions.

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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

The present study was conceived and designed by SZ. MD acquired, analyzed and interpreted the data. MD drafted the manuscript and SZ edited the manuscript. Both authors read and approved the final manuscript. MD and SZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present retrospective study received approval from the Ethics Committee of Hubei Cancer Hospital (approval no. 2020-KYLL-S08; Wuhan, China) prior to the initiation of data extraction. All data were retrospectively retrieved from archived medical records after the included patients had completed their full treatment courses and the requirement for written informed consent was waived by the ethics committee for the use of de-identified clinical data, ultrasound images and pathological staining/fluorescence images.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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