

Prediction of Human Epidermal Growth Factor Receptor 2 Expression Status in Breast Cancer Using Multimodal Radiomics

Yiwen Wu¹, Shiyao Chen¹, Wenjie Lu¹, Yunyong Lin¹, Fei Chen¹, Shaodong Qiu¹, Lin Mao^{1*}

¹ Department of Ultrasound, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

*Correspondence: Lin Mao

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Abstract:

Objective: To investigate the predictive value of multimodal radiomics models based on two-dimensional ultrasound (2D US), automated breast volume scanner (ABVS), and magnetic resonance imaging (MRI) for human epidermal growth factor receptor 2 (HER-2) expression status in patients with breast cancer. **Methods:** A total of 106 patients with pathologically confirmed breast cancer before surgery were retrospectively enrolled and randomly assigned to a training group (n = 85) and a test group (n = 21) at an 8:2 ratio. Regions of interest (ROIs) were delineated on the largest tumor section on 2D US, ABVS, and contrast-enhanced MRI images, respectively. Least absolute shrinkage and selection operator (LASSO) regression was used to select the optimal radiomic features. Seven predictive models were developed with the random forest (RF) algorithm, including the US, ABVS, MRI, US-ABVS, US-MRI, ABVS-MRI, and US-ABVS-MRI models. Model performance was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC). **Results:** The AUC values of the seven models ranged from 0.947 to 1.000 in the training group and from 0.668 to 0.878 in the test group. Pairwise DeLong tests showed no statistically significant differences among the models (all P > 0.05). **Conclusion:** Multimodal radiomics models showed promising performance for predicting HER-2 expression status in breast cancer. In this cohort, single-modality models based on 2D US, ABVS, or MRI achieved predictive performance comparable to that of the multimodal models.

Keywords:

Breast Cancer, HER-2 Expression Status, Multimodal Radiomics, Ultrasound, Magnetic Resonance Imaging

1. Introduction

In recent years, the incidence of breast cancer has continued to increase among female malignant tumors, and breast cancer has become one of the leading causes of cancer-related death in women [1]. Human epidermal growth factor receptor 2 (HER-2) is a key biomarker for the molecular classification of breast cancer, and approximately 20%-30% of patients with breast cancer show HER-2 overexpression

[2-4]. HER-2-positive breast cancer is generally regarded as a highly invasive subtype characterized by aggressive biological behavior and an unfavorable prognosis [5,6]. Accurate assessment of HER-2 expression status is therefore essential for selecting standardized treatment strategies. At present, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) remain the main clinical methods for evaluating HER-2 expression [7,8]. However, both approaches have clear limitations: they require invasive tissue sampling and relatively long testing cycles. In addition, FISH requires specialized equipment, and the limited shelf life of staining reagents further restricts its broad clinical application. As an emerging non-invasive analytical approach, radiomics can extract high-throughput quantitative features from medical images, characterize intratumoral heterogeneity, and support longitudinal monitoring of tumor biological behavior [9,10,11]. To address these clinical challenges, this study integrated radiomic features derived from ultrasound and MRI to construct predictive models for the non-invasive preoperative evaluation of HER-2 expression status in breast cancer, thereby providing auxiliary evidence for individualized treatment planning and prognostic assessment.

2. Materials and Methods

2.1. Study Subjects

Clinical data were collected from patients with pathologically confirmed breast cancer who were admitted to our hospital between December 2021 and December 2023. All patients provided written informed consent before imaging examinations, and the study protocol was approved by the Ethics Committee of our hospital.

The inclusion criteria were as follows: (1) breast cancer confirmed by pathological examination after core needle biopsy or surgical resection; (2) initial assessment of HER-2 expression by IHC, with additional FISH testing performed when the IHC result was 2+; and (3) completion of both ultrasound and MRI examinations before biopsy or surgery, with an interval of less than 2 weeks between the two examinations.

The exclusion criteria were as follows: (1) incomplete clinical or pathological data; (2) receipt of anti-tumor treatment, including radiotherapy, chemotherapy, or endocrine therapy, before biopsy or surgery; (3) suboptimal image quality caused by excessively large lesions or other factors that prevented reliable analysis; and (4) multiple lesions or distant metastasis. Finally, 106 patients who met the eligibility criteria were included in the analysis, including 72 HER-2-negative cases and 34 HER-2-positive cases.

2.2. Imaging Examinations

Ultrasound examinations were performed using a Siemens ACUSON OXANA2 ultrasound diagnostic system. An 18L-5BV probe (frequency range, 5-14 MHz) was used for ABVS scanning, whereas a 9L-4 probe was used for handheld high-resolution ultrasound (HHUS). For ABVS scanning, patients were placed in the supine position with both arms abducted to fully expose the breasts and axillae. Images were acquired in the central, medial, and lateral planes during quiet breathing, and each plane was scanned for approximately 60 seconds. After complete coverage of the target lesion was confirmed, images were stored and transferred to the ABVS workstation for three-dimensional reconstruction at a slice thickness of 0.5 mm to obtain clear 3D images. For HHUS scanning, patients remained in the supine position with both arms raised and abducted to expose the breasts and axillary regions. The

nipple, areola, and four breast quadrants (upper outer, lower outer, upper inner, and lower inner) were scanned systematically. Once a suspicious lesion was identified, sonograms showing the complete ultrasonographic characteristics of the lesion were stored and recorded as fully as possible. MRI examinations were performed on a Philips Ingenia 3.0-T scanner equipped with a dedicated 4-channel breast coil. Patients were positioned prone with their arms raised beside the head, allowing both breasts to hang naturally into the coil. The scan range extended from the axillary level to the inferior margin of the breasts. The parameters for the plain axial sequences were as follows: T1WI, TR 578 ms and TE 8.0 ms; T2WI, TR 4668 ms and TE 70 ms; T2WI DIXON fat-suppressed sequence, TR 4243.56 ms and TE 70 ms; and DWI, TR 8276 ms, TE 72 ms, and $b = 800$ s/mm. The slice thickness was 4 mm, the slice gap was 1 mm, and the field of view (FOV) was $224 \text{ mm} \times 320 \text{ mm}$. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) consisted of 8 phases, including 1 pre-contrast mask phase and 7 post-contrast phases, with each phase lasting approximately 57.9 seconds. The DCE-MRI parameters were as follows: FOV, $192 \text{ mm} \times 320 \text{ mm}$; slice gap, -1.2 mm; slice thickness, 2.4 mm; matrix, 560×560 ; and flip angle, 15° . Gadopentetate dimeglumine was administered as the contrast agent at a dose of 0.2 mmol/kg and an injection rate of 2.5 mL/s.

3. Pathological Evaluation

HER-2 expression status was determined jointly by IHC and FISH according to the joint guidelines issued by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) [12-14]. IHC 3+ was defined as HER-2 positive, whereas IHC 0 or 1+ was defined as HER-2 negative. Patients with an IHC 2+ result underwent subsequent FISH testing; a FISH ratio ≥ 2.0 indicated HER-2 positivity, whereas a ratio < 2.0 indicated HER-2 negativity.

4. Radiomics Model Construction

4.1. ROI Delineation

For ultrasound images, two sonographers (Reader A and Reader B) reviewed all two-dimensional US and ABVS images, including the central, lateral, and medial planes, for each patient. Images requiring delineation were identified and recorded after consensus discussion when disagreement occurred. ITK-SNAP software (<https://www.itksnap.org>) was used by both readers to manually delineate ROIs layer by layer on 2D US and ABVS images of breast tumors (Figure 1). Forty randomly selected image sets were independently delineated by both readers for inter-reader consistency analysis.

For MRI images, an attending physician with 5 years of experience and an associate chief physician with 15 years of experience delineated lesions on DCE-MRI images using 3D-Slicer software, without access to the patients' clinical or pathological information. The two delineations were performed at a 2-week interval. The phase 4 or phase 5 image showing the most prominent enhancement on the DCE sequence was selected for ROI drawing (Figure 2). Another 40 randomly selected image sets were used to evaluate inter-reader consistency.

4.2. Feature Extraction

The ONEKEY AI platform was used to extract radiomic features, including statistical, shape, texture, and wavelet features, from DCE-MRI and ultrasound

images. All features were standardized by Z-score normalization before feature screening. Intraclass correlation coefficients (ICCs) were calculated to assess segmentation variability, and only features with $ICC > 0.8$ were retained. The feature-selection workflow was as follows: (1) the Mann-Whitney U test was used for preliminary screening of features associated with HER-2 expression ($P < 0.1$); (2) LASSO regression was applied to remove features with zero coefficients and retain the most discriminative features; and (3) Spearman correlation analysis was performed to eliminate highly redundant features. After these procedures, 1,023 radiomic features were retained for subsequent analysis.

4.3. Model Establishment

Seven radiomics models were constructed using the random forest (RF) algorithm: the US, ABVS, DCE-MRI, US-ABVS, US-MRI, ABVS-MRI, and US-ABVS-MRI models. ROC curves were generated, and the corresponding AUC values were calculated to evaluate the predictive performance of each model.

4.4. Statistical Analysis

Statistical analyses were performed using SPSS 25.0 software. The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed data were expressed as mean $\pm$ standard deviation and compared using the independent-samples t-test, whereas non-normally distributed data were expressed as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables were summarized as frequencies and percentages, and inter-group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Ordered categorical variables were analyzed using the rank-sum test. Model performance was evaluated in terms of accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. Decision curve analysis (DCA) was conducted to assess clinical utility. A P -value < 0.05 was considered statistically significant.

5. Results

5.1. Clinical, imaging, and pathological baseline characteristics.

A total of 106 patients were included in the final cohort, comprising 34 HER-2-positive cases and 72 HER-2-negative cases. The cohort was randomly allocated to a training set ($n = 85$) and a test set ($n = 21$) at a ratio of 8:2. The clinical and imaging characteristics of the two sets are summarized in Table 1. In the training set, age, Ki-67 expression, maximum tumor diameter, lesion shape, posterior acoustic features, calcification, and vascularity did not differ significantly between the HER-2-positive and HER-2-negative groups (all $P > 0.05$). By contrast, estrogen receptor (ER) and progesterone receptor (PR) expression differed significantly between the two groups ($P < 0.05$). However, when ER and PR status were entered into multivariate logistic regression, neither variable remained an independent predictor of HER-2 expression status ($P > 0.05$) (Table 1).

Table 1. Clinicopathological characteristics of the 106 patients.

Clinicopathological data	training group (n=85)		P value	test group (n=21)		P value
	HER-2 positive	HER-2 negative		HER-2 positive	HER-2 negative	

	(n=27)	(n=58)		(n=7)	(n=14)	
Age (years)	54.7±8.1	54.9±11.3	0.922	56.4±7.3	56.1±11.0	0.951
ER expression status			0.004			1.000
+	15 (55.6%)	49 (84.5%)		5 (71.4%)	10 (71.4%)	
-	12 (44.4%)	9 (15.5%)		2 (28.6%)	4 (28.6%)	
PR expression status			0.019			1.000
+	13 (48.1%)	43 (74.1%)		5 (71.4%)	10 (71.4%)	
-	14 (51.9%)	15 (25.9%)		2 (28.6%)	4 (28.6%)	
KI-67			0.727			0.255
≥ 14%	21 (77.8%)	47 (81.0%)		7 (100.0%)	10 (71.4%)	
< 14%	6 (22.2%)	11 (19.0%)		0 (0.0%)	4 (28.6%)	
Maximum tumor diameter (cm)	3.4±1.9	3.6±1.6	0.742	3.5±0.8	3.2±1.6	0.635
Shape			1.000			1.000
Regular	0 (0.0%)	1 (1.7%)		0 (0.0%)	0 (0.0%)	
Irregular	27 (100.0%)	57 (98.3%)		7 (100.0%)	14 (100.0%)	
Calcification presence			0.872			0.346
Yes	21 (77.8%)	46 (79.3%)		1 (14.3%)	1 (7.1%)	
No	6 (22.2%)	12 (20.7%)		6 (85.7%)	13 (92.9%)	
Posterior acoustic shadowing			0.392			0.397
Yes	9 (33.3%)	25 (43.1%)		3 (42.9%)	9 (64.3%)	
No	18 (66.7%)	33 (56.9%)		4 (57.1%)	5 (35.7%)	
Tumor vascularity			0.746			0.892
Grade 0	0 (0.0%)	3 (5.2%)		0 (0.0%)	1 (7.1%)	
Grade 1	5 (18.5%)	14 (24.1%)		2 (28.6%)	2 (14.3%)	
Grade 2	8 (29.6%)	16 (27.6%)		2 (28.6%)	6 (42.9%)	
Grade 3	14 (51.9%)	25 (43.1%)		3 (42.8%)	5 (35.7%)	
ER: estrogen receptor; PR: progesterone receptor						

Table 2. Performance data of the seven models.

Model	Dataset	AUC	95%CI	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Youden Index
2D	training group	0.947	0.885-1.000	1.000	0.977	0.955	1.000	0.977
	test group	0.704	0.434-0.934	1.000	0.500	0.500	1.000	0.500
ABVS	training group	1.000	1.000-1.000	1.000	1.000	1.000	1.000	1.000
	test group	0.668	0.423-0.914	0.714	0.692	0.818	0.667	0.406
MRI-DCE	training group	0.997	0.991-1.000	1.000	0.953	0.913	1.000	0.953
	test group	0.735	0.452-1.000	0.857	0.643	0.545	0.900	0.500
2D-ABVS	training group	1.000	1.000-1.000	1.000	1.000	1.000	1.000	1.000
	test	0.816	0.620-	0.714	0.857	0.714	0.857	0.571

	group		1.000					
2D-MRI	training group	0.984	0.965-1.000	0.952	0.930	0.870	0.976	0.882
	test group	0.767	0.545-0.989	0.714	0.714	0.556	0.833	0.428
ABVS-MRI	training group	0.988	0.973-1.000	1.000	0.907	0.840	1.000	0.907
	test group	0.755	0.500-1.000	0.714	0.786	0.625	0.846	0.500
2D-ABVS-MRI	training group	1.000	1.000-1.000	1.000	1.000	1.000	1.000	1.000
	test group	0.878	0.711-1.000	0.857	0.714	0.600	0.909	0.571

5.2. Radiomic Feature Selection

A total of 1,125 radiomic features were extracted from the delineated US, ABVS, and DCE-MRI images using the Onekey AI research platform. After features with ICC values below 0.8 were excluded, the remaining features were subjected to sequential screening with the Mann-Whitney U test and LASSO regression. This procedure retained 16, 3, and 5 discriminative features for the US, ABVS, and DCE-MRI single-modality models, respectively. For the multimodal feature sets, the same selection pipeline identified 16, 3, 5, and 3 features for the US-ABVS, US-MRI, ABVS-MRI, and US-ABVS-MRI models, respectively.

5.3. Model Construction and Validation

All prediction models were developed using the RF algorithm. In the test set, the multimodal US-ABVS-DCE-MRI model yielded an AUC of 0.878 (95% confidence interval [CI]: 0.711-1.000), which was numerically higher than the AUCs of the single-modality models (Table 2). Nevertheless, pairwise comparisons with the DeLong test showed no statistically significant differences among the seven models (all $P > 0.05$), and the detailed pairwise results are presented in Figure 3. The DCA curves for the seven models are shown in Figure 3. These curves suggested that the RF model integrating 2D US, ABVS, and MRI features provided the greatest clinical net benefit for preoperative prediction of HER-2 expression status in patients with breast cancer.

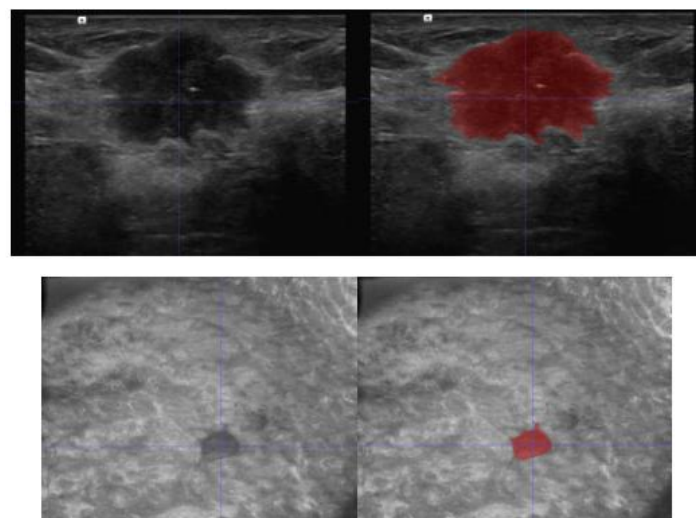


Figure 1. Schematic illustration of ROI delineation on US and ABVS

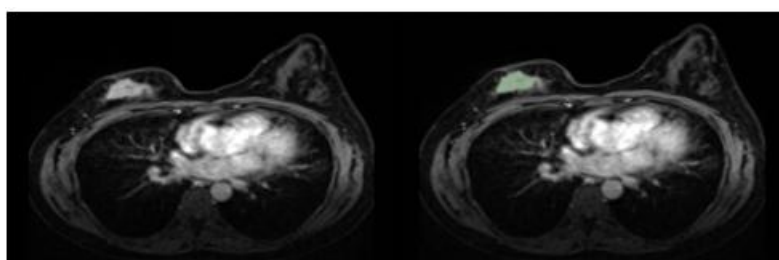


Figure 2. Schematic illustration of ROI delineation on DCE-MRI.

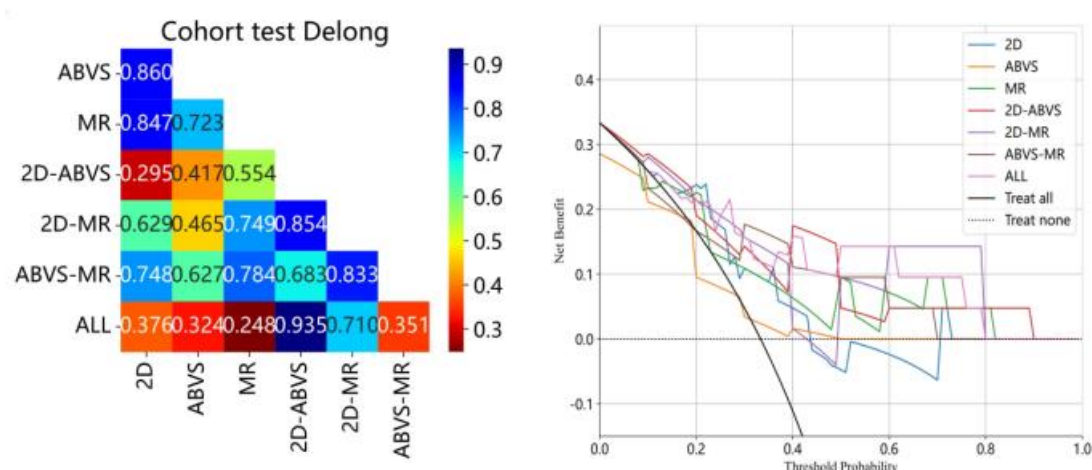


Figure 3. DeLong test results for the seven models and DCA curves in the test cohort.

6. Discussion

Breast cancer remains one of the most common malignant tumors in women, and treatment selection is closely associated with pathological subtype, clinical stage, and other clinicopathological factors [15,16]. HER-2 overexpression can accelerate tumor-cell proliferation, promote angiogenesis, and increase intratumoral heterogeneity [17]. As an important oncogenic driver and therapeutic target in breast cancer, HER-2 status is therefore central to treatment planning and prognostic assessment. Conventional assessment of HER-2 expression, however, depends largely on tissue sampling and laboratory testing, which are invasive, time-consuming, and relatively costly. Radiomics provides a non-invasive analytical approach that converts medical images into quantitative features and may help characterize tumor heterogeneity before surgery. Several previous studies have examined associations between radiomic signatures and HER-2 expression. Cao et al. [18] developed a radiomics model based on intratumoral and peritumoral multiparametric MRI features, including DWI, T2WI, and DCE-MRI, and reported AUC values of 0.822, 0.823, and 0.813 in the training, internal validation, and external test sets, respectively. This performance was superior to that of single-sequence or single-region models. Xu et al. [19] constructed an ultrasound-based nomogram that combined longitudinal and transverse radiomic features with tumor size, and this model predicted HER-2 status in invasive breast cancer with a test-set AUC of 0.774. These findings indicate that radiomics models derived from ultrasound or MRI can provide useful preoperative information for evaluating HER-2 expression in breast cancer. More recently, multimodal radiomics has shown increasing value in this field. Wang et al. [20] integrated radiomic and deep-learning features from MRI and mammography to build a non-

invasive multimodal model for three-category prediction of HER-2 status. Compared with single-modality radiomics, which reflects only a subset of tumor characteristics captured by one imaging technique, multimodal radiomics combines complementary information from different modalities and may therefore provide a more comprehensive description of intratumoral biology. However, evidence on models that combine 2D US, 3D ABVS, and MRI for predicting HER-2 expression remains limited. In this context, the present study constructed multimodal radiomics models for non-invasive preoperative assessment of HER-2 expression, with the aim of supporting individualized clinical decision-making. Our results showed that the integrated US-ABVS-MRI model achieved favorable predictive performance in both the training and test sets, with a test-set AUC of 0.878. Although this model showed the highest numerical performance, the single-modality models also demonstrated comparable predictive ability, and DeLong tests did not identify significant differences among the models. This lack of statistical separation may be related to the relatively small sample size and the limited number of HER-2-positive cases in the test set. Even so, the DCA results indicated that the US-ABVS-MRI model provided the highest clinical net benefit, suggesting that multimodal feature integration may still offer practical value when applied in clinical decision-making. This study has several limitations. First, the sample size was limited and all patients were recruited from a single center; therefore, multicenter external validation is needed to assess model robustness and generalizability. Second, the present study used conventional machine-learning methods, whereas deep-learning approaches may capture higher-order imaging patterns with stronger discriminative information. Third, only DCE-MRI sequences were included in the MRI radiomics analysis; future work should incorporate multiparametric MRI sequences to determine whether additional imaging information can further improve predictive performance.

7. Conclusions

This study showed that multimodal fusion radiomics models had favorable diagnostic performance for predicting HER-2 expression status in breast cancer. These models may provide a useful non-invasive adjunct for preoperative HER-2 assessment. In particular, radiomics-based prediction could help support individualized treatment planning and contribute to more precise diagnostic and management strategies for patients with breast cancer.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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