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RESEARCH ARTICLE

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HER-2 expression is correlated with multimodal imaging features in breast cancer: a pilot study

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ABSTRACT

Objective: A pilot study to evaluate the correlation between multimodal imaging features and the expression of the human epidermal growth factor receptor type 2 (HER-2) in breast cancer to provide a basis for clinical treatment and prognosis evaluation.

Methods: We included a total of 62 patients with breast cancer admitted to the Affiliated Hospital of Hebei University between 2018 and 2022. All of them underwent the relevant investigations, including ultrasound, mammography, and enhanced magnetic resonance imaging (MRI), in the hospital within one month before surgery or biopsy. HER-2 expression level was divided into negative and positive by immunohistochemistry(IHC). Using SPSS 24.0 statistical software to analyze the differences in imaging features between the HER-2 positive and the HER-2 negative groups.

Results: There was a statistically significant difference between the HER-2 positive and the HER-2 negative groups (p = 0.005) in the hyperechoic halo sign around the lesion detected by ultrasonography as well as in the apparent diffusion coefficient (ADC) on MRI (p = 0.047). The sensitivity and specificity of the hyperechoic halo sign in predicting HER-2 positivity was 48.3% and 84.8% respectively, and the area under the curve (AUC) for the ADC value to predict HER-2 expression was 0.533. When b was equal to 800 and the ADC value (cutoff value) was 0.000888 mm^2/s, the sensitivity and specificity were 65.5% and 51.5%, respectively.

Conclusion: A combination of multimodal imaging features and HER-2 gene expression can provide more valuable information for clinical diagnosis and therapeutic schedule in breast cancer.

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ADC; breast cancer; HER-2; hyperechoic halo; multimodal imaging

1. Introduction

Breast cancer is the leading cause of malignancy death in women worldwide [1–3]. Molecular subtypes of breast cancer are important predictors of tumor behavior and patient prognosis, as well as key factors in determining treatment schedule, and at present are classified based on the expression levels of immunohistochemical indicators, namely estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER-2), and cell proliferation index (Ki67). Early diagnosis is crucial in the treatment of breast cancer [4].

HER-2 overexpression is the most clinically significant molecular alteration in breast cancer, which accelerates tumor cell growth, increases tumor aggressiveness [5], and upregulates the vascular endothelial growth factor to generate new blood vessels [6]. Data from The Cancer Genome Atlas (TCGA) and results from clinical trials of anti-HER-2 targeted therapies suggest that HER-2-positive breast cancers tend to be characterized by high grade, rapid growth, and early systemic metastasis. Therefore, breast cancer patients with HER-2-positive expression often have a poor prognosis [7].

The expression level of HER-2 plays a crucial role in prognostic evaluation and the selection of the treatment schedule for patients with HER-2-positive breast cancer, and such patients may benefit from anti-HER-2 therapy such as trastuzumab [8]. HER-2 expression in breast cancer is often evaluated using

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immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH), which are recommended internationally and both require biopsy or invasive surgery to obtain pathology specimens [9–11].

However, the use of these techniques is often limited, and these methods have their associated complications. For example, the biopsy may lead to mastitis, pyoderma gangrenosum, or breast fistula, and the surgery can lead to infection, hematoma, suture abscesses, or other complications [12]. Therefore, it is crucial to develop an accurate, noninvasive method to evaluate the expression of HER-2 in patients with breast cancer. In this pilot study, we aim to explore the correlation between multimodal imaging features (ultrasound, mammography, and Magnetic Resonance Imaging (MRI) and the expression of HER-2 in breast cancer to provide a basis for clinical treatment and prognosis evaluation.

2. Materials and methods

2.1. Study population

Female patients with breast cancer who were admitted to the Affiliated Hospital of Hebei University between 2018 and 2022 were included in this study. Inclusion criteria: patients with a diagnosis of breast cancer for the first time, with no treatment prior to surgery or biopsy, and those who had undergone ultrasound, mammography, and enhanced MRI in our hospital within one month prior to surgery or biopsy. Exclusion criteria: patients with a previous history of breast cancer or other malignant tumors, poor imaging quality, and incomplete postoperative pathology data. We analyzed data obtained from 62 patients who fulfilled the inclusion criteria (median age: 49.6 ± 10.4 years, range: 29–70 years). The study was approved by the ethics committee of the hospital.

2.2. Methods

All patients underwent ultrasound, mammography, and MRI, and two physicians who were blinded to the pathology findings retrospectively analyzed the imaging results. In case of disagreement, another attending physician was asked to evaluate the findings, and a consensus was obtained only after all the three physicians agreed.

2.2.1. Ultrasound imaging and evaluation

We used the Philips iU22 and the GE logics 9 with a 6–14 MHz ultrasound probe to obtain two-dimensional images, color Doppler images, and measure the flow resistance index within the lesions. The age and the maximum diameter of the mass, aspect ratio, margins, constituents, posterior acoustic attenuation, hyperechoic halo, and arterial high-resistance flow (RI > 0.7) were recorded.

2.2.2. Mammography imaging and evaluation

We used the senograph mammography machine manufactured by GE in the United States, and imaging was performed in two orientations: craniocaudal (CC) and mediolateral oblique (MLO). We recorded the presence or absence of microcalcifications in the patient's mammogram imaging.

2.2.3. MRI imaging and evaluation

We used a 3.0T superconducting MR scanner (GE Medical Systems Discovery MR750) with an 8-channel breast-specific coil. The scan sequence included axial T1WI, axial fat suppression T2WI, bilateral sagittal fs-T2WI, and diffusion-weighted imaging (DWI); the enhancement sequence was performed with a 3D volumetric multi-phase dynamic scan. The DWI parameters were as follows: TE: 78.5 ms, TR: 3,500 ms, matrix: 128 × 128, FOV: 350 × 350 mm, gap: 5 mm, slice thickness: 4 mm; b value = 800; enhancement sequence parameters were as follows: TE: 2.2 ms, TR: 3.9 ms, matrix: 320 × 320, FOV: 360 × 360 mm, gap: 1.4 mm, slice thickness: 1.4 mm, and a total of 8 phases were scanned. The contrast agent was gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA), injected at a rate of approximately 2.5 mL/s with an injection dose of 0.15 mL/kg. The ADC values and TIC curve (time signal intensity curve) types, including types of inflow, plateau, and outflow, were recorded from each patient's MRI scan.

2.2.4. Immunohistochemistry

All cases were diagnosed by immunohistochemistry by senior pathologists, and the specimens were routinely collected, transparent, waxed and embedded in paraffin wax to make wax blocks. The detection methods and dyeing procedures were carried out according to the product instructions. HER-2 was positively expressed in cell membrane. The cells with brown-yellow particles on the cell membrane were taken as positive cells, and the proportion of positive cells in all cells was used to evaluate the positive expression intensity. The proportion of positive cells was observed under a high-power microscope, and the results were interpreted according to the 2019 Chinese Guidelines for HER-2 Detection of Breast Cancer [5]: 0: no staining or weak cell membrane staining, and the percentage of stained cancer cells was ≤10%; 1+: weak cell membrane staining of cancer cells,

but the percentage of stained cancer cells was >10%; 2+: consisted of two scenarios: the first, with weak-moderate intensity of cell membrane staining, and the percentage of stained cancer cells was >10%, the second, with strong and complete cell membrane staining of cancer cells, but the percentage of stained cancer cells was ≤10%; and 3+: cancer cells with strong and complete cell membrane staining, and the percentage of stained cancer cells was >10%. '0' and '1+' were defined as negative, and '3+' was defined as positive. For HER-2 (2+) patients, FISH was used to further detect whether there was amplification of HER-2 gene, and amplification patients were determined to be positive, while non-amplification patients were determined to be negative.

2.3. Statistical analysis

Data were analyzed using SPSS statistical package version 24.0. Measurement data conforming to normal distribution were expressed as $\bar{x} \pm s$, and we used a t test to compare between groups; count data were expressed as cases (%), and we used χ^2 test for comparison between groups. The correlation between variables was examined by Spearman's rank correlation. We used the receiver operating characteristic curve (ROC curve) to analyze the best ADC cutoff value for predicting HER-2, and a statistically significant difference was considered when $p < 0.05$.

3. Results

3.1. General information

We included 62 patients in the study, and all of them had single lesions; thus, we analyzed 62 lesions. 29 cases were HER-2-positive (median age: 47.8 ± 10.9 years) and 33 cases were HER-2-negative (median age: 51.1 ± 9.8 years) as per immunohistochemistry (Table 1). There was no statistically significant difference in the general information between two groups. All lesions were surgically resected, and these included 43 cases of invasive ductal carcinoma, 13 cases of mixed carcinoma, 4 cases of ductal carcinoma *in situ*, 1 case of invasive lobular carcinoma, and 1 case of invasive cribriform carcinoma.

3.2. Imaging features

3.2.1. Analysis of ultrasound signs

All 62 lesions were solid masses, and the HER-2 positive and negative groups did not differ significantly with regard to the maximum diameter of the masses. There were 52 cases with an aspect ratio that was >1 and 10 cases with an aspect ratio <1. The difference in aspect ratio between the two groups was not statistically significant. There were 12 cases of lesions with smooth and complete margins and 50 cases of margins that were not smooth and complete, and the two groups did not differ significantly in the type of lesion margins. There were 19 cases of lesions with posterior acoustic attenuation and 43 cases of lesions without posterior acoustic attenuation, and the difference in this feature of acoustic attenuation between the two groups was not statistically significant. We found arterial high resistance blood flow signals in 54 lesions, while 8 lesions did not show arterial high resistance blood flow; there was no significant difference between the two groups. A total of 43 lesions showed hyperechoic halo (Figure 1A) and 19 lesions showed no hyperechoic halo, and the difference in this feature between the groups was statistically significant ($p = 0.005$) (Table 1).

Table 1. Correlation between clinical/imaging features and HER-2 expression.

Clinical/imaging features	HER-2 (+)	HER-2 (–)	t/χ^2 value	p value
Age (years)	47.8 ± 10.9	51.1 ± 9.8	1.236	0.221
Maximum diameter (cm)	3.0 ± 2.2	2.7 ± 1.2	0.839	0.406
Aspect ratio			0.220	0.639
>1	4 (40.0%)	6 (60.0%)		
<1	25 (48.1%)	27 (51.9%)		
Margin			0.062	0.803
Smooth and complete	6 (50.0%)	6 (50.0%)		
Not smooth and complete	23 (54.0%)	27 (46.0%)		
Posterior acoustic attenuation			2.541	0.111
Yes	6 (31.6%)	13 (68.4%)		
No	23 (53.5%)	20 (46.5%)		
Arterial high resistance blood flow			0.912	0.333
Yes	24 (44.4%)	30 (55.6%)		
No	5 (62.5%)	3 (37.5%)		
Hyperechoic halo			7.968	0.005
Yes	15 (34.9%)	28 (65.1%)		
No	14 (73.7%)	5 (26.3%)		
Sand-like calcification (mammography)			0.839	0.406
Yes	20 (47.6%)	22 (52.4%)		
No	9 (45.0%)	11 (55.0%)		
ADC (mm^2/s)	0.00097 ± 0.00035	0.00181 ± 0.00230	2.059	0.047
TIC classification			2.104	0.349
Inflow type	2 (33.3%)	4 (66.7%)		
Plateau type	24 (52.2%)	22 (47.8%)		
Outflow type	3 (30.0%)	7 (70.0%)		

3.2.2. Correlation analysis between ultrasound imaging features and HER-2 expression in breast cancer

The difference between the HER-2-negative and HER-2-positive groups with respect to the presence of hyperechoic

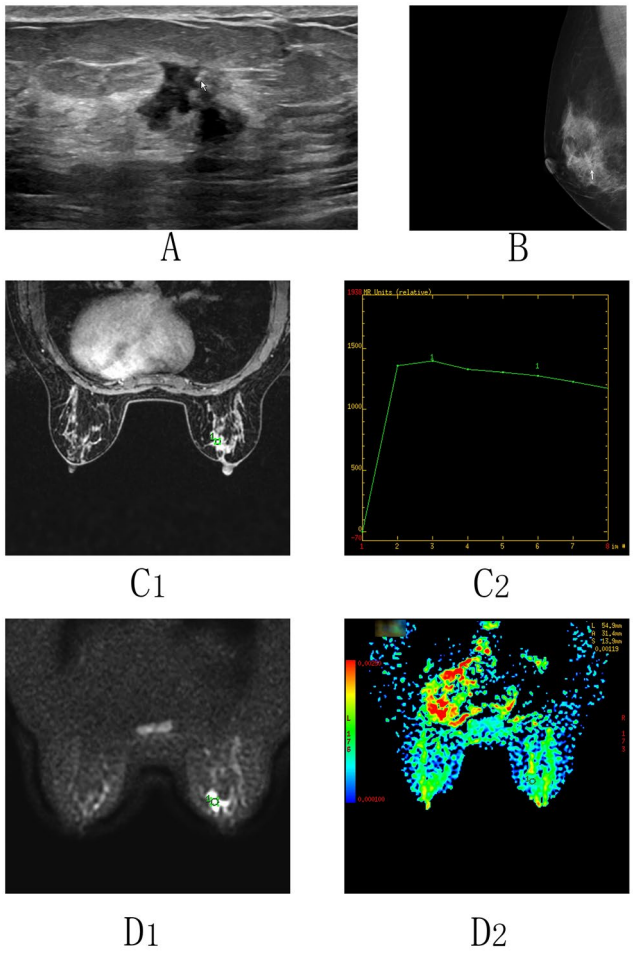

Figure 1. Ultrasound, mammography, and MRI images of breast cancer patients with HER-2 expression (1+). Female, 51 years old, infiltrating ductal carcinoma in the right breast, HER-2 (1+). A: Ultrasound shows the hypoechoic mass surrounded by hyperechoic halo (white arrow). B: Mammography shows local glandular aggregation with sandy-like calcification (white arrow). C1: Enhanced MRI image shows the mass is clearly enhanced with high signal. C2: The TIC (time–intensity curve) shows a slow outflow type. D1: Significantly high signal of the mass seen in DWI imaging. D2: Mean ADC value in the corresponding region of interest is 0.000818.

halo was statistically significant ($p=0.005$), and the correlation was negative ($R=-0.359$, $p=0.004$). Hyperechoic halo had a sensitivity of about 48.3% in predicting HER-2 positivity, and its specificity was 84.8% (Table 2).

3.2.3. Analysis of signs found in mammography

42 out of 62 (67.7%) lesions showed sand-like calcification on mammography (Figure 1B), and 20 did not show sand-like calcification; the groups did not differ significantly in this feature.

3.2.4. Analysis of enhanced MRI parameters

Enhanced MRI revealed 6 cases of inflow type, 46 cases of plateau type, and 10 cases of outflow type (Figure 1C1 and C2), and there was no statistically significant difference between HER-2-positive and HER-2-negative groups in the TIC curve typing of lesions. The mean ADC of HER-2-negative and positive group was $0.00181\pm0.00040\,mm^2/s$ and $0.00097\pm0.00006\,mm^2/s$ respectively, with statistically significant differences between the groups ($p=0.047$) (Table 1; Figure 1D1 and D2).

3.2.5. Correlation analysis of ADC value and HER-2 expression in breast cancer

The area under the curve of the ADC predicting HER-2 expression was 0.533, and when the *b* value was 800 and the ADC cutoff value was $0.000888\,mm^2/s$, the sensitivity was 65.5%, the specificity was 51.5%, and the Jorden index was 0.17 (Table 2; Figure 2).

Table 2. Value of hyperechoic halo and ADC in predicting HER-2 expression.

Image indicator	Sensitivity	Specificity	Cutoff value	Jordan index
Hyperechoic halo	48.3%	84.8%		
ADC value (mm^2/s)	65.5%	51.5%	0.000888	0.17

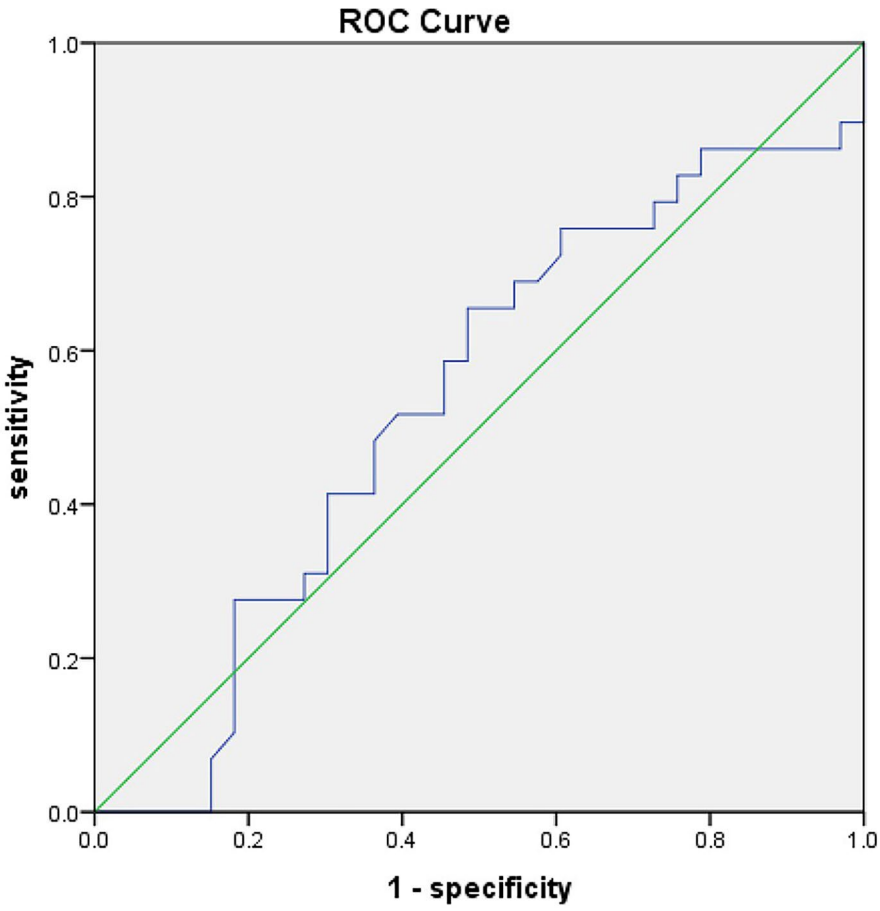

Figure 2. ROC curve of ADC predicting HER-2 expression. The area under the ROC curve is 0.533. When the *b* value is 800 and the ADC cutoff value is 0.000888 mm^2/s, the sensitivity of ADC predicting HER-2 expression is 65.5%, the specificity is 51.5%.

4. Discussion

Several researchers have investigated the correlation between various imaging features and parameters and the expression level of HER-2, but only a few studies have reported on the predictive value of multimodal imaging (ultrasound, mammography, and MRI) for the expression level of HER-2. Ultrasound has advantages in the diagnosis of breast disease as it is easy to operate, non-radiative, can provide arbitrary multiple sections, and displays the blood flow spectrum within the tumor, but its disadvantage is its poor sensitivity to calcification. The advantage of mammography is the high detection rate of microcalcifications within the lesion, while the availability of multiple parameters, DWI imaging (diffusion-weighted imaging), and enhancement in MRI can compensate for the deficiencies of ultrasound and mammography. Therefore, in this study, we included ultrasonography parameters such as maximum tumor diameter, aspect ratio, constituents, margins, posterior acoustic attenuation, hyperechoic halo, and arterial high resistance blood flow; we used mammography only for the detection of microcalcifications; and we included ADC values in DWI sequences and TIC curve types from the enhanced MRI in the MRI examination.

In recent years, a large number of literatures have discussed the correlation between ultrasound characteristics and immunohistochemistry of breast cancer, but the research results are different and have not been unified. For example, Huang et al. [13] believe that HER-2 expression is not significantly correlated with the edge, shape, echo and rear acoustic attenuation of the tumor, but is positively correlated with tumor size. Some scholars believe that there is a significant correlation between tumor heterogeneity and positive HER-2 [7]. However, there are few studies on the correlation between breast cancer hyperechoic halo and positive expression of HER-2. In this study, the results of ultrasound signs showed that 43 of 62 (69.4%) patients showed hyperechoic halo around the lesions, of which 15 (34.9%) were positive for HER-2 and 28 (65.1%) were negative. There were 19 cases with no hyperechoic halo, among which 14 cases were positive for HER-2 (73.7%) and 5 cases were negative (26.3%). The display rate of hyperechoic halo in the HER-2

negative group was higher than that in the HER-2 positive group, the difference between groups was statistically significant ($p=0.005$), and it was negatively correlated with the expression of HER-2 ($R=-0.359$, $p=0.004$). This is similar to the results of previous studies. It was reported that breast cancer hyperechoic halo refers to the fuzzy ring hyperecho between breast tumor and surrounding tissue, and hyperecho refers to the ring hyperecho formed by the infiltration of cancer cells around the tumor leading to the proliferation of surrounding fibrous connective tissue, or the ring hyperecho formed by the infiltration of cancer cells around the tumor and the intermixing of adipose tissue and fibrous tissue [14]. Wang et al. [15] analyzed that the malignant risk of breast nodules with hyperechoic halo is higher than that without hyperechoic halo, which is the most important feature of ultrasound diagnosis of breast cancer, that is, hyperechoic halo can be used as a malignant index to judge breast nodules, which is consistent with the result of the present study (69.4% showed hyperechoic halo around the lesions). Furthermore, some scholars have further studied the correlation between hyperechoic halo in malignant breast nodules and the differentiation degree, invasiveness and prognosis of the tumor. Some studies have shown that breast masses without hyperechoic halo are more invasive and have a poor prognosis, while breast masses with hyperechoic halo are less invasive, which may be due to the proliferation of fibrous connective tissue around them restricting the spread of cancer cells to the surrounding areas [16]. But the specific physiological mechanism is not clear. Moreover, previous studies have shown that HER-2 negative breast cancer is less invasive and has a good prognosis [5]. Our results were similar to the above. In this study, hyperechoic halo of breast cancer was negatively correlated with HER-2 expression, that is, breast cancer with hyperechoic halo had a higher negative rate of HER-2 (65.1%) and a lower aggressiveness. The sensitivity and specificity of hyperechoic halo predicting HER-2 positive were 48.3% and 84.8% respectively. In addition, this study included the maximum diameter, aspect ratio, edge, rear acoustic attenuation, and arterial blood flow in ultrasonic signs, and the results showed no significant correlation with HER-2 expression.

Due to the high sensitivity of mammography to sand-like calcification in breast cancer, previous studies have shown that sand-like calcification is a characteristic of breast cancer, and the microscopic structure of mammography is superior to that of ultrasound and MRI [17]. Therefore, sand-like calcification in mammography is taken as the only evaluation index in this study, and our result (67.7% patients showed sand-like calcification around the lesion) was consistent with the results of previous studies. HER-2 is involved in the local metabolism of breast cancer tissues and accelerates the aggressive growth of tumors, while sand-like calcification is caused by local degeneration and necrosis of cancer cells and calcium salt deposition due to rapid growth and malnutrition of cancer cell [18]. Therefore, breast cancer with HER-2 positive is more prone to sand-like calcification. A number of studies have further analyzed the correlation between sand-like calcification and HER-2 expression, but the conclusion is still not unified. Some studies found that sand-like calcification in mammography examination is the characteristic of breast tumors with HER-2 overexpression, and it is believed that sand-like calcification is significantly positively correlated with the positive expression level of HER-2. However, several studies showed that the positive rate of HER-2 in breast cancer in the non-calcification group was higher than that in the calcification group, but the difference was not significant [17, 19]. Our results showed that there was no significant correlation between sand-like calcification and HER-2 expression. The inconsistent conclusions of these studies may be related to the sample size, patient age and pathological classification.

The ADC value of MRI was mainly affected by the diffusion of water molecules in tissues and microvascular perfusion, and the ADC value would decrease when the diffusion was limited. High cell density in breast cancer tissues restricts the diffusion of water molecules in tumor tissues during DWI imaging, resulting in a decrease in ADC value [20]. Some scholars have found that the more active the proliferation of breast cancer cells, the higher the density of tumor cells, the more limited the diffusion of water molecules, and the ADC value will be lower [21]. HER-2 is an indicator to evaluate the proliferative activity of breast cancer cells. Overexpression of HER-2 can affect cell proliferation, survival, movement and increase invasiveness, and achieve new angiogenesis by increasing the production of vascular endothelial growth factor [5]. As a result, it can increase tumor cell density and limit the diffusion of water molecules, resulting in a decrease in ADC value and a higher expression of HER-2. The more vigorous the cell proliferation, which corresponds to the more active the cell proliferation, the lower the ADC value. In the current study, ADC value of the HER-2 high expression group was significantly lower than that of the HER-2 low expression group, that is, the ADC value was negatively correlated with the positive expression of HER-2. The accuracy, sensitivity and specificity of ADC value in predicting HER-2 expression is 53.3%, 65.5% and 51.5%

respectively. Compared with hyperechoic halo in ultrasound, although the specificity is reduced, the sensitivity is increased (Table 2). Therefore, in clinical work, it is possible to comprehensively evaluate hyperechoic halo and ADC value to predict the expression of HER-2 in breast cancer.

TIC curve is a non-parametric index reflecting the blood perfusion flow rate of breast cancer in dynamic enhanced MRI [22]. According to the strengthening method, the curve was divided into three types: after strengthening, it was continuously strengthened into inflow type; the early strengthening was obvious, and the late strengthening degree <10% was the platform type; the early strengthening was obvious, the middle and late strengthening decreased, and the decrease of >10% was outflow type [20]. Inflow type is more common in benign tumors, outflow type is more common in malignant tumors, and plateau type is more common in benign and malignant tumors. Studies have shown that this is due to the difference in microvascular density in the lesion. The higher the malignant degree of the tumor, the more new blood vessels, the faster the contrast agent enters the vein, and the faster the outflow. In this study, similar to the results of previous studies, there were 6 cases of inflow type and 56 cases of platform type and outflow type among the 62 cases, indicating that the number of microvessels in the enrolled patients was too large, and most of them were somewhat invasive. Previous studies have suggested that the high expression of HER-2 in breast cancer can promote tumor microangiogenesis, and the typing of TIC curve in MRI examination reflects the blood perfusion of tumor microvessels. Theoretically, there should be a certain correlation between TIC curve type and HER-2 expression. Yuan et al. [21] showed that TIC type of breast cancer was positively correlated with positive expression of HER-2 and pathological grade, while Szep et al. [23] showed that positive expression of HER-2 was not significantly correlated with TIC curve type. These inconsistent results may be related to the small number of cases included. Our result showed that there is no significant correlation between the type of TIC curve and the expression of HER-2, which is also inconsistent with theoretical speculation. It may be related to the small number of cases with outflow type, and the possibility of error is not excluded.

The present study has some limitations. First, in order to ensure strict enrollment criteria, the number of cases included in this study is small, which may increase the possibility of error in statistical analyses. Second, the interpretation of ultrasound images in the study is subjectively influenced by doctors, which will affect the consistency of image evaluation. Third, the sensitivity of the hyperechoic halo in predicting HER-2 positivity was 48.3% and the specificity was 84.8%, while the sensitivity of the ADC value in predicting HER-2 positivity was 65.5% and the specificity was 51.5%; both have low diagnostic efficacy, cannot completely replace pathological examination at present and can only provide clinical reference value. Fourth, this is currently a pilot study. It needs to recruit more cases to clarify the correlation between HER-2 expression and features of three types of imaging examinations, and further validate the results of this study.

5. Conclusion

The study preliminarily showed that HER-2 expression in breast cancer tissue is correlated with hyperechoic halo on ultrasound and ADC value of MRI. As a non-invasive examination method, multimodal imaging can be used to roughly evaluate the expression of HER-2 in the case of pre-operation, non-surgical treatment or unconditional immunohistochemical determination of breast cancer, or for elderly patients who are not convenient for biopsy. It will be great helpful for the preoperative diagnosis, treatment choice and prognosis evaluation of breast cancer.

Ethics approval and consent to participate

I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of Affiliated Hospital of Hebei University(Approval number: HDFYLL-KY-2023-029; HDFYLL-KY-2023-077). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure statement

The authors declare that they have no competing interests.

Availability of data and materials

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Authors' contributions

Conception and design of the research: Xiao-Dan Zhang, Min Kou, Ze-Peng Ma; Acquisition of data: Xiao-Dan Zhang, Min Kou, Ze-Peng Ma, Wei-Yan Zou, Xu Duan, Gui-Xin Di, Wei-Qin, Li-Hui Bian; Analysis and interpretation of the data: Xiao-Dan Zhang, Min Kou, Ze-Peng Ma, Wei-Yan Zou, Xu Duan, Wei-Qin; Statistical analysis: Xiao-Dan Zhang, Ze-Peng Ma; Obtaining financing: Xiao-Dan Zhang, Min Kou, Ze-Peng Ma, Wei-Yan Zou, Xu Duan, Gui-Xin Di, Wei-Qin, Li-Hui Bian; Writing of the manuscript: Xiao-Dan Zhang, Ze-Peng Ma; Critical revision of the manuscript for intellectual content: Min Kou, Ze-Peng Ma. All authors read and approved the final draft.

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