Original Article

# Predictors of pathological complete response to neoadjuvant treatment in invasive breast cancer with different human epidermal growth factor receptor 2 (HER2) subcategories

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**Background:** Among human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients who receive anti-HER2 treatment, a noteworthy correlation between pathological complete response (pCR) and longer survival has been observed. The rate of pCR varies with the tumor's degree of HER2 protein expression. The aim of this study was to assess the correlations between clinicopathological characteristics, magnetic resonance imaging (MRI) parameters, and pCR in breast cancer with different HER2 subcategories.

**Methods:** A total of 281 invasive breast cancer patients diagnosed with HER2-positivity were included. HER2-positive translated to immunohistochemistry (IHC) 3+ or IHC 2+/fluorescence in situ hybridization (FISH)(+). All enrolled patients underwent baseline MRI examination and received neoadjuvant chemotherapy, dual anti-HER2 therapy, and subsequent therapeutic surgery from January 2021 to May 2022. A logistic regression model was used to evaluate the effects of covariates on pCR.

**Results:** Compared to the IHC 2+/FISH(+) group, patients with IHC 3+ tumors had a higher pCR rate (58.1% *vs.* 26.7%, P<0.001), clinical stage (58.6% *vs.* 40%, P=0.038), apparent diffusion coefficient (ADC) value (0.96 *vs.* 0.88 $mm^2/s$, P=0.004), and were more likely to be estrogen receptor (ER) negative (55.9% *vs.* 31.1%, P=0.002) and progesterone receptor (PR) negative (72.5% *vs.* 46.7%, P=0.001). In both groups, univariate analysis showed that the pCR group more often had ER-negative and PR-negative status than the non-pCR group (P<0.001). The final multivariable analysis showed that ER-negativity was associated with pCR in the IHC 2+/FISH(+) group (P=0.004). ER-negativity and the longest diameter were two independent predictors of pCR in the IHC 3+ group (P<0.001 for ER, P=0.026 for longest diameter).

**Conclusions:** The IHC 3+ group had a higher pCR rate than the IHC 2+/FISH(+) group. Along with clinicopathological characteristics, MRI parameters were supplemental predictors of pCR, particularly in IHC 3+ patients.

**Keywords:** Human epidermal growth factor receptor 2-positive breast cancer (HER2-positive breast cancer);

pathological complete response (pCR); clinicopathological characteristics; magnetic resonance imaging parameter (MRI parameter)

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## Introduction

Pathological complete response (pCR), serving as a surrogate for survival evaluation, requires fewer patients and a shorter follow-up period (1,2). Particularly in patients with human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor-negative (HR-negative) tumors, the attainment of a pCR has been strongly correlated with a favorable long-term survival rate after anti-HER2 therapy (3-5).

As research on anti-HER2 therapy has advanced, some studies have found that the response to treatment varies in HER2-positive invasive breast cancer. In previous studies (6,7), a considerable proportion of patients did not respond to dual anti-HER2 therapy. Some experts have emphasized that formulating a personalized anti-HER2 therapy plan based on endocrine responsiveness would be an important challenge in the upcoming years (8). In the KRISTINE study, researchers began to assess the possibility of excluding traditional systemic chemotherapy in the neoadjuvant phase (1). These findings highlight the demand for predictive biomarkers that could indicate the response to new treatment methods.

Predictive biomarkers for response have been investigated in the fields of pathology and radiology. Some researchers have aimed to identify predictive factors for pCR across different HER2-positive categories, and found that HER2 immunohistochemistry (IHC) 3+ and histological grade 3 were independent predictors of pCR for patients receiving anti-HER2 therapy (9). Others similarly revealed that the achievement of pCR was associated with the HER2 IHC expression level and that IHC 3+ was a significant predictor of pCR, in addition to other factors (10). The ACRIN 6657/I-SPY TRIAL observed that compared to clinical assessment, the magnetic resonance imaging (MRI) factor (volumetric of tumor) was a more influential predictor of pathologic response in neoadjuvant chemotherapy (11).

Since the HER2 IHC categories have demonstrated a robust correlation with pCR rates, our objective was to find clinicopathological and MRI features linked to pCR in different categories of HER2 breast cancer. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-397/rc).

## Methods

### *Case selection*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute & Hospital (No. bc20240060). The requirement for informed consent was waived due to the retrospective nature of the study. A total of 281 invasive breast cancer patients with HER2 IHC 3+ or IHC 2+/fluorescence in situ hybridization (FISH)(+) were included in this study from January 2021 to May 2022. All patients in our study received trastuzumab and pertuzumab therapy. The exclusion criteria were as follows: (I) lack of FISH results in pretreatment specimens for IHC 2+ tumors; (II) patients who did not receive dual anti-HER2 therapy; (III) lack of baseline magnetic resonance (MR) images in our hospital; (IV) intense artifacts on pretreatment dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI); (V) lack of information on pathological response in the final surgical specimen; and (VI) patients had a history of breast cancer or other cancers.

We assessed the following clinicopathological factors: age, family history, menstrual status, body mass index (BMI), clinical nodal status, clinical stage, histological grade, estrogen receptor (ER), progesterone receptor (PR), and Ki-67. Meanwhile, MR factors included background parenchymal enhancement (BPE), type of lesion, longest diameter, multifocal or multicentric disease, edema, necrosis, kinetics, early enhancement ratio (EER), peak enhancement ratio (PER), late enhancement ratio (LER), time to peak (TTP), and apparent diffusion coefficient (ADC) value.

### *Pathologic assessment*

On the pretreatment specimens of core biopsies, histological

 

grade was assessed according to the Nottingham modification of the Bloom Richardson grading system (12). ER (clone SP1, Zymed) and PR (clone SP2, Zymed) were assessed according to the American Society of Clinical Oncology (ASCO)/ College of American Pathologists (CAP) guidelines (13). An expression level on immunohistochemical staining of ≥1% was considered to indicate ER and PR positivity.

At our center, we routinely evaluated the HER2 expression of breast cancer specimens by IHC. HER2 (HercepTest TM; DAKO, Glostrup, Denmark) were also assessed according to ASCO/CAP guidelines. Only membrane staining of the invasive tissues should be considered when scoring HER2. HER2 IHC was scored as positive (3+), equivocal (2+), or negative (0 or 1+) (14). HER2 IHC 3+ tumors required no further testing, and IHC 2+ cases mandated further assessment of HER2 amplification by FISH. HER2 FISH results were interpreted according to the HER2 2018 ASCO/ CAP updated guidelines (15).

In all resected specimens, pathologic response was evaluated by an experienced pathologist. It has been demonstrated that a stringent definition of pCR (including lymph node status) is more closely related to better survival than the eradication of tumors from the breast alone (3). In our study, pCR was defined as the absence of detectable residual invasive tumor in breast tissue and the absence of lymph node metastasis, regardless of the presence of residual ductal carcinoma *in situ* (ypT0/is ypN0).

### *MRI technique and evaluation*

MRI was conducted on a 1.5-T scanner with a dedicated 4-channel phased-array breast coil (Signa Infinity Excite II; GE Healthcare, Chicago, IL, USA) and a 3.0-T scanner with a dedicated 8-channel phased-array breast coil (Discovery MR750; GE Healthcare). The following protocol was used before neoadjuvant chemotherapy: An axial T1-weighted sequence: repetition time (TR) =700 ms; echo time (TE) =10 ms; flip angle =90°; matrix =384×224; field of view (FOV) =30×30 cm; slice thickness =5 mm.

A fat-saturated T2-weighted sequence: TR =4,500 ms, TE =85 ms; flip angle =90°; matrix =384×224; FOV =30×30 cm; slice thickness =5 mm.

Diffusion-weighted imaging (DWI): single-shot echo-planar imaging (EPI) with diffusion-sensitizing gradients: TR/ TE =6,300/64 ms; field of view =30×30 cm; slice thickness =5 mm; matrix =128×128; b values =500 and 1,000 s/mm$^2$.

DCE-MRI: A sagittal DCE sequence was obtained before and after administration of contrast agent using the volume imaging for breast assessment (VIBRANT) bilateral breast imaging technique: TR =6.1 ms, TE =2.9 ms, matrix size =256×128, FOV =26 × 26 cm, and slice thickness =1.8 mm.

The paramagnetic contrast agent gadopentetate dimeglumine (Gd-DTPA; 0.2 mL/kg body weight, flow rate 2.0 mL/s) was administered intravenously using a power injector followed by an equal volume of saline solution.

The largest diameter was measured on the slice (plane) as the largest area of the whole tumor region from early post-contrast MRI images that were captured about 90 seconds after the injection of contrast agent. If there were unifocal lesions, the total extent of the lesion was measured; if there were multifocal lesions, the longest diameter of the largest lesion was measured.

Pretreatment MRI examinations were independently interpreted by two radiologists with 4 and 10 respective years of experience in breast imaging, according to the 2013 MRI Breast Imaging Reporting and Data System (BI-RADS) lexicon of the American College of Radiology (16). Both radiologists were blinded to the pathological results. In cases of discordance, consensus was reached through image review and discussion under the BIRADS standard.

### *Statistical analyses*

Statistical analysis was conducted using SPSS 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for each variable are reported. For numeric covariates, the median and interquartile range are presented. Frequencies and percentages are shown for categorical variables. The Mann-Whitney U test was performed to compare numerical covariates, and the chi-square test or Fisher's exact test was employed to compare categorical covariates (clinicopathological and MRI variables) between different HER2-positive groups.

A logistic regression model was used to evaluate the effect of covariates on pCR in the HER2 IHC 3+ and HER2 IHC 2+/FISH(+) groups. If a variable still had $P<0.15$, it was incorporated into the final multivariable stepwise regression model. The significance level was set at 0.05.

## Results

### *Clinicopathological and MRI characteristics stratified by HER2 expression*

In the pretreatment biopsy specimens, HER2 IHC was 3+ in 236 cases (84%) and IHC 2+/FISH(+) in 45 cases

 

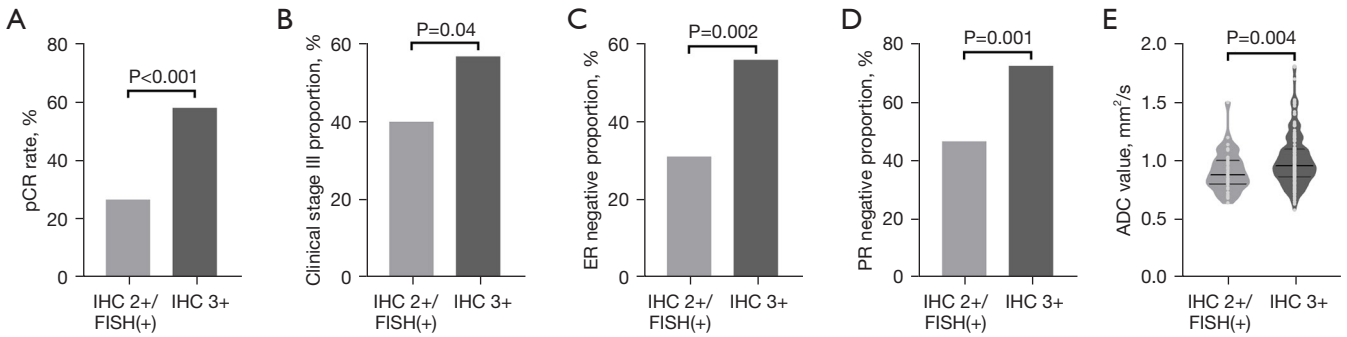


**Figure 1** Differences in clinicopathological and MRI characteristics between the IHC 2+/FISH(+) and IHC 3+ groups. (A) pCR rate, (B) clinical stage III proportion, (C) ER-negative proportion, (D) PR-negative proportion, and (E) median and IQR of ADC value. pCR, pathological complete response; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ER, estrogen receptor; PR, progesterone receptor; MRI, magnetic resonance imaging; IQR, interquartile range; ADC, apparent diffusion coefficient.

(16%). Most (44/45, 97.8%) of the IHC 2+/FISH(+) cases had a HER2/CEP17 ratio ≥2.0 and ≥4.0 HER2 signals/cell (ASCO/CAP ISH Group 1). One (2.2%) case had a HER2/CEP17 ratio <2.0 but ≥6.0 HER2 signals/cell (ASCO/CAP ISH Group 3). Among the 45 IHC 2+ patients with *HER2* amplification detected by FISH, the median HER2/CEP17 ratio by FISH was 2.42 (range, 1.22–6.49), and the median HER2 signals/cell was 6.4 (range, 4.20–16.55).

When we compared the clinicopathological and MRI characteristics of the study cohort across HER2 categories, the key finding was that IHC 3+ tumors had a higher pCR rate than IHC 2+/FISH(+) tumors (58.1% *vs.* 26.7%, P<0.001) (*Figure 1*). Similarly, the differences in clinical staging (P=0.04), ER (P=0.002), and PR (P=0.001) expression were statistically significant between IHC 2+/FISH(+) and IHC 3+ groups (*Figure 1*). Compared with the IHC 2+/FISH(+) group, patients with IHC 3+ tumors had a higher clinical stage (58.6% *vs.* 40% of clinical stage III, P=0.04), along with more frequent ER-negative status (55.9% *vs.* 31.1%, P=0.002) and PR-negative status (72.5% *vs.* 46.7%, P=0.001) (*Figure 1*). Besides, HER2 IHC 3+ tumors had a higher ADC value than IHC 2+/FISH(+) tumors on MRI (0.96 *vs.* 0.88 $mm^2/s$, P=0.004) (*Figure 1*).

### *Identification of predictive factors according to HER2 categories*

The associations between clinicopathological and MRI parameters and the attainment of a pCR were examined in the different HER2 categories using univariate and multivariate stepwise regression models.

In the univariate analysis of the IHC 2+/FISH(+) group (*Table 1*), the differences in ER (P=0.004) and PR (P=0.029) expression were statistically significant between pCR and non-pCR groups (P<0.001 for both). The clinicopathological variables with P<0.15 included family history, clinical stage, and clinical nodal status. Compared with patients in the non-pCR group, patients in the pCR group had a higher frequency of family history (33.3% *vs.* 9.1%, P=0.06), lower clinical stage (16.7% *vs.* 48.5% of stage III, P=0.07), and less lymph node metastasis (58.3% *vs.* 81.8%, P=0.11). Some MRI variables were also incorporated into the multivariate stepwise regression model. In the pCR group, the median longest diameter was smaller (3.4 *vs.* 5.5 cm, P=0.05), multifocal or multicentric disease was less common (41.7% *vs.* 72.7%, P=0.06), and TTP was longer (41.7% *vs.* 15.2% taking 2 mins, P=0.07).

Among those with IHC 3+ tumors (*Table 2*), univariate analysis confirmed that ER and PR were more often negative in the pCR group than in the non-pCR group (P<0.001 for both). Some MRI features also presented differences between these two groups. The median longest diameter was smaller (5.5 *vs.* 6.2 cm, P=0.12) and the LER was higher (165.5% *vs.* 164.5%, P=0.10) in the pCR group than in the non-pCR group. However, these differences were not statistically significant.

All variables that still had P<0.15 were incorporated into the final multivariable stepwise regression model. The results showed that ER-negativity was associated with pCR both in the IHC 2+/FISH(+) group [odds ratio (OR) =0.11, 95% confidence interval (CI): 0.03–0.49, P=0.004] and in the IHC 3+ group (OR =0.26, 95% CI: 0.15–0.45, P<0.001). Additionally, the median longest diameter from MRI was also identified as an independent predictor of pCR. The

 

**Table 1** Univariate analysis of factors associated with pCR in the IHC2+/FISH(+) group

| Parameters | Non-pCR | pCR | OR (95% CI) | P value |
|---|---|---|---|---|
| Age (years) | 49 (42, 55.5) | 53 (41, 58.5) | 1.02 (0.95–1.10) | 0.52 |
| Family history of cancer | | | 5.00 (0.93–27.04) | 0.06 |
| No | 30 (90.9) | 8 (66.7) | | |
| Yes | 3 (9.1) | 4 (33.3) | | |
| Menstrual status | | | 0.91 (0.24–3.49) | 0.89 |
| Postmenopausal | 13 (39.4) | 5 (41.7) | | |
| Premenopausal | 20 (60.6) | 7 (58.3) | | |
| Unknown | 0 (0) | 0 (0) | | |
| BMI (kg/m$^2$) | | | 0.86 (0.23–3.26) | 0.82 |
| ≤24 | 18 (54.5) | 7 (58.3) | | |
| >24 | 15 (45.5) | 5 (41.7) | | |
| Maximum diameter (cm) | 5.5 (3.55, 7.1) | 3.4 (2.5, 5.2) | 0.70 (0.49–1.00) | 0.05 |
| Clinical nodal status | | | 0.31 (0.07–1.33) | 0.11 |
| Negative | 6 (18.2) | 5 (41.7) | | |
| Positive | 27 (81.8) | 7 (58.3) | | |
| Clinical stage | | | 0.21 (0.04–1.12) | 0.07 |
| II | 17 (51.5) | 10 (83.3) | | |
| III | 16 (48.5) | 2 (16.7) | | |
| Histological grade | | | 1.37 (0.54–3.50) | 0.514 |
| I/II | 19 (57.6) | 6 (50.0) | | |
| III | 11 (33.3) | 4 (33.3) | | |
| Unknown | 3 (9.1) | 2 (16.7) | | |
| ER | | | 0.11 (0.03–0.49) | 0.004* |
| Negative | 6 (18.2) | 8 (66.7) | | |
| Positive | 27 (81.8) | 4 (33.3) | | |
| PR | | | 0.19 (0.04–0.84) | 0.029* |
| Negative | 12 (36.4) | 9 (75.0) | | |
| Positive | 21 (63.6) | 3 (25.0) | | |
| Ki-67 | | | 0.71 (0.06–8.62) | 0.79 |
| ≤20% | 2 (6.1) | 1 (8.3) | | |
| >20% | 31 (93.9) | 11 (91.7) | | |
| BPE | | | 1.06 (0.28–3.98) | 0.93 |
| Minimal or mild | 17 (51.5) | 6 (50.0) | | |
| Moderate or marked | 16 (48.5) | 6 (50.0) | | |
| Type of lesion | | | 0.64 (0.24–1.73) | 0.38 |
| NME | 4 (12.1) | 1 (8.3) | | |
| Mass | 13 (39.4) | 8 (66.7) | | |
| Mass and NME | 16 (48.5) | 3 (25.0) | | |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Parameters | Non-pCR | pCR | OR (95% CI) | P value |
|---|---|---|---|---|
| Multifocal or multicentric disease | | | 0.27 (0.07–1.07) | 0.06 |
| Absent | 9 (27.3) | 7 (58.3) | | |
| Present | 24 (72.7) | 5 (41.7) | | |
| Edema | | | 1.00 (0.25–4.06) | 1.00 |
| Absent | 11 (33.3) | 4 (33.3) | | |
| Present | 22 (66.7) | 8 (66.7) | | |
| Necrosis | | | 1.12 (0.19–6.72) | 0.90 |
| Absent | 28 (84.8) | 10 (83.3) | | |
| Present | 5 (15.2) | 2 (16.7) | | |
| Kinetics | | | 0.54 (0.11–2.70) | 0.45 |
| Plateau | 5 (15.2) | 3 (25.0) | | |
| Washout | 28 (84.8) | 9 (75.0) | | |
| EER (%) | 205.0 (180.2, 235.2) | 195.4 (167.5, 224.8) | 0.10 (0.98–1.02) | 0.72 |
| PER (%) | 205.0 (185.3, 235.2) | 195.4 (173.5, 248.4) | 0.10 (0.98–1.02) | 0.93 |
| LER (%) | 162.4 (152.5, 184.9) | 167.9 (140.0, 209.3) | 0.10 (0.99–1.02) | 0.61 |
| TTP | | | 4.00 (0.90–17.76) | 0.07 |
| 1 min | 28 (84.8) | 7 (58.3) | | |
| 2 mins | 5 (15.2) | 5 (41.7) | | |
| ADC value ($mm^2/s$) | 0.87 (0.80, 1.0) | 0.92 (0.81, 1.08) | 14.40 (0.25–840.66) | 0.20 |

Data are presented as median (IQR) or n (%). *, P<0.05. pCR, pathological complete response; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; OR, odds ratio; CI, confidence interval; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; BPE, background parenchymal enhancement; NME, non-mass enhancement; EER, early enhancement ratio; PER, peak enhancement ratio; LER, late enhancement ratio; TTP, time to peak; ADC, apparent diffusion coefficient; IQR, interquartile range.

cut-off value was 2.75 cm. A higher pCR rate was identified in the smaller longest diameter group (OR =0.88, 95% CI: 0.79–0.99, P=0.026) (*Table 3*).

## Discussion

In this study, we aimed to evaluate clinicopathological and MRI data associated with pCR in different HER2 categories of breast cancer. Our results showed that the pCR rate of IHC 2+/FISH(+) tumors was 26.7%, compared to 58.1% in those with HER2 IHC 3+. This is consistent with earlier studies showing that HER2 IHC 3+ invasive breast cancer had a significantly higher pCR rate than IHC 2+/FISH(+) tumors when double anti-HER2 therapy was given (9,10). Considering that the major targets for anti-HER2 therapy were the extracellular domain of the HER2 protein, the higher pCR rate observed in IHC 3+ tumors may be attributed to higher HER2 protein expression. A previous study (17) found that HER2 IHC 3+ tumors had more HER2 enriched molecular subtype than IHC 2+/FISH(+). Several studies (18,19) concluded that the HER2-enriched biomarker can identify patients who are more likely to achieve pCR after neoadjuvant anti-HER2 therapy.

The pCR rate of HER2 IHC 3+ breast cancer was within the range (38–58%) reported in other clinical trials of single or dual anti-HER2 therapy. In contrast, the pCR rate of IHC 2+/FISH(+) tumors was slightly higher than that in other studies (17–21%) (9,10). This difference may be attributed to the fact that all patients in our study received double anti-HER2 therapy. Trastuzumab and pertuzumab have complementary effects due to their different binding sites. This complementary mechanism of action is reflected in trastuzumab inhibiting ligand-independent signaling, whereas pertuzumab exerts its effects by inhibiting ligand-dependent signaling (20-22).

We found that pathological and MRI characteristics

 

**Table 2** Univariate analysis of factors associated with pCR in IHC3+ group

| Parameters | Non-pCR | pCR | OR (95% CI) | P value |
|---|---|---|---|---|
| Age (years) | 50 (39.3, 56.9) | 49 (41, 55.5) | 0.99 (0.97–1.02) | 0.50 |
| Family history of cancer | | | 0.99 (0.49–2.01) | 0.98 |
| No | 83 (83.8) | 115 (83.9) | | |
| Yes | 16 (16.2) | 22 (16.1) | | |
| Menstrual status | | | 0.91 (0.57–1.45) | 0.69 |
| Postmenopausal | 43 (43.4) | 61 (44.5) | | |
| Premenopausal | 52 (52.5) | 73 (53.3) | | |
| Unknown | 4 (4.0) | 3 (2.2) | | |
| BMI (kg/m$^2$) | | | 1.16 (0.69–1.94) | 0.58 |
| ≤24 | 52 (52.5) | 67 (48.9) | | |
| >24 | 47 (47.5) | 70 (51.1) | | |
| Maximum diameter (cm) | 6.2 (3.7, 7.7) | 5.5 (3.3, 7.2) | 0.92 (0.83–1.02) | 0.12 |
| Clinical nodal status | | | 0.70 (0.38–1.29) | 0.25 |
| Negative | 21 (21.2) | 38 (27.7) | | |
| Positive | 78 (78.8) | 99 (72.3) | | |
| Clinical stage | | | 0.82 (0.49–1.39) | 0.46 |
| II | 40 (40.4) | 62 (45.3) | | |
| III | 59 (59.6) | 75 (54.7) | | |
| Histological grade | | | 1.30 (0.91–1.85) | 0.15 |
| I/II | 46 (46.5) | 57 (41.6) | | |
| III | 41 (41.4) | 51 (37.2) | | |
| Unknown | 12 (12.1) | 29 (21.2) | | |
| ER | | | 0.29 (0.17–0.49) | 0.000* |
| Negative | 38 (38.4) | 94 (68.6) | | |
| Positive | 61 (61.6) | 43 (31.4) | | |
| PR | | | 0.30 (0.17–0.55) | 0.000* |
| Negative | 58 (58.6) | 113 (82.5) | | |
| Positive | 41 (41.4) | 24 (17.5) | | |
| Ki-67 | | | 0.78 (0.22–2.74) | 0.70 |
| ≤20% | 4 (4.0) | 7 (5.1) | | |
| >20% | 95 (96.0) | 130 (94.9) | | |
| BPE | | | 0.76 (0.45–1.28) | 0.30 |
| Minimal or mild | 57 (57.6) | 88 (64.2) | | |
| Moderate or marked | 42 (42.4) | 49 (35.8) | | |
| Type of lesion | | | 0.74 (0.49–1.13) | 0.16 |
| NME | 4 (4.0) | 15 (10.9) | | |
| Mass | 47 (47.5) | 62 (45.3) | | |
| Mass and NME | 48 (48.5) | 60 (43.8) | | |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Parameters | Non-pCR | pCR | OR (95% CI) | P value |
|---|---|---|---|---|
| Multifocal or multicentric disease | | | 1.08 (0.64–1.85) | 0.77 |
| Absent | 38 (38.4) | 50 (36.5) | | |
| Present | 61 (61.6) | 87 (63.5) | | |
| Edema | | | 1.44 (0.77–2.69) | 0.25 |
| Absent | 25 (25.3) | 26 (19.0) | | |
| Present | 74 (74.7) | 111 (81.0) | | |
| Necrosis | | | 0.94 (0.43–2.03) | 0.87 |
| Absent | 86 (86.9) | 120 (87.6) | | |
| Present | 13 (13.1) | 17 (12.4) | | |
| Kinetics | | | 1.27 (0.66–2.44) | 0.48 |
| Plateau | 21 (21.2) | 24 (17.5) | | |
| Washout | 78 (78.8) | 113 (82.5) | | |
| EER (%) | 200.6 (171.8, 229.9) | 205.1 (172.4, 241.5) | 1.003 (0.997–1.008) | 0.30 |
| PER (%) | 203.9 (174.9, 233.7) | 206.3 (175.7, 245.7) | 1.003 (0.997–1.009) | 0.28 |
| LER (%) | 164.5 (141.1, 186.2) | 165.5 (146.5, 196.3) | 1.006 (0.999–1.013) | 0.10 |
| TTP | | | 0.866 (0.473–1.585) | 0.64 |
| 1 min | 74 (74.7) | 106 (77.4) | | |
| 2 mins | 25 (25.3) | 31 (22.6) | | |
| ADC value ($mm^2$/s) | 0.96 (0.87, 1.1) | 0.96 (0.86, 1.1) | 1.23 (0.35–4.32) | 0.75 |

Data are presented as median (IQR) or n (%). *, P<0.05. pCR, pathological complete response; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; OR, odds ratio; CI, confidence interval; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; BPE, background parenchymal enhancement; NME, non-mass enhancement; EER, early enhancement ratio; PER, peak enhancement ratio; LER, late enhancement ratio; TTP, time to peak; ADC, apparent diffusion coefficient; IQR, interquartile range.

**Table 3** Multivariate analysis of factors associated with pCR according to HER2 categories

| Parameters | Reference | B | S.E. | Wals | P value | OR (95% CI) |
|---|---|---|---|---|---|---|
| IHC2+ group | | | | | | |
| ER | –* | | | | | |
| | + | –2.20 | 0.76 | 8.34 | 0.004 | 0.11 (0.03–0.49) |
| IHC3+ group | | | | | | |
| ER | –* | | | | | |
| | + | –1.36 | 0.29 | 22.59 | 0.000 | 0.26 (0.15–0.45) |
| Maximum diameter | | –0.12 | 0.06 | 4.93 | 0.026 | 0.88 (0.79–0.99) |

*, control group. pCR, pathological complete response; HER2, human epidermal growth factor receptor 2; S.E., standard error; OR, odds ratio; CI, confidence interval; IHC, immunohistochemistry; ER, estrogen receptor.

differed between HER2 IHC 3+ and HER2 IHC 2+/FISH(+) tumors: IHC 3+ tumors tended to be larger, to be more often ER-negative and PR-negative, and to have higher ADC values. A previous study reported (23) that HER2 IHC 3+ tumors were also larger, often ER-negative and PR-negative, and had higher histological grades than

 

HER2 IHC 2+/FISH(+) tumors. Combining the results of these studies, IHC 3+ tumors tend to have higher ADC values and histological grades. However, we usually expect higher-grade tumors to generate lower ADC values. Cellularity, as a representative factor for histological grade, has also been confirmed to be inversely correlated with the ADC value by most previous studies (24-26). Although some experts have only found a similar trend without statistical significance (27), 1 study (28) found that the ADC value is positively correlated with tumor cellularity in evaluating the correlation between ADC histogram parameters and prognostic factors and provided an explanation for this result. The assumption that high cellularity would lower ADC values in high-grade tumors was attributed to the subjectivity of the Nottingham modification of the Bloom-Richardson grading system (12,29). However, in addition to subjective evaluation, there were also other related factors, such as the spatial focus of evaluation, the morphology of tumor cells, and cellular displacement. Under the influence of these factors, Kim *et al.* (27) demonstrated that high-grade tumors had higher ADC values (ADCmax) than low-grade tumors in their study, which was consistent with our result.

In our study, ER-negative status was more common in HER2 IHC 3+ tumors than in the IHC 2+/FISH(+) group. A previous study (30) also observed a negative correlation between ER and HER2 levels in breast cancer. Meanwhile, similar to some previous reports (3,6,9,31), we found that ER status was an independent predictor of pCR in both the IHC 2+/FISH(+) group and the HER2 IHC 3+ group. ER-negative tumors presented a significantly higher pCR rate than ER-positive tumors in both univariate and multivariate analyses. In fact, early preclinical data (32) have shown that estrogen (rather than progestin) was able to change *HER-2/neu* messenger RNA (mRNA) or protein levels in a dose-dependent manner. This mechanism may further influence the response of HER2-positive tumors to combined chemotherapy and anti-HER2 therapy (33-35). Some previous studies demonstrated that tumors not only exhibited a high dependence on the *HER2* gene during growth but also exhibited good response to anti-HER2 therapy in the HR–/HER2+ subtype (35,36).

Since MRI mainly displays cancer through contrast enhancement associated with tumor angiogenesis, we supposed that it could provide both physiological tumor information and more accurate markers of tumor response than simple anatomical imaging. In multiple studies, MRI has better demonstrated the extent of cancer than traditional mammography and ultrasonography (37-40) and is the most accurate modality for evaluating tumor response to neoadjuvant chemotherapy (41-43). To our knowledge, this is the first report to not involve artificial intelligence to predict pCR based on pretreatment MRI data according to the HER2 category of breast cancer. Longest diameter was a significant factor of pCR in the HER2 IHC 3+ group. The ACRIN 6657/I-SPY TRIAL (11) concluded that MR image findings are more predictive of pathologic response to neoadjuvant chemotherapy than clinical assessment. The utilization of volumetric measurements demonstrated the greatest advantage in terms of tumor response early in treatment. Furthermore, another two studies showed that tumor volume measured by MRI was a predictor of recurrence-free survival in breast cancer patients (44,45). Similarly, research on triple-negative breast cancer has indicated that tumor volume measured by pretreatment MRI is an independent predictive factor for pCR (43).

Our study used longest diameter rather than volumetric measurement because we focused on baseline MR images rather than data after neoadjuvant chemotherapy. In another study, initial (before neoadjuvant therapy) MRI diameter and volume measurement methods were substituted in the Cox model, with little loss of predictive value (46). Therefore, MRI diameter can be a reasonable substitute for MRI volume to illustrate the association with pCR before neoadjuvant chemotherapy. This study was also successful in assessing the value of MRI measurements of longest diameter before neoadjuvant chemotherapy treatment for predicting pCR in comparison with established prognostic factors from the clinical and pathological domains.

Our study has some limitations. First, this was a retrospective study, and our small sample was collected from a single center, which may have introduced a selection bias. Second, all pathologic factors were based on core biopsy, which might lead to false-negative results. Previous research demonstrated that core biopsy samples and surgical resection samples may produce discrepant findings with respect to HER2-low status because of intratumoral heterogeneity in protein expression and preanalytical variables (47). Therefore, specimen from core biopsy might lead to false-negative results. Finally, most tumors in the IHC 2+/HER2 amplification group belonged to ASCO/CAP FISH Group 1. As Group 2, 3, and 4 tumors are uncommon (48), our results are not representative of all IHC 2+/HER2 amplification tumors.

In conclusion, the benefit of neoadjuvant anti-HER2 therapy was different between patients with HER2 IHC

 

3+ tumors and those with IHC 2+/FISH(+) tumors. ER negativity independently predicted pCR in both groups. The median longest diameter measured by MRI was another independent predictor for pCR in the HER2 IHC 3+ group. We anticipate further analyses enrolling larger cohorts to validate these results and the exploration of other research methods, such as artificial intelligence applications, to find more biomarkers for achieving personalized treatment for HER2-positive patients.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-397/rc

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute & Hospital (No. bc20240060) and the requirement for informed consent was waived due to the retrospective nature of the study.



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