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ORIGINAL RESEARCH

Comparison of the pCR Rate and DFS Among Breast Cancer Patients with Different Hormone Receptor and HER2 Statuses

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Background: Recent studies have investigated the features of breast cancer (BC) with low human epidermal growth factor receptor 2 (HER2) expression or HER2-0 expression. However, the results were inconsistent. In this study, we investigated the differences in the pathological complete response (pCR) rate and disease-free survival (DFS) between HER2-low and HER2-0 BC patients and between subgroups.

Methods: HER2-negative BC patients who received neoadjuvant chemotherapy between January 2013 and December 2019 in our hospital were retrospectively reviewed. First, the pCR rate and DFS were compared between HER2-low and HER2-0 patients and among different hormone receptor (HR) and HER2 statuses. Subsequently, DFS was compared between different HER2 status populations with or without pCR. Finally, a Cox regression model was used to identify the prognostic factors.

Results: Overall, 693 patients were selected: 561 were HER2-low, and 132 were HER2-0. Between the two groups, there were significant differences in N stage ($P = 0.008$) and HR status ($P = 0.007$). No significant difference in the pCR rate (12.12% vs 14.39%, $P = 0.468$) or DFS was observed, independent of HR status. HR+/HER2-low patients had a significantly worse pCR rate ($P < 0.001$) and longer DFS ($P < 0.001$) than HR-/HER2-low or HER2-0 patients. In addition, a longer DFS was found in HER2-low patients versus HER2-0 patients among those who did not achieve pCR. Cox regression showed that N stage and HR status were prognostic factors in the overall and HER2-low populations, while no prognostic factor was found in the HER2-0 group.

Conclusion: This study suggested that HER2 status is not associated with the pCR rate or DFS. Longer DFS was found only among patients who did not achieve pCR in the HER2-low versus HER2-0 population. We speculated that the interaction of HR and HER2 might have played a crucial role in this process.

Keywords: HER2-low, HER2-0, hormone receptor, pCR, DFS

Introduction

In recent decades, the number of breast cancer (BC) patients has increased rapidly, and BC is the most common malignant tumor in women around the world.[1] Currently, according to the 2018 ASCO guidelines, BC subtypes are defined by the statuses of the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67.[2] HER2 status, which is evaluated by immunohistochemistry (IHC), historically is classified as positive (IHC score of 3+ or 2+ and amplification of the ERBB2 gene) or negative (IHC score of 0, 1+, or 2+ with nonamplification of the ERBB2 gene).[3]

However, in recent years, several clinical trials have reported the existence of a novel subtype among HER2-negative BC patients. The results showed that there was a significant difference in characteristics between HER2-0 (IHC score of 0) patients and HER2-low (IHC score of 1+ or 2+ without detecting ERBB2 gene amplification) patients.[4–6] Novel antibody-drug conjugates (ADCs) targeting HER2 could significantly improve the prognosis of BC patients with low

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HER2 expression.[7,8] Subsequent studies have been conducted to explore the differences in response to neoadjuvant chemotherapy (NAC), as well as in DFS of BC patients with HER2-low or HER2-0 status.[9–16] However, these results have been inconsistent and even conflicting.

Therefore, in this study, we retrospectively reviewed data from our hospital. This study aimed to compare the pathological complete response (pCR) rate and disease-free survival (DFS) between HER2-low and HER2-0 BC patients, as well as between subgroups.

Methods

Patient Selection and Study Design

This retrospective study was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University (ID: No. 2020–59) and was performed according to the Declaration of Helsinki. We retrospectively reviewed BC patients at the First Affiliated Hospital of Chongqing Medical University from January 2013 to December 2019. Patients who received NAC were selected for the subsequent analysis. We compared the pCR rate and DFS between the HER2-low group and the HER2-0 group. Next, the pCR rate and DFS were compared among the following 4 subgroups: 1) HR+/HER2-low patients; 2) HR-/HER2-low patients; 3) HR+/HER2-0 patients; and 4) HR-/HER2-0 patients. DFS was further compared among patients with different HER2 statuses and with different responses to NAC. Finally, we identified prognostic factors using a Cox regression model. The flowchart of this study is shown in Figure 1.

Treatment Protocol

NAC was performed according to the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) guidelines.[17,18] Once the patients were diagnosed as needing to receive NAC, treatment started within a week. The treatment protocol was TEC (docetaxel 75 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2) or EC (epirubicin 75 mg/m^2 and cyclophosphamide 500 mg/m^2), and drugs were administered at

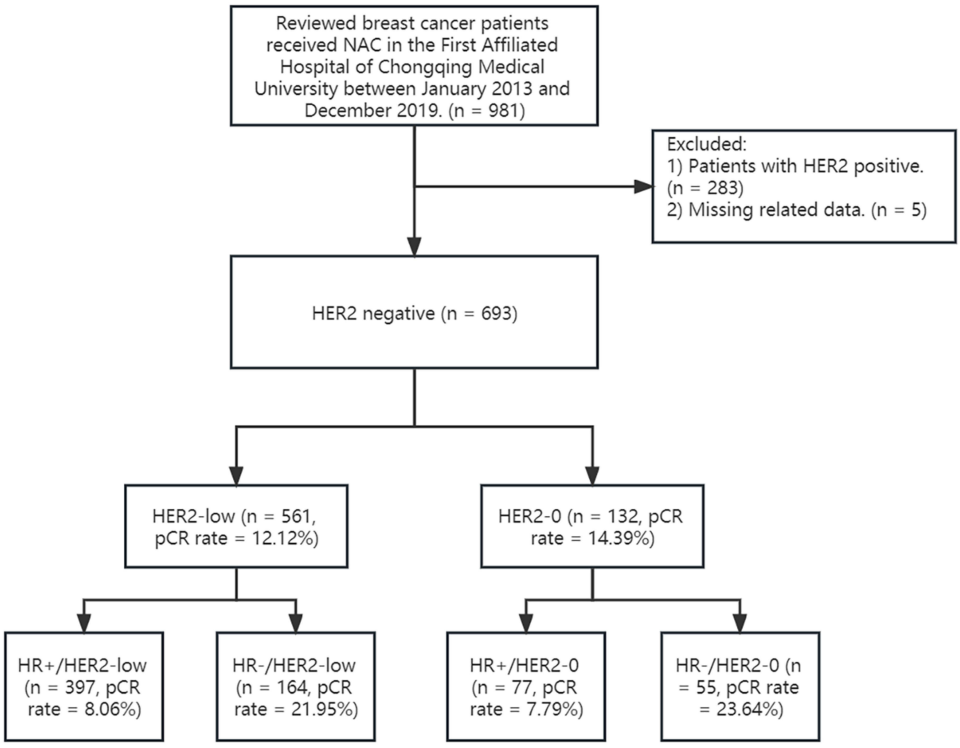

Figure 1 The flowchart of this study.

21-day intervals. After 4–6 cycles of NAC, the response was evaluated by both the clinicians and the pathologists. Mastectomy or breast-conserving surgery plus axillary lymphadenectomy was subsequently performed.

Pathological Evaluation

The IHC index was assessed based on the core needle biopsy of the tumor. Hormone receptor (HR) positivity was defined as an estrogen receptor (ER)- or progesterone receptor (PR)-expressing cell percentage > 10% by IHC. pCR was defined as no residual invasive tumor in either the breast or axillary lymph nodes (ypT0ypN0).[19] HER2 was evaluated by IHC and FISH. The possible IHC scores were as follows: 1) 0: no staining is observed or membrane staining that is incomplete and faint/barely perceptible in ≤ 10% of tumor cells; 2) 1+: incomplete membrane staining that is faint/barely perceptible in > 10% of tumor cells; 3) 2+: weak to moderate complete membrane staining observed in > 10% of tumor cells; and 4) 3+: circumferential membrane staining that is complete, intense, and in > 10% of tumor cells. An IHC score of 0 was defined as HER2-0. An IHC core of 1+ or 2+ with negative FISH was defined as HER2-low. An IHC core of 3+ or 2+ with positive FISH was defined as HER2-positive.[20] These results were evaluated by two pathologists independently and blindly.

Follow-Up

All patients were interviewed by telephone from discharge to February 1st, 2021. DFS was selected for assessing patient prognoses. DFS was defined as the period between surgery and either 1) the first relapse of the tumor locally, regionally, or distantly; 2) a diagnosis of secondary malignant tumor or contralateral BC; or 3) death due to any reason.

Statistical Analysis

We used IBM SPSS 23.0 (Chicago, IL, USA), Stata/SE 16.0 and RStudio 1.1.456 (R version 4.2.1) software for statistical analysis. For each patient, age; histological type of tumor; T stage; N stage; ER, PR, and HR status; HER2 score; Ki67 index; P53; and pCR were recorded. ER, PR, HR, and Ki67 were divided according to current guidelines. P53 was divided based on the ideal cutoff value, which was determined using receiver operating characteristic (ROC) curves. The chi-square test was used to compare categorical data, and the *t*-test was used to compare continuous data. Kaplan–Meier curves were used to describe the survival probability, and the Log rank test was used for comparisons between groups. A Cox proportional hazard model was used to identify prognostic factors in the whole cohort, HER2-low cohort, and HER2-0 cohort. A p value < 0.05 was considered to indicate a significant difference.

Results

Patient Characteristics

Overall, a total of 693 HER2-negative BC patients were selected, and the median age was 48 years old (range 20–72). Of them, 132 patients had HER2-0 expression, and 561 patients had HER2-low expression. We first compared the characteristics and response to NAC between the HER2-low group and the HER2-0 group. There were significant differences in N stage and ER, PR, and HR status. Compared with HER2-0 patients, HER2-low patients were significantly associated with positive ER, PR, and HR and N1 stage. Moreover, HER2-low patients exhibited lower Ki67 and higher P53 levels, but the differences were not statistically significant. Table 1 displays the characteristics of the patients.

Comparison of pCR Rate

We analyzed the pCR rate among BC patients with HER2-low or HER2-0 status. Although the pCR rate of HER2-low patients was slightly lower than that of HER2-0 patients, no significant difference was observed (12.12% vs 14.39%, P = 0.468). Additionally, no significant difference was found between the HR+ and HR- populations (P = 0.937 and P = 0.795, respectively). Moreover, in line with consensus, the results showed that patients with HR-/HER2-low or HER2-0 status had a significantly higher pCR rate than patients with HR+/HER2-low or HER2-0 status (P < 0.001, Figure 2).

Table 1 Characteristics of the Patients at Diagnosis

Variable	HER2-Low (n = 561)	HER2-0 (n = 132)	Total	P value
Age	48 (20–72)	49 (26–70)	48 (20–72)	0.399
Histologic type				0.431
Invasive ductal carcinoma	543 (96.79%)	126 (95.45%)	669	
Other	18 (3.21%)	6 (4.55%)	24	
T				0.444
T1	61 (10.87%)	10 (7.58%)	71	
T2	385 (68.63%)	97 (73.48%)	482	
T3	115 (20.50%)	25 (18.94%)	140	
N				0.008
N0	205 (36.54%)	58 (43.94%)	263	
N1	271 (48.31%)	47 (35.61%)	318	
N2	74 (13.19%)	19 (14.39%)	93	
N3	11 (1.96%)	8 (6.06%)	19	
ER				0.007
≤ 10	200 (45.65%)	64 (48.48%)	264	
> 10	361 (64.35%)	68 (51.52%)	429	
PR				0.018
≤ 10	314 (55.97%)	89 (67.42%)	403	
> 10	247 (44.03%)	43 (32.58%)	290	
HR				0.007
HR+	397 (70.77%)	77 (58.33)	474	
HR-	164 (29.23%)	55 (41.67%)	219	
Ki67				0.253
≤ 20	290 (51.69%)	58 (43.94%)	348	
21–30	128 (22.82%)	33 (25.00%)	161	
> 30	143 (25.49%)	41 (31.06%)	184	
p53				0.384
≤ 17.5	284 (50.62%)	73 (55.30%)	357	
> 17.5	277 (49.38%)	59 (44.70%)	336	
pCR				0.468
pCR	68 (12.12%)	19 (14.39%)	87	
Non-pCR	493 (87.88)	113 (85.61%)	606	

Comparison of DFS

The median follow-up time was 43 months (IQR: 23–68). In total, 140 events were detected (109 cases in the HER2-low group and 31 cases in the HER2-0 group). The 3-year DFS rates for HER2-low and HER2-0 patients were 85.0% and 77.9%, respectively. The 5-year DFS rates for HER2-low and HER2-0 patients were 81.6% and 76.3%, respectively. Although we observed that HER2-low BC patients had a longer DFS than HER2-0 BC patients, there was no significant difference (P = 0.156, Figure 3A).

Next, we compared DFS between BC patients with different HR and HER2 statuses. No significant difference existed between the HER2-low and HER2-0 groups in either the HR+ or HR- populations (P = 0.229 and P = 0.535, respectively). However, HR+/HER2-low patients had significantly longer DFS than patients with HR-/HER2-low or HER2-0 status (P < 0.001 and P = 0.005, respectively). Moreover, we observed that HR+/HER2-0 patients had longer DFS than patients with HR-/HER2-low or HER2-0 status, although the difference was not significant (P = 0.179 and P = 0.106, respectively) (Figure 3B).

Additionally, we compared DFS between BC patients with different HER2 statuses with or without pCR to NAC. The results showed that patients with HER2-0/non-pCR had significantly worse DFS than both patients with HER2-0/pCR and patients with HER2-low/non-pCR (P = 0.027 and P = 0.036, respectively, Figure 3C).

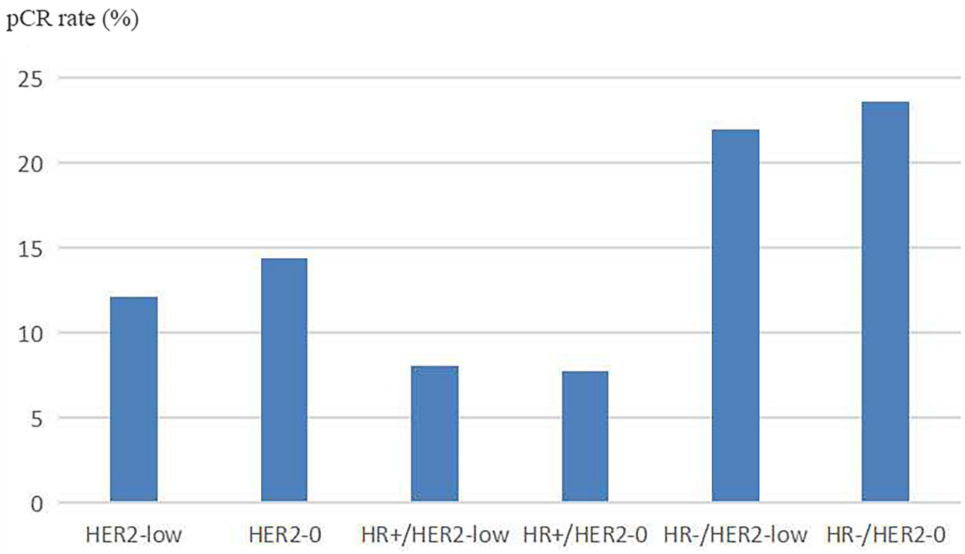

Figure 2 The pCR rate of patients with HER2-low, HER2-0, HR+/HER2-low, HR+/HER2-0, HR-/HER2-low, and HR-/HER2-0. No significant difference was observed in the whole, HR+ and HR- populations (P = 0.468, P = 0.937 and P = 0.795, respectively).

We further investigated the predictive factors in the overall patient group, HER2-low patient group, and HER2-0 patient group by using Cox regression analysis. Both univariate and multivariate analyses identified that N stage and HR status were prognostic factors in the whole population and in the HER2-low population, while no factor was associated with DFS in the HER2-0 population (Table 2).

Discussion

In recent decades, BC was classified according to the evaluation of ER, PR, Ki67, and HER2 status. HER2 status is traditionally divided into positive and negative, and only HER2-positive patients can benefit from anti-HER2 targeted therapy.[19,21] However, with novel evidence emerging, researchers have observed that patients with HER2 1+ or 2+ scores without ERBB2 gene overexpression could also have better prognoses after receiving anti-HER2 therapy, and these patients were defined as having HER2-low expression.[22,23] Recently, studies have debated whether a significant biological and prognostic difference exists between HER2-low patients and HER2-0 patients.

Zhou et al indicated that there was no difference in the pCR rate between HER2-low and HER2-0 patients.[10,14] In contrast, a pooled analysis by Denkert et al showed that the pCR rate was significantly lower in HER2-low patients than in HER2-0 patients, and the same trend was also found in the hormone receptor-positive subgroup. Similarly, controversy has also arisen in the study of prognosis. Denkert et al have argued that HER2-low patients had significantly longer OS and DFS than HER2-0 patients,[24] while Alves observed that no differences existed.[14] Moreover, two other large cohort studies concluded that HER2-low patients had a better prognosis than HER2-0 patients.[25,26] A recent meta-analysis concluded that HER2-low status is associated with enhanced DFS and OS in early-stage BC, regardless of HR status.[27] Furthermore, almost all of these studies demonstrated that HR+ was strongly positively associated with HER2-low expression and lower tumor stage. Denkert et al further indicated that HER2-low expression was correlated with lower Ki67 and lower TP53 levels. He suggested that these might result in HER2-low patients having lower pCR rates and better survival outcomes.[24] Most importantly, a Phase 3 trial by Modi et al revealed that trastuzumab deruxtecan could significantly improve the survival time of patients with HER2-low status.[7]

In this retrospective study, we first compared the characteristics between the two groups, and the results were mostly consistent with those of previous works. Then, we analyzed whether the pCR rate and DFS were different between the two groups and subgroups. However, no significant differences were observed in the whole, HR+ and HR- groups. Subgroup analysis indicated that compared with patients with HR-/HER2-low or HER2-0 status, patients with HR +/HER2-low status had significantly lower pCR rates and better prognoses. Interestingly, among patients who did not achieve pCR, HER2-low patients had significantly longer DFS than HER2-0 patients. Furthermore, the Cox regression

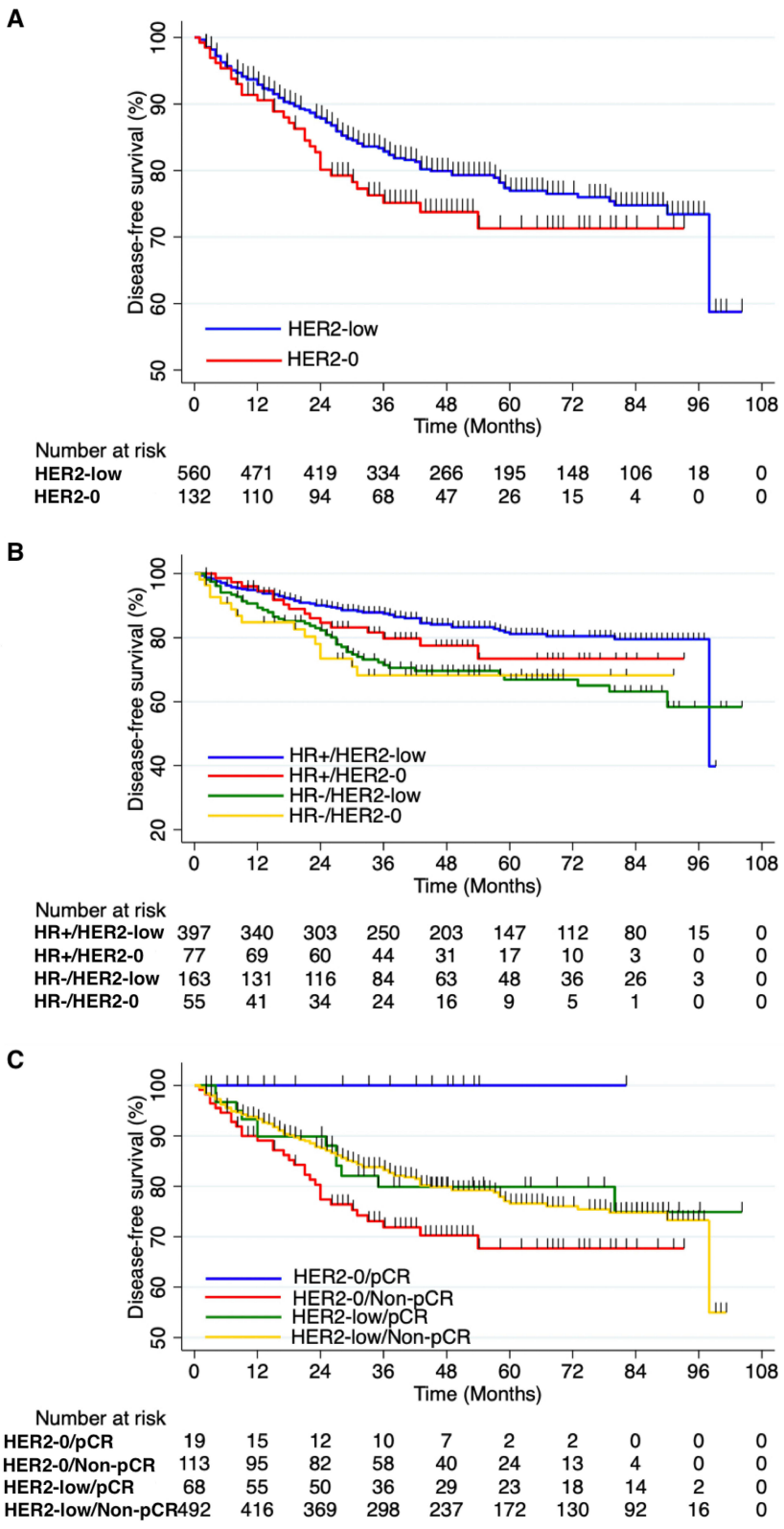

Figure 3 DFS analysis (**A**) Comparison of DFS between patients with HER2-low and patients with HER2-0. Although HER2-low BC patients exhibited a longer DFS compared to HER2-0 BC patients, the difference was not statistically significant (P = 0.156). (**B**) Comparison of DFS between patients with different HR and HER2 status. No statistically significant difference existed between the HER2-low and HER2-0 groups within both the HR+ and HR- populations (P = 0.229 and P = 0.535, respectively). HR+/HER2-low patients had significantly longer DFS than patients with HR-/HER2-low or HER2-0 status (P < 0.001 and P = 0.005, respectively). (**C**) Comparison of DFS between patients with different HER2 status and with or without pCR. Patients with HER2-0/non-pCR status demonstrated a significantly worse DFS when compared to both patients with HER2-0/pCR and patients with HER2-low/non-pCR status. (P = 0.027 and P = 0.036, respectively).

Table 2 Univariate and Multivariate Analyses for DFS

The Whole Patients' Group							
Univariate Analysis				**Multivariate Analysis**			
	p	**Hazard Ratio**	**95% CI**		***p***	**Hazard Ratio**	**95% CI**
T1+T2 vs T3	0.188	0.767	0.517–1.138	T1+T2 vs T3	0.301	0.811	0.545–1.206
N0+N1 vs N2+N3	0.008	0.587	0.396–0.872	N0+N1 vs N2+N3	0.011	0.598	0.401–0.891
HR- vs HR+	< 0.001	1.942	1.39–2.713	HR- vs HR+	< 0.001	2.063	1.453–2.929
HER2-low vs HER2-0	0.159	0.75	0.502–1.119	HER2-low vs HER2-0	0.334	0.819	0.546–1.228
Ki67	0.72	1.002	0.993–1.01	Ki67	0.768	0.999	0.99–1.008
Non-pCR vs pCR	0.217	1.205	0.896–1.62	Non-pCR vs pCR	0.118	1.627	0.884–2.995
The HER2-low group							
Univariate analysis				**Multivariate analysis**			
	p	**Hazard Ratio**	**95% CI**		**p**	**Hazard Ratio**	**95% CI**
T1+T2 vs T3	0.225	0.758	0.485–1.185	T1+T2 vs T3	0.302	0.788	0.502–1.238
N0+N1 vs N2+N3	0.048	0.628	0.396–0.996	N0+N1 vs N2+N3	0.039	0.613	0.284–0.977
HR- vs HR+	< 0.001	2.029	1.388–2.967	HR- vs HR+	< 0.001	2.125	1.431–3.158
Ki67	0.505	1.003	0.994–1.013	Ki67	0.505	1	0.994–1.011
Non-pCR vs pCR	0.846	1.061	0.582–1.934	Non-pCR vs pCR	0.846	1.201	0.646–2.231
The HER2-0 group							
Univariate analysis				**Multivariate analysis**			
	p	**Hazard Ratio**	**95% CI**		**p**	**Hazard Ratio**	**95% CI**
T1+T2 vs T3	0.608	0.802	0.345–1.862	T1+T2 vs T3	0.527	0.755	0.316–1.803
N0+N1 vs N2+N3	0.071	0.489	0.225–1.064	N0+N1 vs N2+N3	0.126	0.537	0.242–1.19
HR- vs HR+	0.21	1.569	0.775–3.176	HR- vs HR+	0.118	1.821	0.86–3.859
Ki67	0.502	0.994	0.978–1.011	Ki67	0.702	0.996	0.978–1.015
Non-pCR vs pCR	0.113	1.677	0.884–3.180	Non-pCR vs pCR	0.969	/	/

model confirmed that HR was a prognostic factor for DFS in both the overall patient group and the HER2-low group. Additionally, we noticed that HR+ was strongly associated with HER2-low status.

Zhang et al indicated that mediator subunit 1 (MED1), a biomarker that coamplified with HER2 and a coactivator of ER, played a key role in tamoxifen resistance.[28] Yang et al revealed that there was a significantly positive correlation between MED1 and insulin-like growth factor 1 (IGF-1), and IGF-1 pathways were of vital importance in mediating MED1 functions during tumorigenesis.[29] Meanwhile, Groot et al reported that BC patients with decreased expression of IGF-1 receptor after NAC could have a better prognosis than those with normal expression.[30] In addition, an earlier finding by Bellacosa et al demonstrated that MLH1, the most abundantly expressed mismatch repair protein, forms a complex and interacts with MED1.[31,32] The loss of mismatch repair could develop during chemotherapy and lead to chemotherapy resistance.[33] Recently, Wang et al discovered that the MLH1-positive rate was lower in the HR+ group than in the HR- group. Based on these findings, we speculated that the reason for HER2-low BC patients having a worse pCR rate and better prognosis in several studies may lie in HR, IGF-1, MED1 and MLH1. Previous studies had inconsistent conclusions, which might be explained by the different expression rates of IGF-1, MED1 and MLH1 in each center.

To the best of our knowledge, this is the first study to compare the pCR rate and DFS between BC patients with different HR and HER2 statuses. However, there were limitations in our work. First, this was a single-center retrospective study, which might lead to bias in the results. Second, we have not performed studies using animal or cell models to validate our hypothesis. Regardless, we hope our work will have significance for clinical procedures and future research. BC patients with HER2-low expression could benefit from these studies.

In summary, our findings indicated that there was no difference in the pCR rate or DFS between HER2-low and HER2-0 BC patients in the overall, HR+ and HR- populations. DFS was significantly longer in HER2-low patients than in HER2-0 patients only when pCR was not achieved. Future studies should focus on the interaction between HR and HER2, especially changes in the expression levels of IGF-1, MED1 and MLH1 among HER2-low or HER2-0 patients pre- and post-NAC.

Data Sharing Statement

The data are available and can be requested from the corresponding author.

Ethics Approval and Informed Consent

This retrospective study was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University (ID: No. 2020–59) and was performed according to the Declaration of Helsinki. And informed consent has been obtained from the study participants prior to study commencement. We declared that patient data was maintained with confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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