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Original Article

Effect of HER2-low-positive status on neoadjuvant chemotherapy and survival outcome of breast cancer: a 10-year dual-center retrospective study

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Abstract: Various novel HER2-targeted antibody-conjugated drugs (ADCs) have shown satisfactory antitumor activity in HER2-low-positive breast cancer (BC). It is urgent to clarify whether HER2-low-positive tumors have unique biological behavior and should be considered a new molecular subtype. We screened eligible BC patients and collected relevant information at the First Hospital of Jilin University and the First Affiliated Hospital of Xi'an Jiaotong University from January 2010 to December 2020. A total of 1027 patients were included in our study cohort, and 66.0% (678/1027) had HER2-low-positive tumors. Compared to HER2-zero patients, HER2-low-positive patients tended to have more lymph node metastasis, a larger proportion of hormone receptor (HR)-positive tumors, and a lower proliferation rate (Ki-67). The pathologic complete response (pCR) rate of HER2-low-positive patients was lower than that of HER2-zero patients (19.3% vs 26.1%), especially in the HR-positive subgroup (12.00% vs 20.29%). However, multivariate logistic regression analysis showed that HER2 status was not an independent factor for predicting pCR. HER2-low-positive patients had a higher overall survival (OS) rate in the HR-positive subgroup. The Cox regression model analysis suggested that HER2-low-positive status did not statistically significantly affect the survival outcomes, regardless of disease-free survival (DFS) (P=0.308) or OS (P=0.066). In conclusion, HER2-low-positive tumors have unique clinical and pathological characteristics, with a lower pCR rate in the HR-positive subgroup and better survival in the HR-negative subgroup compared to HER2-zero tumors. However, the effect of HER2-low-positive status on pCR or survival outcomes was not statistically significant.

Keywords: Breast neoplasms, female, retrospective studies, neoadjuvant therapy, HER2

Introduction

The human epidermal growth factor receptor 2 (HER2) is a significant driver gene in breast cancer (BC) and also a gene locus for anti-HER2 targeted therapy. Amplification of the HER2 gene often indicates poor prognosis [1]. The traditional classification of HER2 adopts a binary system, which includes HER2-negative and HER2-positive. The 2018 edition of the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines standardized the classification of HER2 test results. According to immunohistochemistry (IHC) and in situ hybridization (ISH) results, IHC 0 was classified as HER2-negative, IHC 1+ or IHC 2+/ISH- were considered HER2-low-positive, and IHC 2+/ISH+ or IHC 3+ was classified as HER2-positive.

There are multiple studies with different conclusions regarding the effect of different subtypes of HER2 expression on neoadjuvant chemotherapy (NAC) response [2-10]. A pooled analysis by the German research group showed that the pathologic complete response (pCR) rate in HER2-low-positive patients was lower than that in HER2-zero patients (29.2% vs 39.0%), and this difference was only present in the hormone receptor (HR)-positive subgroup (17.5% vs 23.6%). However, this difference disappeared in the multivariate analysis [4]. Some studies have proposed opposite results, with a Brazilian study suggesting that HER2-low-

positive patients have a higher pCR rate in the HR-positive group (13% vs 9.5%), while there was no significant difference in the HR-negative group (51% vs 47%) [11]. One United States study considered that HER2-low-positive had a lower pCR rate (17% vs 27%) but was not related to HR status [10]. The inconsistency of reported results may be caused by factors such as differences in population selection, race, therapeutic regime, etc. Based on HER2-negative tumors adopting the same treatment plan currently, the pCR rate may represent the sensitivity and resistance of tumors to drugs, and the unique efficacy of NAC in HER2-low-positive tumors can provide clues for future antibody-conjugated drug (ADC) development.

Currently, the impact of HER2 status on NAC and patient survival is controversial, and it is urgent to clarify whether HER2-low-positive status has unique tumor biological behavior and should be considered a new molecular subtype. In our study, a 10-year dual-center retrospective study was conducted to analyze the effect of HER2-low-positive status on NAC and survival outcome of BC.

Materials and methods

Clinical cohort

We screened eligible patients from the electronic medical records and collected relevant information for retrospective analysis in the First Hospital of Jilin University and the First Affiliated Hospital of Xi'an Jiaotong University. The inclusion criteria were as follows: 1) unilateral invasive BC diagnosed by pathology from January 2010 to December 2020; 2) age 18-70 years old; 3) clinical stage I, II or III; 4) received taxane- and/or anthracycline-based NAC and underwent surgical treatment after NAC ended; 5) HER2 2+/ISH-, HER2-zero or HER2 1+ status determined by IHC and ISH; and 6) received telephone follow-up every 3 months on time. Patients with incomplete medical records, nonstandard therapeutic regimens, or metastasis discovered during the NAC process were excluded. Researchers collected information on patients' pathological results, age, tumor stage, histological subtype, hormone receptor status, Ki-67 index, HER2 status, surgical method, etc. Histological subtypes were evaluated by pathological results of puncture biopsy. Hormone receptor status and Ki-67 index were determined by IHC and ISH. The basic characteristics of patients were recorded from medical records before NAC.

Standardized treatment plans for patients were developed according to the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines. The clinical stage of patients was classified based on the 8th edition of the American Joint Committee on Cancer (AJCC) breast cancer clinical stage guidelines. The HER2 status of patients was determined according to the ASCO/CAP guidelines. HER2 1+ and HER2 2+/ISH- are considered HER2-low-positive. The flowchart for our research was shown in **Figure 1**.

This is a retrospective study and has been approved by the Ethics Review Committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2023LSK-301) and the Ethical Review Committee of the First Hospital of Jilin University (No. 2023-510).

End points

In our study, the major outcome indicator was pCR. The secondary outcome indicators were overall survival (OS) and disease-free survival (DFS). The pCR was defined as the absence of residual invasive tumors in the primary site and axillary lymph nodes indicated by postoperative pathological results (ypT0/is ypN0). The OS was calculated as the time from disease onset to death from any cause. The DFS refers to the time from disease onset to patient recurrence, metastasis, or death.

Statistical analysis

Descriptive statistics were conducted to elucidate the characteristics and distribution of the study cohort and were displayed in the form of frequency, count, and average (mean plus standard deviation). We applied the Pearson χ^2 test to compare the distribution differences between the HER2-low-positive and HER2-zero subgroups. Univariable and multivariable binary forward stepwise logistic regression were used to analyze the factors affecting pCR. The Kaplan-Meier method was used for survival analysis, and Cox regression analysis was performed to determine factors that affect surviv-

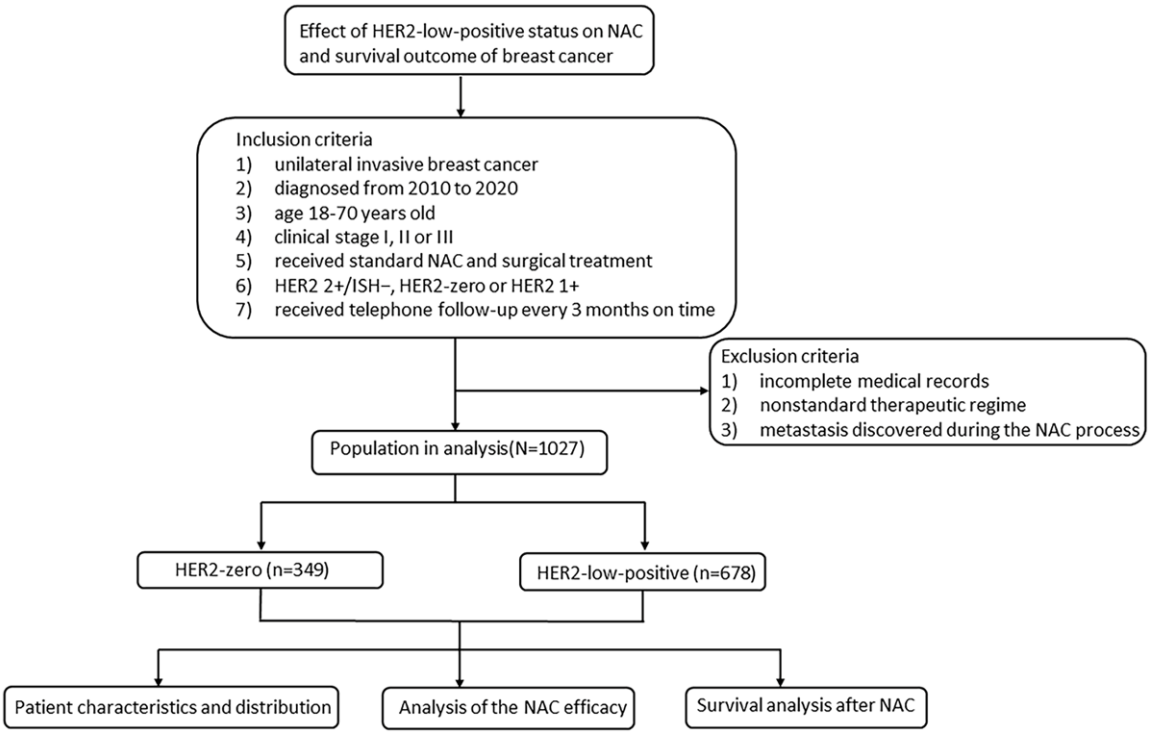

Figure 1. The flowchart of the research. Note: HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy.

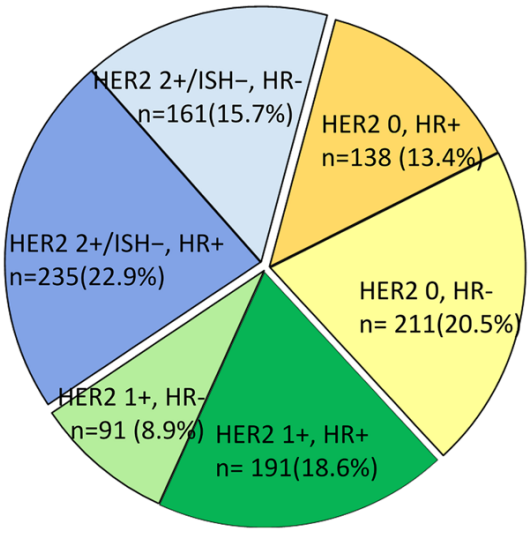

Figure 2. Population classification of HER2-negative breast cancer according to HER2 expression and HR expression. Note: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

al. The statistical test was bilateral, and the significance level was 0.05. IBM SPSS Statistics software was used to complete all statistical analyses.

Results

Patient characteristics and distribution

A total of 1027 patients were included in our cohort: 34.0% (349/1027) had HER2-zero tumors, 27.5% (282/1027) had HER2 1+ tumors, and 38.6% (396/1027) had HER2 2+/ISH- tumors. The population classification of HER2-negative BC according to HR and HER2 expression was shown in **Figure 2**. HR-positive tumors accounted for 39.5% (138/349), 66.7% (191/282), and 59.3% (235/396) in the HER2-zero, HER2 1+ and HER2 2+/ISH- subgroups, respectively.

There were significant differences in the Ki-67 index, HR status, and lymph node stage between HER2-zero and HER2-low-positive tumors (**Table 1**). Compared to HER2-zero patients, HER2-low-positive patients tended to have more lymph node metastasis, a larger proportion of HR-positive tumors, and a lower Ki-67 proliferation rate. In terms of age, clinical stage, histological subtype, tumor size, and surgical treatment method, there were no significant

Table 1. Clinical pathological characteristics of patients and the correlation with HER2 status

Characteristics	Total	HER2-zero	HER2-low-positive	*P*-Value
N (%)	1027 (100%)	349 (34.0%)	678 (66.0%)	
Age (years, mean ± SD)	48.4±10.0	46.9±10.2	49.1±9.8	0.367
Clinical stage				0.462
I	50 (4.9%)	21 (6.0%)	29 (4.3%)	
II	765 (74.5%)	258 (73.9%)	507 (74.8%)	
III	212 (20.6%)	70 (20.1%)	142 (20.9%)	
Clinical T stage				0.834
cT1	210 (20.4%)	71 (20.3%)	139 (20.5%)	
cT2	699 (68.1%)	235 (67.3%)	464 (68.4%)	
cT3	89 (8.7%)	34 (9.7%)	55 (8.1%)	
cT4	29 (2.8%)	9 (2.6%)	20 (2.9%)	
Clinical N stage				0.040
cN0	262 (25.5%)	108 (30.9%)	154 (22.7%)	
cN1	618 (60.2%)	195 (55.9%)	423 (62.4%)	
cN2	116 (11.3%)	37 (10.6%)	79 (11.7%)	
cN3	31 (3.0%)	9 (2.6%)	22 (3.2%)	
Histological subtype				0.059
Ductal	906 (88.2%)	298 (85.4%)	608 (89.7%)	
Lobular	88 (8.6%)	40 (11.5%)	48 (7.1%)	
Other	33 (3.2%)	11 (3.2%)	22 (3.2%)	
Hormone receptor				<0.001
Negative	463 (45.1%)	211 (60.5%)	252 (37.2%)	
Positive	564 (54.9%)	138 (39.5%)	426 (62.8%)	
Ki-67, %	42.1±22.7	47.0±24.1	39.6±21.5	<0.001
Breast surgery				0.266
Breast conserving surgery	109 (10.6%)	32 (9.2%)	77 (11.4%)	
Mastectomy	879 (85.6%)	300 (86.0%)	579 (85.4%)	
Breast reconstruction	39 (3.8%)	17 (4.9%)	22 (3.2%)	
Axillary surgery				0.731
SLNB	113 (11.0%)	37 (10.6%)	76 (11.2%)	
SLNB+ALND	82 (8.0%)	31 (8.9%)	51 (7.5%)	
ALND	832 (81.0%)	281 (80.5%)	551 (81.3%)	

Note: HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

differences between the HER2-low-positive and HER2-zero subgroups.

HER2-low-positive and pCR

A total of 26.1% of HER2-zero patients obtained pCR, while 19.3% of HER2-low-positive patients obtained pCR (P=0.013, **Figure 3**). In the subgroup analysis, there was no significant difference in response to NAC between HER2-low-positive and HER2-zero in HR-negative tumors. Among the HR-positive population, the pCR rate of HER2-zero patients was higher than that of HER2-low-positive patients (20.29% vs 12.00%, P=0.014).

We conducted logistic regression analysis to determine the factors that affect pCR (**Table 2**). In univariate analysis, the pCR rate of HER2-low-positive tumors was lower than that of HER2-zero tumors. The collinearity analysis was performed on indicators with P<0.05 in univariate analysis. The variance inflation factor (VIF) value showed that there was no multicollinearity between various factors (VIF<10). Subsequently, multivariate logistic regression

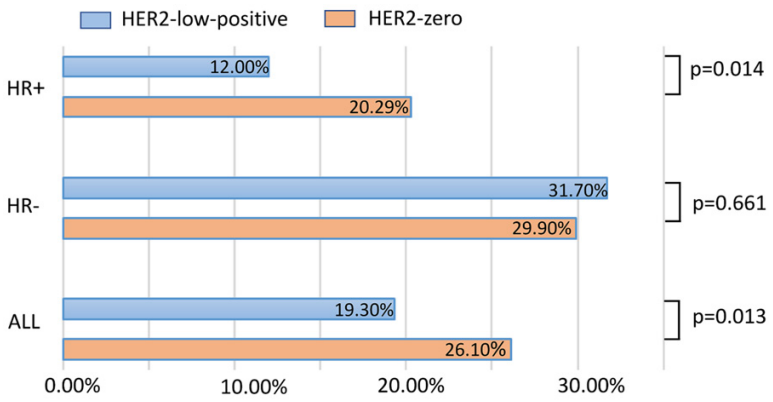

Figure 3. Pathological complete response rate of HER2-zero and HER2-low-positive breast cancer according to HR expression. Note: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

analysis was further used for variables with P<0.05 to exclude the influence of confounding factors. However, in the multivariate analysis, we did not observe an effect of HER2 status on pCR. The results of multivariate logistic regression indicated that pCR was correlated with clinical stage, tumor diameter, lymph node metastasis, and Ki-67 index.

HER2-low-positive and survival

The median follow-up time of the cohort was 56.0±1.1 months (**Figure 4**). The 5-year and 10-year DFS rates of HER2-low-positive tumors were 82.1% and 68.1%, and the 5-year and 10-year OS rates were 83.5% and 74.6%, respectively, which were higher than those of HER2-zero tumors (5-year and 10-year DFS: 77.0%, 59.2%; 5-year and 10-year OS: 77.7%, 61.7%). However, the difference was not significant. The HR-positive subgroup displayed similar results, and log-rank test P<0.05 between HER2-low-positive and HER2-zero tumors on OS. For the HR-negative subgroup, HER2-low-positive (5-year and 10-year DFS: 82.1%, 65.3%; 5-year and 10-year OS: 84.3%, 71.2%) and HER2-zero tumors (5-year and 10-year DFS: 81.0%, 72.4%; 5-year and 10-year OS: 82.5%, 78.6%) had similar survival outcomes.

To further demonstrate whether HER2 status affects patient survival outcomes, we conducted univariate and multivariate Cox regression model analyses. HER2-low-positive tumors did not statistically significantly affect the survival outcome, regardless of DFS (**Table 3**, P=0.308) or OS (**Table 4**, P=0.066). Multivariate analysis showed that T stage, N stage, Ki-67 index and axillary surgery were predictive factors for survival in the complete population.

Discussion

In the past 20 years, HER2-targeted drugs have significantly improved the clinical survival of HER2-positive BC patients [12]. Unfortunately, studies have shown that traditional targeted anti-HER2 therapy cannot benefit HER2-low-positive patients, and trastuzumab has failed to improve the survival of HER2-low-positive patients [13]. Recently, various novel HER2-targeted ADCs have shown satisfactory antitumor activity in HER2-low-positive BC. The clinical trial DESTINY-Breast 04 reported a new anti-HER2 target drug, trastuzumab deruxtecan (T-DXd), which can significantly improve the survival of metastatic HER2-low-positive BC with good safety and tolerance [14]. The success of this research quickly rewrote the 2022 National Comprehensive Cancer Network (NCCN) Guidelines, becoming a landmark discovery for the treatment of HER2-low-positive BC.

The successful clinical application of novel ADC drugs in HER2-low-positive patients has led researchers to pay more attention to this subtype of tumors. Whether the traditional dichotomy for HER2 status is no longer applicable has become a focus of debate. We applied a large cohort to analyze the differences in clinical pathological features, NAC efficacy, and survival among different HER2 expression subtypes. Our study indicated that HER2-low-positive patients have unique clinical and pathological characteristics, with a lower pCR rate in the HR-positive subgroup and better survival in the HR-negative subgroup than HER2-zero tumors. However, HER2-low-positive status is not an independent predictor of pCR and survival.

HER2-low-positive tumors account for a large proportion of the BC population. Previous data show that 40% to 50% of BC patients have HER2-low-positive expression [15]. At the 2022 ASCO Conference, a multicenter retrospective study from Australia, Japan, South Korea, and

Table 2. The correlation between clinical pathological factors and pCR in univariate and multivariate logistic regression analyses

Patient characteristic	Univariate analysis			VIF	Multivariate analysis		
	OR	95% CI	*p* value		OR	95% CI	*p* value
HER2 status			0.013	1.093			
HER2-zero	1						
HER2-low-positive	0.679	0.500-0.922					
Age	0.996	0.981-1.011	0.609				
Clinical stage			<0.001	3.352			0.035
I	1				1		
II	0.251	0.140-0.449	<0.001		0.549	0.236-0.941	0.029
III	0.094	0.046-0.192	<0.001		0.242	0.109-0.536	0.034
Clinical T stage			<0.001	1.819			<0.001
cT1	1				1		
cT2	0.249	0.178-0.347	0.249		0.155	0.100-0.240	<0.001
cT3	0.056	0.020-0.158	0.056		0.090	0.018-0.231	<0.001
cT4	0.042	0.006-0.317	0.042		0.030	0.015-0.069	<0.001
Clinical N stage			<0.001	2.979			<0.001
cN0	1				1		
cN1	0.449	0.324-0.622	<0.001		0.270	0.175-0.417	<0.001
cN2	0.224	0.117-0.430	<0.001		0.026	0.002-0.314	0.004
cN3	0.374	0.139-1.007	0.052		0.400	0.311-0.556	0.017
Histological subtype			0.011	1.021			
Ductal	1						
Lobular	1.290	0.776-2.146	0.326				
Other	2.852	1.404-5.795	0.004				
Hormone receptor			<0.001	1.063			<0.001
Negative	1				1		
Positive	0.365	0.268-0.496			0.278	0.197-0.394	
Ki-67, %	1.010	1.003-1.016	0.004	1.033	1.013	1.006-1.021	0.001
Breast surgery			0.065				
Breast conserving surgery	1						
Mastectomy	0.593	0.382-0.921	0.020				
Breast reconstruction	0.691	0.295-1.616	0.394				
Axillary surgery			<0.001	1.384			
SLNB	1						
SLNB+ALND	0.506	0.269-0.950	0.034				
ALND	0.368	0.243-0.557	<0.001				

Note: HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; pCR, pathologic complete response; VIP, variance inflation factor.

Europe showed that the proportion of HER2-low-positive tumors was as high as 63.2%. Previously, HER2-low-positive tumors adopted the same treatment scheme as HER2-zero BC patients, but in recent years, researchers found that HER2-low-positive is a special heterogeneous tumor population that has different clinicopathological characteristics from HER2-zero [9, 16, 17]. Rossi et al believed that HER2-low-positive patients tended to present a larger tumor diameter, higher histopathology grade and higher Ki-67 index and were more prone to axillary lymph node involvement [18]. A large clinical trial cohort of 2310 patients confirmed that different subtypes of HER2 expression have significant differences in HR status, tumor proliferation and tumor grade [3]. These studies indicate that HER2-low-positive is a BC

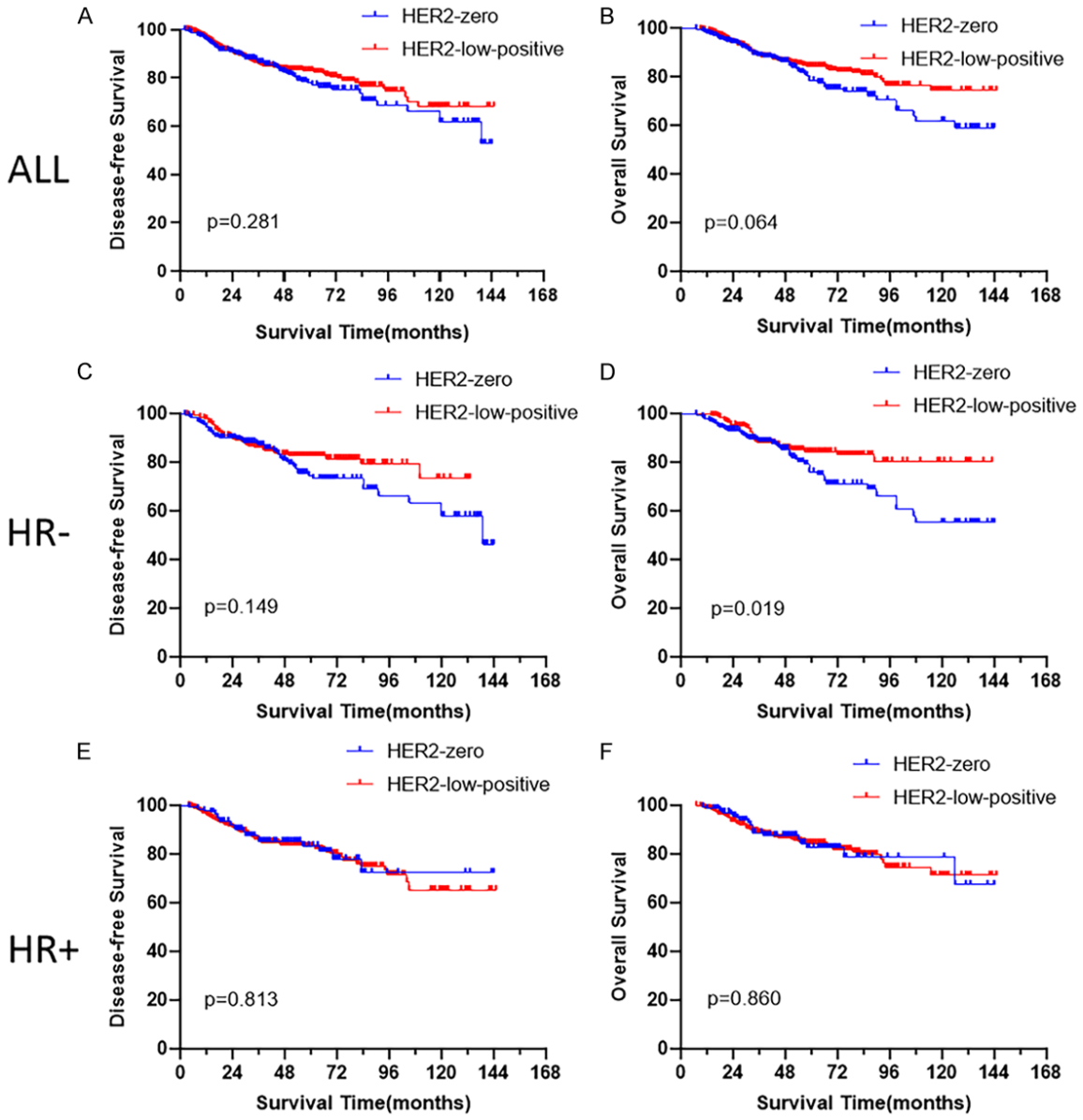

Figure 4. Kaplan-Meier survival curves for disease-free survival and overall survival for HER2-zero and HER2-low-positive breast cancer in all patients (A, B), HR-negative patients (C, D) and HR-positive patients (E, F). Note: HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

subtype different from HER2-zero with unique biological characteristics. Our research also found similar results: HER2-low-positive patients tended to have more lymph node metastasis, a larger proportion of HR-positive tumors, and a lower proliferation rate (Ki-67) than HER2-zero patients.

There are contradictory results regarding the predictive value of HER2-low-positive status on NAC. Multiple studies, including our own, have shown that when considering multivariate analysis, HER2-low-positive is not an independent prognostic factor, although HER2-low-positive tumors show a better prognosis than HER2-zero tumors [2, 5, 10, 11, 19]. The low pCR rate of HER2-low-positive tumors may be related to a higher proportion of patients with lymph node metastasis and the luminal B subtype. Some studies suggest that in the HR-negative subgroup, HER2-low-positive patients have a longer survival time [4, 20]. Next-generation sequencing studies report that HER2-low-positive is different from HER2-zero at the

Table 3. Univariate and multivariate Cox regression model analyses of disease-free survival in HER2-negative breast cancer

Patient characteristic	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
HER2 status			0.308			
HER2-zero	1					
HER2-low-positive	0.858	0.639-1.152				
Age	1.000	0.986-1.015	0.969			
Clinical stage			<0.001			
I	1					
II	2.391	0.881-6.491	0.087			
III	5.027	1.825-13.844	0.002			
Clinical T stage			<0.001			<0.001
cT1	1			1		
cT2	2.393	1.466-3.908	<0.001	2.117	1.293-3.467	0.003
cT3	3.882	2.146-7.023	<0.001	3.035	1.666-5.527	<0.001
cT4	4.848	4.197-8.656	0.008	4.717	3.166-7.104	0.047
Clinical N stage			<0.001			<0.001
cN0	1			1		
cN1	1.847	0.596-2.207	0.359	1.547	0.371-3.807	0.201
cN2	2.350	1.562-3.533	<0.001	2.333	1.858-4.072	0.002
cN3	3.149	2.050-6.397	0.036	3.393	0.965-2.915	0.379
Histological subtype			0.305			
Ductal	1					
Lobular	0.669	0.364-1.231	0.196			
Other	0.640	0.237-1.724	0.377			
Hormone receptor			0.486			
Negative	1					
Positive	0.904	0.681-1.201				
Ki-67, %	0.993	0.987-1.000	0.039	0.993	0.987-1.000	0.047
Breast surgery			0.105			
Breast conserving surgery	1					
Mastectomy	1.752	0.976-3.145	0.060			
Breast reconstruction	0.948	0.267-3.363	0.934			
Axillary surgery			0.001			<0.001
SLNB	1			1		
SLNB+ALND	2.120	0.735-6.113	0.164	2.087	0.722-6.031	0.174
ALND	3.902	1.729-8.805	0.001	4.502	1.903-10.651	0.001

Note: HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

genome and transcriptome levels, suggesting that HER2-low-positive has unique characteristics at the molecular level [21, 22]. However, further research is needed to determine whether this difference implies a difference in prognosis.

Our research also has certain limitations. First, previous reports have shown notable inconsistencies in the detection of HER2 status, especially in distinguishing between HER2-zero and HER2-low-positive tumors, in the judgment of pathologists [9, 23, 24]. New and more precise methods are needed to detect HER2 levels. Second, HER2 level detection was completed before NAC in our research, but the HER2 phenotype may change with treatment [19]. Finally, although this was a

Table 4. Univariate and multivariate Cox regression model analyses of overall survival in HER2-negative breast cancer

Patient characteristic	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
HER2 status			0.066			
HER2-zero	1					
HER2-low-positive	0.745	0.544-1.020				
Age	1.014	0.998-1.030	0.091			
Clinical stage			<0.001			
I	1					
II	3.911	0.964-15.869	0.056			
III	8.903	2.173-36.477	0.002			
Clinical T stage			<0.001			0.003
cT1	1					
cT2	2.042	1.228-3.394	0.006	1.765	1.058-2.942	0.029
cT3	3.603	1.954-6.641	<0.001	2.729	1.470-5.065	0.001
cT4	4.486	3.065-6.651	0.043	4.408	2.054-6.069	0.038
Clinical N stage			<0.001			<0.001
cN0	1					
cN1	1.846	0.573-3.248	0.398	1.517	0.341-3.785	0.122
cN2	2.658	1.724-4.096	<0.001	2.432	1.903-4.270	0.002
cN3	2.849	0.914-4.595	0.082	3.208	0.529-8.759	0.066
Histological subtype			0.285			
Ductal	1					
Lobular	0.576	0.283-1.174	0.129			
Other	0.773	0.286-2.087	0.611			
Hormone receptor			0.409			
Negative	1					
Positive	0.879	0.647-1.194				
Ki-67, %	0.994	0.987-1.001	0.088			
Breast surgery			0.206			
Breast conserving surgery	1					
Mastectomy	1.599	0.867-2.951	0.133			
Breast reconstruction	0.786	0.174-3.549	0.754			
Axillary surgery			0.001			<0.001
SLNB	1			1.000		
SLNB+ALND	1.003	0.240-4.197	0.997	0.988	0.235-4.412	0.986
ALND	4.001	1.642-9.752	0.002	4.748	1.857-12.135	0.001

Note: HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

dual-center study, limitations of retrospective research, such as patient selection bias, still apply.

Conclusion

HER2-low-positive tumors have unique clinical and pathological characteristics, with a lower pCR rate in the HR-positive subgroup and better survival in the HR-negative subgroup compared to HER2-zero tumors. However, the effect of HER2-low-positive status on pCR or survival outcomes was not statistically significant.

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Disclosure of conflict of interest

None.

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References

[1] Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J and Cardoso F. Breast cancer. Nat Rev Dis Primers 2019; 5: 66.

[2] Alves FR, Gil L, Vasconcelos de Matos L, Baleiras A, Vasques C, Neves MT, Ferreira A, Fontes-Sousa M, Miranda H and Martins A. Impact of human epidermal growth factor receptor 2 (HER2) low status in response to neoadjuvant chemotherapy in early breast cancer. Cureus 2022; 14: e22330.

[3] de Nonneville A, Houvenaeghel G, Cohen M, Sabiani L, Bannier M, Viret F, Goncalves A and Bertucci F. Pathological complete response rate and disease-free survival after neoadjuvant chemotherapy in patients with HER2-low and HER2-0 breast cancers. Eur J Cancer 2022; 176: 181-188.

[4] Denkert C, Seither F, Schneeweiss A, Link T, Blohmer JU, Just M, Wimberger P, Forberger A, Tesch H, Jackisch C, Schmatloch S, Reinisch M, Solomayer EF, Schmitt WD, Hanusch C, Fasching PA, Lubbe K, Solbach C, Huober J, Rhiem K, Marme F, Reimer T, Schmidt M, Sinn BV, Janni W, Stickeler E, Michel L, Stotzer O, Hahnen E, Furlanetto J, Seiler S, Nekljudova V, Untch M and Loibl S. Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol 2021; 22: 1151-1161.

[5] Domergue C, Martin E, Lemarie C, Jezequel P, Frenel JS, Augereau P, Campone M and Patsouris A. Impact of HER2 status on pathological response after neoadjuvant chemotherapy in early triple-negative breast cancer. Cancers (Basel) 2022; 14: 2509.

[6] Gampenrieder SP, Rinnerthaler G, Tinchon C, Petzer A, Balic M, Heibl S, Schmitt C, Zabernigg AF, Egle D, Sandholzer M, Singer CF, Roitner F, Hager C, Andel J, Hubalek M, Knauer M and Greil R. Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry. Breast Cancer Res 2021; 23: 112.

[7] Hein A, Hartkopf AD, Emons J, Lux MP, Volz B, Taran FA, Overkamp F, Hadji P, Tesch H, Haberle L, Ettl J, Luftner D, Wurmthaler LA, Wallwiener M, Muller V, Beckmann MW, Belleville E, Wimberger P, Hielscher C, Kurbacher CM, Wuerstlein R, Thomssen C, Untch M, Fasching PA, Janni W, Fehm TN, Wallwiener D, Brucker SY, Schneeweiss A and Kolberg HC. Prognostic effect of low-level HER2 expression in patients with clinically negative HER2 status. Eur J Cancer 2021; 155: 1-12.

[8] Kang S, Lee SH, Lee HJ, Jeong H, Jeong JH, Kim JE, Ahn JH, Jung KH, Gong G, Kim HH, Lee S, Lee J and Kim SB. Pathological complete response, long-term outcomes, and recurrence patterns in HER2-low versus HER2-zero breast cancer after neoadjuvant chemotherapy. Eur J Cancer 2022; 176: 30-40.

[9] Schettini F, Chic N, Braso-Maristany F, Pare L, Pascual T, Conte B, Martinez-Saez O, Adamo B, Vidal M, Barnadas E, Fernandez-Martinez A, Gonzalez-Farre B, Sanfeliu E, Cejalvo JM, Perrone G, Sabarese G, Zalfa F, Peg V, Fasani R, Villagrasa P, Gavila J, Barrios CH, Lluch A, Martin M, Locci M, De Placido S and Prat A. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. NPJ Breast Cancer 2021; 7: 1.

[10] Tarantino P, Jin Q, Tayob N, Jeselsohn RM, Schnitt SJ, Vincuilla J, Parker T, Tyekucheva S, Li T, Lin NU, Hughes ME, Weiss AC, King TA, Mittendorf EA, Curigliano G and Tolaney SM. Prognostic and biologic significance of ERBB2-low expression in early-stage breast cancer. JAMA Oncol 2022; 8: 1177-1183.

[11] de Moura Leite L, Cesca MG, Tavares MC, Santana DM, Saldanha EF, Guimaraes PT, Sa DDS, Simoes MFE, Viana RL, Rocha FG, Loose SK, Silva SF, Pirolli R, Fogassa CAZ, Mattos BRS, Campos FAB, Sanches SM, de Lima VCC and Ponde NF. HER2-low status and response to neoadjuvant chemotherapy in HER2 negative early breast cancer. Breast Cancer Res Treat 2021; 190: 155-163.

[12] Mendes D, Alves C, Afonso N, Cardoso F, Passos-Coelho JL, Costa L, Andrade S and Batel-Marques F. The benefit of HER2-targeted therapies on overall survival of patients with metastatic HER2-positive breast cancer--a systematic review. Breast Cancer Res 2015; 17: 140.

[13] Fehrenbacher L, Cecchini RS, Geyer CE Jr, Rastogi P, Costantino JP, Atkins JN, Crown JP,

Polikoff J, Boileau JF, Provencher L, Stokoe C, Moore TD, Robidoux A, Flynn PJ, Borges VF, Albain KS, Swain SM, Paik S, Mamounas EP and Wolmark N. NSABP B-47/NRG oncology phase III randomized trial comparing adjuvant chemotherapy with or without trastuzumab in high-risk invasive breast cancer negative for HER2 by FISH and with IHC 1+ or 2. J Clin Oncol 2020; 38: 444-453.

[14] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N and Cameron DA; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022; 387: 9-20.

[15] Giuliani S, Ciniselli CM, Leonardi E, Polla E, Decarli N, Luchini C, Cantaloni C, Gasperetti F, Cazzolli D, Berlanda G, Bernardi D, Pellegrini M, Triolo R, Ferro A, Verderio P and Barbareschi M. In a cohort of breast cancer screened patients the proportion of HER2 positive cases is lower than that earlier reported and pathological characteristics differ between HER2 3+ and HER2 2+/Her2 amplified cases. Virchows Arch 2016; 469: 45-50.

[16] Agostinetto E, Rediti M, Fimereli D, Debien V, Piccart M, Aftimos P, Sotiriou C and de Azambuja E. HER2-low breast cancer: molecular characteristics and prognosis. Cancers (Basel) 2021; 13: 2824.

[17] Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, Marra A, Viale G, Trapani D, Cardoso F, Penault-Llorca F, Viale G, Andre F and Curigliano G. HER2-low breast cancer: pathological and clinical landscape. J Clin Oncol 2020; 38: 1951-1962.

[18] Rossi V, Sarotto I, Maggiorotto F, Berchialla P, Kubatzki F, Tomasi N, Redana S, Martinello R, Valabrega G, Aglietta M, Ponzone R and Montemurro F. Moderate immunohistochemical expression of HER-2 (2+) without HER-2 gene amplification is a negative prognostic factor in early breast cancer. Oncologist 2012; 17: 1418-1425.

[19] Miglietta F, Griguolo G, Bottosso M, Giarratano T, Lo Mele M, Fassan M, Cacciatore M, Genovesi E, De Bartolo D, Vernaci G, Amato O, Porra F, Conte P, Guarneri V and Dieci MV. HER2-low-positive breast cancer: evolution from primary tumor to residual disease after neoadjuvant treatment. NPJ Breast Cancer 2022; 8: 66.

[20] Li Y, Abudureheiyimu N, Mo H, Guan X, Lin S, Wang Z, Chen Y, Chen S, Li Q, Cai R, Wang J, Luo Y, Fan Y, Yuan P, Zhang P, Li Q, Ma F and Xu B. In real life, low-level HER2 expression may be associated with better outcome in HER2-negative breast cancer: a study of the national cancer center, China. Front Oncol 2022; 11: 774577.

[21] Berrino E, Annaratone L, Bellomo SE, Ferrero G, Gagliardi A, Bragoni A, Grassini D, Guarrera S, Parlato C, Casorzo L, Panero M, Sarotto I, Giordano S, Cereda M, Montemurro F, Ponzone R, Crosetto N, Naccarati A, Sapino A and Marchio C. Integrative genomic and transcriptomic analyses illuminate the ontology of HER2-low breast carcinomas. Genome Med 2022; 14: 98.

[22] Zhang G, Ren C, Li C, Wang Y, Chen B, Wen L, Jia M, Li K, Mok H, Cao L, Chen X, Lin J, Wei G, Li Y, Zhang Y, Balch CM and Liao N. Distinct clinical and somatic mutational features of breast tumors with high-, low-, or non-expressing human epidermal growth factor receptor 2 status. BMC Med 2022; 20: 142.

[23] Fernandez AI, Liu M, Bellizzi A, Brock J, Fadare O, Hanley K, Harigopal M, Jorns JM, Kuba MG, Ly A, Podoll M, Rabe K, Sanders MA, Singh K, Snir OL, Soong TR, Wei S, Wen H, Wong S, Yoon E, Pusztai L, Reisenbichler E and Rimm DL. Examination of low ERBB2 protein expression in breast cancer tissue. JAMA Oncol 2022; 8: 1-4.

[24] Lambein K, Van Bockstal M, Vandemaele L, Geenen S, Rottiers I, Nuyts A, Matthys B, Praet M, Denys H and Libbrecht L. Distinguishing score 0 from score 1+ in HER2 immunohistochemistry-negative breast cancer: clinical and pathobiological relevance. Am J Clin Pathol 2013; 140: 561-566.