The Oncologist, 2024, **29**, e309–e318
https://doi.org/10.1093/oncolo/oyad275
Advance access publication 28 September 2023
Original Article

HER2-Low Status Was Associated With Better Breast Cancer-Specific Survival in Early-Stage Triple-Negative Breast Cancer

Youzhao Ma[1], Dechuang Jiao[1], Jingyang Zhang[1], Minhao Lv[1], Xiuchun Chen[*,1], Zhenzhen Liu[*,1]

[1]Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, People's Republic of China

[*]Corresponding author: Xiuchun Chen, MM, Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, No. 127, Dongming Road, Zhengzhou 450008, People's Republic of China. Tel: +1 86-371-65587005; Email: zlyychenxiuchun3921@zzu.edu.cn; or, Zhenzhen Liu, PhD, Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, No. 127, Dongming Road, Zhengzhou 450008, People's Republic of China.
Email: zlyyliuzhenzhen0800@zzu.edu.cn

Abstract

Background: Based on the association between the hormone receptor and the status of human epidermal growth factor receptor 2 (HER2)-low, we investigated the clinicopathological and prognostic characteristics of the HER2-low status in early-stage triple-negative breast cancer (TNBC).

Methods: We collected the data of patients with TNBC who received treatment at our hospital and compared the pathological complete response (pCR) rate, overall survival (OS), and breast cancer-specific survival (BCSS) between the HER2-0 and HER2-low subtypes.

Results: A total of 1445 patients were included in the study, of which 698 patients (48.3%) showed HER2-low status. A similar pCR rate was observed between HER2-0 and HER2-low patients (34.9% vs. 37.4%; $P = .549$). T staging, N staging, and HER2 status were associated with BCSS, whereas T staging and N staging were associated with OS. Patients with the HER2-low status showed better BCSS than those with the HER2-0 status (96.6% vs. 93.7%; log-rank $P = .027$). In patients with non-pCR, the BCSS of the HER2-low subgroup was better than that of the HER2-0 subgroup (log-rank $P = .047$); however, no similar result was observed in patients with pCR. In patients with stage III, the BCSS and OS of the HER2-low subgroup were better than those of the HER2-0 subgroup (BCSS, log-rank $P = .010$; OS, log-rank $P = .047$). No similar results were observed in patients with stages I and II.

Conclusion: The HER2-low expression was associated with better BCSS in TNBC, especially in the high-risk groups, suggesting that HER2-low breast cancer is a potential independent biological subtype.

Key words: triple-negative breast cancer; HER2-low; breast cancer-specific survival; overall survival.

Implications for Practice

Patients with triple-negative breast cancer showed a poor prognosis. A total of 1445 patients with triple-negative breast cancer were included in the study. Patients with the HER2-low status displayed better breast cancer-specific survival than those with the HER2-0 status. This result was confirmed in patients with stage III and those without pathological complete response, suggesting that triple-negative breast cancer could be categorized into the HER2-low subgroup and the HER2-0 subgroup. Novel antibody-drug conjugates targeting HER2 may thus be applied to treat the HER2-low subgroup. For the HER2-0 subgroup with worse prognosis, other treatment methods should be explored.

Introduction

Breast cancer is a malignant tumor that occurs in females and has the highest incidence rate.[1-3] Malignant tumors from the breast epithelium with a negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are categorized as triple-negative breast cancer (TNBC).[4] TNBC is a molecular type with the highest recurrence rate owing to its high degree of malignancy and the lack of treatment targets.[5] In previous studies, differences in the intrinsic characteristics were investigated and TNBC was classified into subcategories to devise precise treatments; however, no effective treatment option has yet been developed.[6] Breast cancer with an HER2 overexpression or amplification is

Received: 5 July 2023; Accepted: 11 September 2023.

sensitive to anti-HER2 targeted therapeutic drugs including trastuzumab[7,8]; however, HER2-negative breast cancer does not respond to trastuzumab treatment.[9,10] HER2-negative breast cancer is categorized into HER2-low and HER2-0 subgroups. HER2-0 implies that the HER2 immunohistochemistry (IHC) test score is 0, and HER2-low means the HER2 IHC test score is 1+ or 2+ with no amplification in the fluorescence in situ hybridization (FISH) test. Trastuzumab deruxtecan, a novel antibody-drug conjugate (ADC), exerts remarkable therapeutic effects on HER2-low advanced breast cancer.[11] Another ADC, trastuzumab duocarmazine exhibited clinical activity in pretreated patients with HER2-low breast cancer in a phase I study.[12] Novel ADCs may be added to the HER2-low early-stage TNBC treatment regimens in the future.

The consideration of HER2-low breast cancer as an independent biological subtype and the effect of the HER2-low status on the prognosis remains controversial.[13,14] Moreover, the gene expression profiles of HER2-0 and HER2-low breast cancer are inconsistent.[15] Furthermore, the gene expression profiles of HER2-low breast cancer in different hormone receptor (HR) statuses are inconsistent.[16] These inconsistencies limit the study of the clinicopathological and prognostic characteristics of HER2-low breast cancer. Several studies have revealed that the HER2-low expression in HR-positive breast cancer does not affect its prognosis[14,17-19] and that the HR expression is associated with HER2-low expression.[14] According to these findings, studying the clinicopathological and prognostic characteristics of the HER2-low status in HR-negative breast cancer will be more reliable than that in HR-positive breast cancer. Based on previous studies, the prognostic value of the HER2-low status in early-stage TNBC is controversial.[13,14,17-21] However, the amount of TNBC data included in most of these studies is relatively small. Therefore, in this study, we investigated the clinicopathological and prognostic characteristics of HER2-low status in a large sample of early-stage TNBC datasets.

Materials and Methods

Study Population

After approval by the Medical Ethics Committee of Henan Cancer Hospital (Approval Number: 2022-299), we obtained the data for TNBC cases at Henan Cancer Hospital from 2015 to 2021. We identified 1445 consecutive female patients with early-stage TNBC. TNBC is defined as the negative expression of ER, PR, and HER2. The definition of basal-like phenotype is the positive expression of cytokeratin 5/6 (CK5/6) and/or epidermal growth factor receptor (EGFR). The data on ER, PR, HER2, CK5/6, EGFR, and Ki-67 were extracted from the pathological reports of biopsy specimens or postoperative specimens. The ER-negative expression is defined as ER IHC test <1%. The PR-negative expression is defined as PR IHC test <1%. The HER2 status is interpreted according to the guidelines for HER2 testing of the American Society of Clinical Oncology/College of American Pathologists. Clinical and pathological TNM staging was based on the TNM staging system of the American Joint Committee on Cancer.

Data Collection and Follow-Up

The clinicopathological characteristics, therapy data, and follow-up data of patients were collected, which included basic characteristics (age at diagnosis, menopausal status, and family history), pathological characteristics (clinical and pathological TNM stage, androgen receptor (AR) expression status, HER2 expression status, Ki-67 level, histological type, and presence of basal-like phenotype), surgical information, radiotherapy, relapse time, relapse site, and the date and cause of death.

The definition of HER2-0 was HER2 IHC test 0, and the definition of HER2-low was HER2 IHC test 1+ or IHC test 2+ and no gene amplification in FISH test. The definition of pathological complete response (pCR) was no residual invasive cancer cells in the specimens of breast and regional lymph nodes (ypT0/ypTis ypN0). The definition of breast cancer-specific survival (BCSS) was the period from the date of operation to the date of death caused by breast cancer or the date of last follow-up. The definition of overall survival (OS) was the period from the date of surgery to the date of death from any cause or the last follow-up.

Statistical Analysis

The TNM staging of patients undergoing surgery first is based on the pathological stage, whereas the TNM staging of patients receiving neoadjuvant chemotherapy (NAC) first is based on the baseline data before chemotherapy (clinical stage). The Chi-square test and logistic regression model were used to analyze the influencing factors for pCR and HER2 status. Univariate and multivariate analyses of independent influencing factors of BCSS and OS were performed using Cox proportional hazards regression models. Two-sided $P < .05$ was considered to indicate statistical significance. The effect of risk factors on BCSS and OS was estimated by the Kaplan-Meier survival curve by comparing differences using the log-rank test. All analyses were conducted using SPSS 23.0 in this study.

Results

Clinicopathological Characteristics According to HER2 Status

We continuously collected the clinicopathological data of 1445 patients with TNBC who received treatment at Henan Cancer Hospital from 2015 to 2021. Most medium to high-risk patients received anthracycline combined with taxane chemotherapy, while the low-risk patients received taxane-based chemotherapy or did not receive chemotherapy. For patients who did not achieve pCR after receiving neoadjuvant chemotherapy, some received capecitabine treatment. The median age of the patients at the time of diagnosis was 50 (19-83) years. The most common histological type was invasive ductal carcinoma (96.7%). There were 747 patients (51.7%) with HER2-0 expression, whereas 698 patients (48.3%) showed HER2-low expression, of which 347 patients showed HER2 IHC 1+ and 351 patients showed HER2 IHC 2+ scores. Compared with patients in the HER2-0 subgroup, those in the HER2-low subgroup were aged more than 55 years (33.2% vs. 18.2%; OR 1.691 [95% confidence interval (CI), 1.206-2.371]; $P = .002$), AR-positive (48.5% vs. 23.2%; OR 2.688 [95% CI, 2.097-3.446]; $P < .001$), Ki-67 ≤ 30% (17.8% vs. 8.4%; OR 0.584 [95% CI, 0.397-0.860]; P = .006), and invasive ductal carcinoma (98.1% vs. 95.3%; OR 0.306 [95% CI, 0.143-0.652]; $P = .002$). HER2-low expression was not associated with the staging (Table 1).

Table 1. Clinicopathological characteristics associated with HER2 status.

Characteristics	Total	HER2-0 N(%)	HER2-low N (%)	Univariate analysis		Multivariate analysis		
				χ^2	*P*-value	OR	95% CI	*P*-value
Age at diagnosis				42.953	<.001			
≤55	1077	611 (81.8)	466 (66.8)			Reference		
>55	368	136 (18.2)	232 (33.2)			1.691	1.206-2.371	.002
Menopausal status				27.688	<.001			
Premenopausal	831	479 (64.1)	352 (50.4)			Reference		
Postmenopausal	614	268 (35.9)	346 (49.6)			1.151	0.857-1.545	.350
Family history				0.020	.886			
No	1410	729(97.6)	681 (97.7)					
Yes	34	18 (2.4)	16 (2.3)					
T stage				1.349	.509			
T1	391	211 (28.2)	180 (25.8)					
T2	951	486 (65.1)	465 (66.6)					
T3 + T4	103	50 (6.7)	53 (7.6)					
N stage				5.121	.077			
N0	789	428 (57.3)	361 (51.7)					
N1	493	244 (32.7)	249 (35.7)					
N2 + N3	163	75 (10.0)	88 (12.6)					
Stage				4.404	.111			
I	276	156 (20.9)	120 (17.2)					
II	969	497 (66.5)	472 (67.6)					
III	200	94 (12.6)	106 (15.2)					
AR status				91.374	<.001			
<1%	841	506(76.8)	335 (51.5)			Reference		
≥1%	469	153 (23.2)	316 (48.5)			2.688	2.097-3.446	<.001
Ki-67 index				27.785	<.001			
≤30%	187	63 (8.4)	124 (17.8)			Reference		
>30%	1257	683 (91.6)	574 (82.2)			0.584	0.397-0.860	.006
Basal-like phenotype				1.843	.175			
No	74	32 (4.6)	42 (6.3)					
Yes	1291	663 (95.4)	628 (93.7)					
Histological type				8.954	.003			
Invasive ductal carcinoma	1397	712 (95.3)	685 (98.1)			Reference		
Other types*	48	35 (4.7)	13 (1.9)			0.306	0.143-0.652	.002

Other types* including invasive lobular carcinoma, metaplastic carcinoma, and carcinoma with medullary features.
Abbreviations: HER2: human epidermal growth factor receptor 2; AR: androgen receptor.

The Association Between HER2 Status and Pathological Complete Response

In this study, 546 patients with TNBC received NAC, 197 of whom reached pathological complete response (pCR), with a rate of 36.1%. The univariate analysis results suggested that factors associated with pCR included T stage, N stage, and AR status. Patients with higher Ki-67 had a tendency to achieve higher pCR rates (37.1% vs. 21.6%, *P* = .058). Incorporating T staging, N staging, AR status, and Ki-67 levels into the multivariate analysis as variables revealed that T staging, N staging, and AR status were associated with pCR, whereas Ki-67 levels were not associated with pCR. Lower T staging (*P* = .028), lower N staging (*P* = .002), and negative AR expression (*P* = .006) were associated with higher pCR rates. The pCR rates of the patients with HER2-low and HER2-0 expression were 34.9% and 37.4%, respectively. No association was observed between HER2 status and the pCR rate in patients with TNBC after NAC (*P* = .549; Table 2).

Survival Analysis of the Whole Population

Using December 31, 2022 as the cutoff date, the median follow-up was 55.1 months (4-102 months). During this period, there were 75 OS events and 65 BCSS events. The 4-year OS was 94.3%, and the 4-year BCSS was 95.0%. The univariate analysis showed that T staging, N staging, surgery type, and radiation therapy were associated with both BCSS and OS, and HER2 status was the additional factor associated with OS. Lower T and N staging, HER2-low expression, breast-conserving surgery, and no radiotherapy were associated with a better prognosis (Table 3). According to the multivariate analysis, T staging (*P* = .041), N staging (*P* < .001), and HER2 status (HR 0.449 [95% CI, 0.263-0.767], *P* = .003)

Table 2. Clinicopathological characteristics associated with pCR.

Characteristics	Total	non-pCR *N* (%)	pCR *N* (%)	Univariate analysis		Multivariate analysis		
				χ^2	*P*-value	OR	95% CI	*P*-value
Age at diagnosis				1.118	.290			
≤55	430	270 (77.4)	160 (81.2)					
>55	116	79 (22.6)	37 (18.8)					
Menopausal status				0.257	.612			
Premenopausal	336	212 (60.7)	124 (62.9)					
Postmenopausal	210	137 (39.3)	73 (37.1)					
Family history				0.001	.977			
No	532	340 (97.4)	192 (97.5)					
Yes	14	9 (2.6)	5 (2.5)					
T stage				7.963	.019			.028
T1	43	23 (6.6)	20 (10.1)			Reference		
T2	409	255 (73.1)	154 (78.2)			0.558	0.271-1.152	.115
T3 + T4	94	71 (20.3)	23 (11.7)			0.317	0.134-0.752	.009
N stage				19.589	<.001			.002
N0	143	79 (22.6)	64 (32.5)			Reference		
N1	258	156 (44.7)	102 (51.8)			0.814	0.513-1.293	.383
N2 + N3	145	114 (32.7)	31 (15.7)			0.371	0.209-0.657	.001
AR status				10.631	.001			
<1%	318	187(61.5)	131 (76.2)			Reference		
≥1%	158	117 (38.5)	41 (23.8)			0.546	0.354-0.843	.006
Ki-67 index				3.598	.058			
≤30%	37	29 (8.3)	8 (4.1)			Reference		
>30%	509	320 (91.7)	189 (95.9)			2.135	0.834-5.464	.114
Basal-like phenotype				0.007	.933			
No	22	14 (4.3)	8 (4.5)					
Yes	479	309 (95.7)	170 (95.5)					
HER2 status				0.359	.549			
0	254	159 (45.6)	95 (48.2)					
Low	292	190 (54.4)	102 (51.8)					
HER2 status				0.405	.524			
0/1+	405	262 (75.1)	143 (72.6)					
2+ and FISH-	141	87 (24.9)	54 (27.4)					
HER2 status				1.699	.428			
0	254	159 (45.6)	95 (48.2)					
1+	151	103 (29.5)	48 (24.4)					
2+and FISH-	141	87 (24.9)	54 (27.4)					

Abbreviations: pCR: pathological complete response; AR: androgen receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization.

were associated with BCSS, whereas T staging ($P = .016$), and N staging ($P < .001$) were associated with OS. Surgery type and radiotherapy were not associated with a better prognosis (Table 4). The BCSS rates of patients with HER2-low and HER2-0 expression were 96.6% and 93.7%, whereas the OS rates were 95.5% and 93.3%, respectively. The BCSS of the HER2-low subgroup was better than that of the HER2-0 subgroup (log-rank $P = .027$) (Fig. 1A). However, there was no remarkable difference in OS between the HER2-0 and HER2-low subgroups (log-rank $P = .150$) (Fig. 1B).

Survival Analysis According to HER2 Status and Pathological Response

In patients with non-pCR after NAC, a significant difference was observed in BCSS between the HER2-low and HER2-0 subgroups (log-rank $P = .047$) (Fig. 2A), whereas in patients with pCR, no difference was observed (log-rank $P = .689$) (Fig. 2B). In patients with non-pCR, HER2-low status was associated with better BCSS. HER2-low status did not affect the OS of patients, regardless of pathological response (Fig. 2C and 2D).

Table 3. Univariate analysis of clinicopathological characteristics associated with BCSS and OS.

Characteristics	BCSS			OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age at diagnosis			.798			.712
≤55	1			1		
>55	0.927	0.520-1.654		1.101	0.660-1.837	
Menopausal status			.315			.704
Premenopausal	1			1		
Postmenopausal	0.769	0.462-1.282		0.914	0.576-1.451	
Histological type			.395			.304
Invasive ductal carcinoma	1			1		
Other types*	0.424	0.059-3.060		0.355	0.049-2.557	
T stage			<.001			<.001
T1	1			1		
T2	2.988	1.272-7.021	.012	2.557	1.211-5.398	.014
T3 + T4	9.833	3.778-25.591	<.001	9.465	4.115-21.770	<.001
N stage			<.001			<.001
N0	1			1		
N1	2.784	1.285-6.032	.009	2.321	1.180-4.564	.015
N2 + N3	18.756	9.286-37.886	<.001	15.264	8.303-28.061	<.001
AR status			.231			.108
<1%	1			1		
≥1%	1.376	0.816-2.322		1.487	0.917-2.411	
Ki-67 index			.958			.598
≤30%	1			1		
>30%	1.020	0.486-2.140		1.218	0.585-2.535	
Basal-like phenotype			.825			.622
No	1			1		
Yes	1.140	0.357-3.638		1.338	0.421-4.252	
HER2 status			.030			.152
0	1			1		
Low	0.555	0.326-0.943		0.710	0.445-1.135	
HER2 status			.353			.445
0/1+	1			1		
2 + and FISH-	0.734	0.383-1.408		0.797	0.446-1.426	
HER2 status			.086			.357
0	1			1		
1+	0.490	0.239-1.005	.052	0.696	0.383-1.265	.235
2 + and FISH-	0.622	0.320-1.207	.160	0.725	0.399-1.317	.291
Type of surgery			.002			.003
Breast-conserving	1			1		
Mastectomy	3.732	1.605-8.636		2.869	1.430-5.758	
Radiation therapy			<.001			<.001
No	1			1		
Yes	3.349	1.748-6.419		3.091	1.729-5.526	

Other types* including invasive lobular carcinoma, metaplastic carcinoma, and carcinoma with medullary features.
Abbreviations: BCSS: breast cancer-specific survival; OS: overall survival; AR: androgen receptor; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization.

Survival Analysis According to HER2 Status and Different Stages

There was no remarkable statistical difference in BCSS between the HER2-low and HER2-0 subgroups in patients with stages I and II (stage I, log-rank $P = .800$; stage II, log-rank $P = .231$) (Fig. 3A and 3B). In patients with stage III, the HER2-low subgroup showed a significantly better BCSS than did the HER2-0 subgroup (log-rank $P = .010$) (Fig. 3C). Similarly, no remarkable difference was found in OS between the HER2-0 and HER2-low subgroups in patients with stages

Table 4. Multivariate analysis of clinicopathological characteristics associated with BCSS and OS.

Characteristics	BCSS			OS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
T stage			.041			.016
T1	1			1		
T2	2.204	0.928-5.234	.073	1.867	0.875-3.987	.107
T3 + T4	3.537	1.318-9.494	.012	3.405	1.428-8.121	.006
N stage			<.001			<.001
N0	1			1		
N1	1.882	0.801-4.423	.147	1.566	0.745-3.291	.236
N2 + N3	11.155	4.865-25.576	<.001	8.661	4.233-17.721	<.001
HER2 status			.003			
0	1					
Low	0.449	0.263-0.767				
Type of surgery			.110			.220
Breast-conserving	1			1		
Mastectomy	2.079	0.847-5.106		1.607	0.753-3.431	
Radiation therapy			.202			.120
No	1			1		
Yes	1.621	0.771-3.408		1.684	0.874-3.244	

Abbreviations: BCSS: breast cancer-specific survival; OS: overall survival; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry.

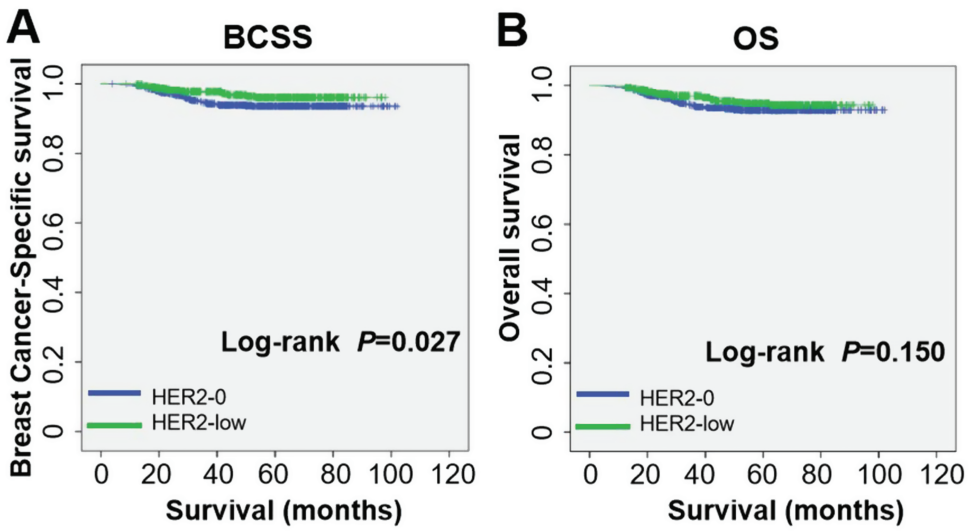

Figure 1. The impact of HER2 status on BCSS (**A**) and OS (**B**).

I and II (stage I, log-rank $P = .335$; stage II, log-rank $P = .281$) (Fig. 3D and 3E). In patients with stage III, the HER2-low subgroup showed a better OS than did the HER2-0 subgroup (log-rank $P = .047$) (Fig. 3F).

Discussion

TNBC is a highly malignant tumor that lacks therapeutic targets. Identifying new therapeutic targets is one of the main directions in TNBC management. Novel ADCs exert therapeutic effects on HER2-low advanced breast cancer,[11,12] offering a potential treatment strategy for early-stage TNBC with HER2-low expression. The consideration of HER2-low breast cancer as an independent biological subtype in previous studies is controversial. In particular, a study by Tarantino et al revealed that the HER2-low status was strongly associated with HR status,[14] indicating that some characteristics of HER2-low breast cancer may be altered by HR-positive expression. To eliminate the effect of HR expression on the results, we investigated the clinicopathological and prognostic characteristics of HER2-low breast cancer in a large sample of TNBC datasets. The results revealed that the HER2-low expression in TNBC was associated with older onset age, lower Ki-67 levels, higher AR-positive expression, and higher invasive ductal carcinoma proportion. The HER2-low expression was associated with better BCSS but not with pCR rate and OS in the entire study population. Furthermore, this study showed that the HER2-low

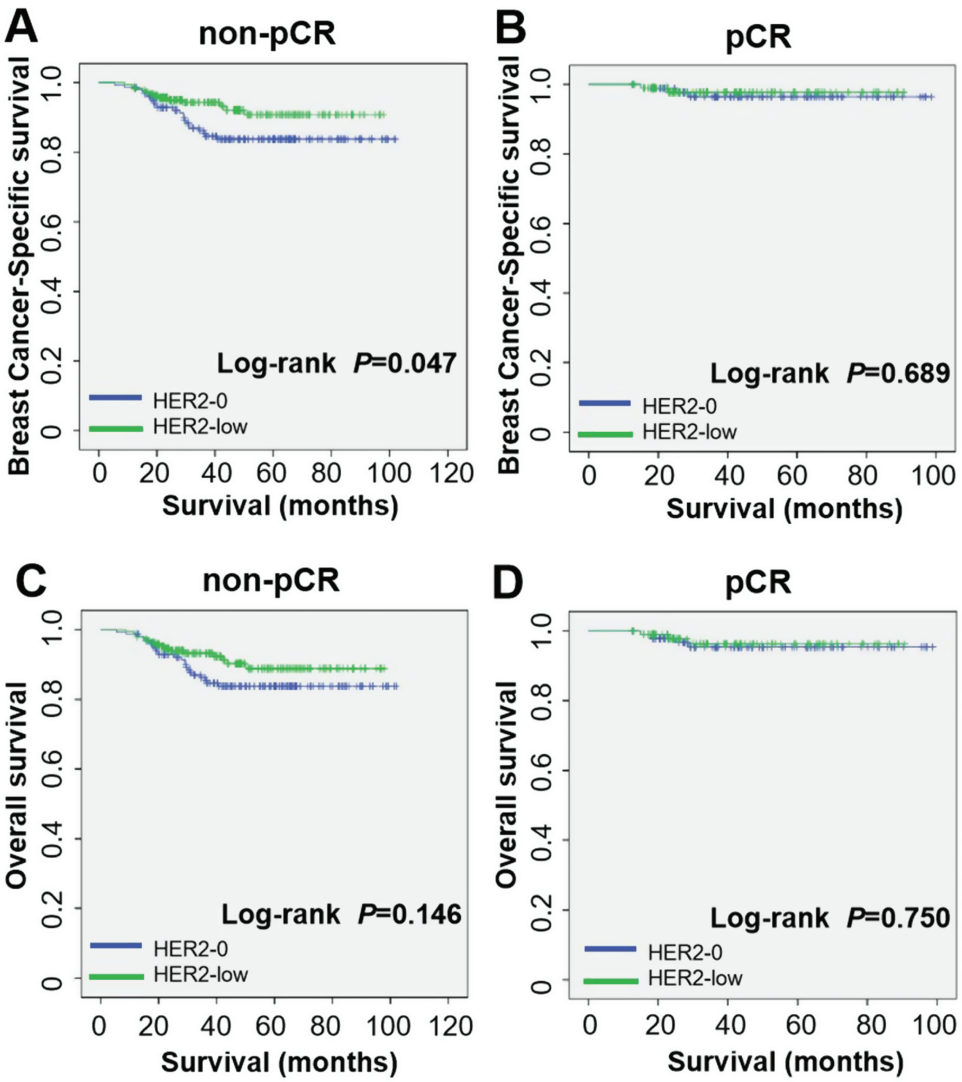

Figure 2. The impact of HER2 status on BCSS (**A** and **B**) and OS (**C** and **D**) based on pathological response.

expression was associated with better BCSS in patients with clinically high-risk characteristics such as non-pCR and stage III. Especially in stage III patients, the HER2-low expression was also associated with better OS. Conversely, the HER2-low expression was not associated with BCSS and OS in patients with clinical low-risk characteristics such as stage I, stage II, and pCR.

We found that 48.3% of the patients with TNBC had a HER2-low status, which agrees with other past results (48.6%).[22] Similar to that showed by previous large-sample studies,[13,18] we found that the HER2-low expression was associated with older age at the time of diagnosis and lower Ki-67 levels, implying that the HER2-low tumor was a lower-risk biological characteristic. Furthermore, the present study showed that the low HER2 expression was associated with the positive AR expression, which is consistent with the result of a previous study on TNBC.[21] The intrinsic association between AR and HER2-low expression is currently unclear. Owing to the limited availability of information, we did not include histological grades in the study. Won et al did not report any association between the HER2-low expression and histological grades in their study with a large sample size,[18] and some studies revealed that the HER2-low expression was associated with lower histological grades.[13,21] The association of the HER2-low status with these low-risk clinical prognostic factors indicated that HER2-low tumors might have better outcomes, indicating the need for further research to investigate the intrinsic characteristics of HER2-low breast cancer.

This study showed that the pCR rate of HER2-low tumors was slightly lower than that of HER2-0 tumors (34.9% vs. 37.4%) with no statistical difference. A large-sample study by Denkert et al also revealed no remarkable statistical difference in the pCR rate between the HER2-low and HER2-0 subgroups, even though the rate of the latter group was slightly lower.[13] In other studies, no association was discovered between the pCR rate and HER2 status in TNBC.[14,17,20,23,24] In some studies, the HER2-low expression led to a lower pCR rate in HR-positive patients.[13,24] The association between HR-positive and HER2-low statuses might have led to this difference. A study on the effect of HER2-low expression on the pCR rate was not altered by the HR-positive status in the TNBC population; thus, the present findings are more reliable.

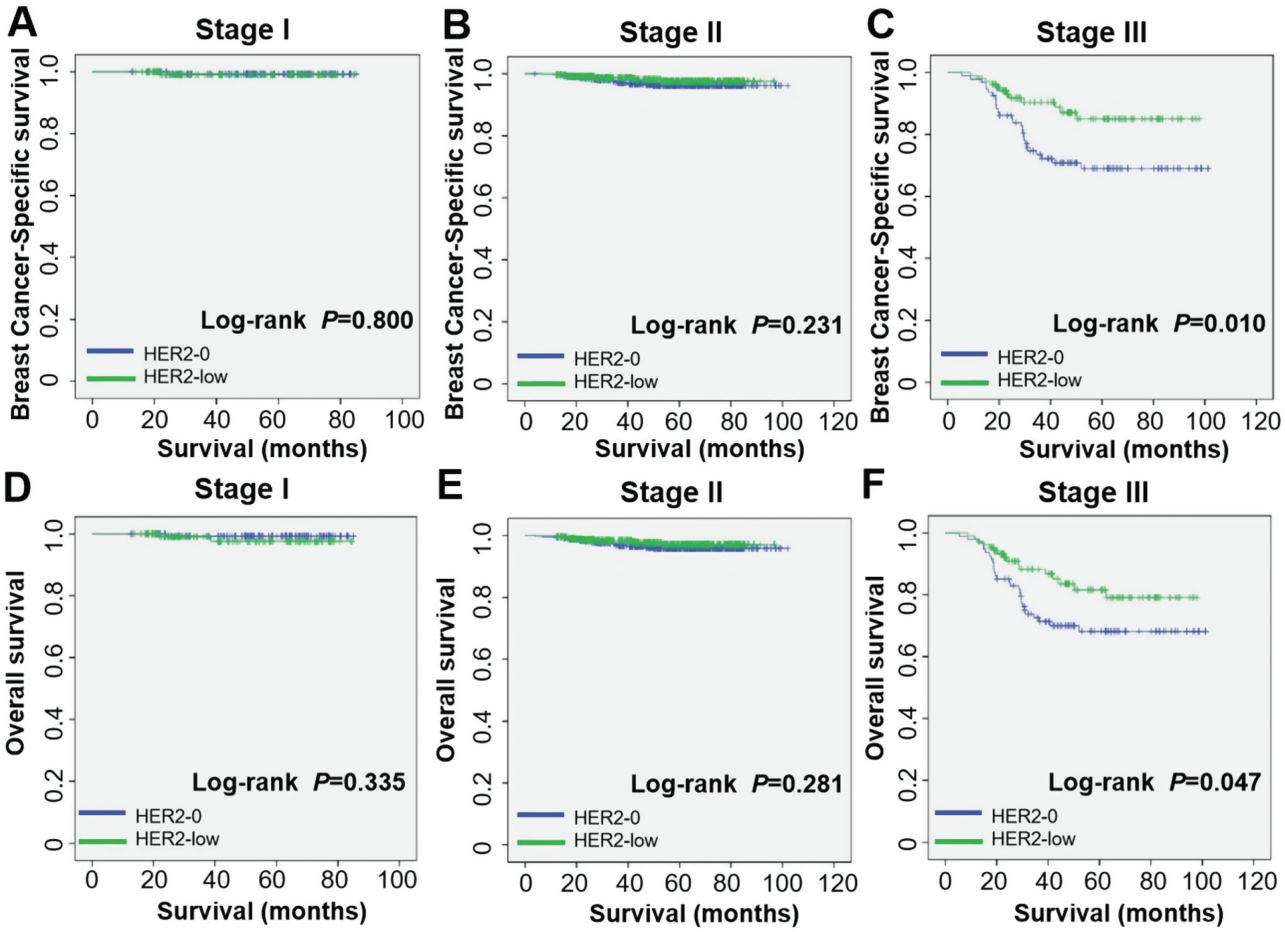

Figure 3. The impact of HER2 status on BCSS (**A**, **B,** and **C**) and OS (**D**, **E**, and **F**) based on TNM stage.

In a meta-analysis of a large-size sample, patients with HER2-low breast cancer tended to have a better OS and disease-free survival (DFS), regardless of HR status.[22] However, several large-sample-size retrospective studies did not fully support this result,[13,14,18] especially in the HR-positive group, the HER2-low expression was not associated with better prognosis.[13,18] The present study showed that the HER2-low status led to better BCSS in patients with TNBC, which was in agreement with the result of a large-sample (6934 TNBC) study.[18] Denkert et al included a large sample size (1162 cases) and found that the low HER2 expression was associated with better OS and DFS in the TNBC population.[13] All these patients including clinically high-risk patients received NAC. Interestingly, in a large-sample-size study on advanced breast cancer (including 4997 TNBC), HER2-low patients showed better OS than HER2-0 patients.[25] This finding suggested that HER2-low expression may have the potential prognostic value in patients with high-risk TNBC. Another study on TNBC showed similar results.[17] Some studies showed that HER2-low expression in TNBC had no prognostic value.[19-21,23,24,26] However, the sample size of TNBC in these studies was generally not large, which may be one of the reasons behind the negative findings of these studies. Another reason can be the inconsistent interpretations of the HER2-low status by pathologists. Moreover, the requirements for distinguishing HER2 IHC 1 + from IHC 0 were not high before the results of the DESTINY-Breast04 trial were published. A study found that there was only 26% consistency in the interpretation of HER2 IHC 0 and IHC 1 + between pathologists.[27] Thus, IHC is not the most accurate method for detecting HER2 expression, and more precise screening techniques are needed for detecting HER2-low expression.

This study showed that the HER2-low expression in pCR patients with TNBC receiving NAC did not affect BCSS; however, the HER2-low expression in non-pCR patients was associated with better BCSS. This finding is similar to the result of Denkert et al,[13] who found that, compared to patients with the HER2-0 expression, those with the HER2-low expression had better OS and DFS in the non-pCR population. The present study showed that the low HER2 expression did not affect BCSS and OS in stages I and II patients, whereas the HER2-low status led to better BCSS and OS in stage III patients. These results confirm the hypothesis that the HER2-low status exhibits a more remarkable prognostic significance in studies on high-risk TNBC with a large sample size. For patients with locally advanced-stage TNBC or those who do not achieve pCR after NAC, HER2-low expression possesses better prognostic value; this finding provides a reference for the precision therapy of TNBC and for developing an individualized treatment scheme.

The strengths of this study are the large sample size and the elimination of the interference of HR-positive expression. However, the study has some limitations. Owing to its retrospective nature, it may lead to selective bias. The interpretation of HER2 expression in this study was based on pathological

reports obtained during the treatment period, and the lack of a pathology centralized revision of HER2 expression contributes to the limitations of the study. Previous pathological reports may not be accurate in distinguishing HER2 IHC 1+ from IHC 0. Because some data were missing, we did not include histological grades in the study, which is also a limitation of the study.

Conclusion

The HER2-low expression in patients with TNBC was associated with older age at diagnosis, a higher proportion of AR-positive, Ki-67 ≤ 30%, and invasive ductal carcinoma; however, these factors are not independent prognostic factors. The HER2-low expression was associated with better BCSS in patients with TNBC. The HER2-low status did not affect the pCR rate and OS of patients with TNBC. In the exploratory subgroup analysis, the HER2-low expression led to better BCSS in patients with non-pCR and better BCSS and OS in patients with stage III. The results of this study indicate that HER2-low breast cancer can be a potential independent biological subtype.

Acknowledgment

We are grateful to MJEditor (www.mjeditor.com) for its linguistic assistance during the preparation of this manuscript.

Funding

This work was sponsored by Training Program for Young and Middle-aged Health and Technology Innovation Leaders in Henan Province from the Health Commission of Henan Province (YXKC2022005).

Conflict of Interest

The authors of the article declare that there are no conflicts of interest related to this manuscript.

Author Contributions

Conception/design: Y.M. Provision of study material or patients: X.C., Z.L. Collection and/or assembly of data: D.J., M.L. Data analysis and interpretation: Y.M., J.Z. Manuscript writing: Y.M., D.J. Final approval of manuscript: All authors.

Data Availability

The data presented in this study are available from the corresponding author on a reasonable request. The data are not publicly available due to ongoing studies and for patient privacy.

Ethical Approval and Consent to Participate

This study was conducted in accordance with the standards set out in the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of Henan Cancer Hospital (Approval Number: 2022-299). The Medical Ethics Committee of Henan Cancer Hospital granted exemption from obtaining informed consent for the study considering its retrospective nature.

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48. https://doi.org/10.3322/caac.21763
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. https://doi.org/10.3322/caac.21660
3. Cao W, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)*. 2021;134(7):783-791. https://doi.org/10.1097/CM9.0000000000001474
4. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. *Lancet*. 2021;397(10286):1750-1769. https://doi.org/10.1016/S0140-6736(20)32381-3
5. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288-300. https://doi.org/10.1001/jama.2018.19323
6. Denkert C, Liedtke C, Tutt A, von Minckwitz G. Molecular alterations in triple-negative breast cancer-the road to new treatment strategies. *Lancet*. 2017;389(10087):2430-2442. https://doi.org/10.1016/s0140-6736(16)32454-0
7. Piccart M, Procter M, Fumagalli D, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer in the APHINITY trial: 6 years' follow-up. *J Clin Oncol*. 2021;39(13):1448-1457. https://doi.org/10.1200/jco.20.01204
8. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519-530. https://doi.org/10.1016/S1470-2045(19)30863-0
9. Fehrenbacher L, Cecchini RS, Geyer CE, et al. 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(5):444-453. https://doi.org/10.1200/JCO.19.01455
10. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol*. 2020;38(17):1951-1962. https://doi.org/10.1200/JCO.19.02488
11. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med*. 2022;387(1):9-20. https://doi.org/10.1056/NEJMoa2203690
12. Banerji U, van Herpen CML, Saura C, et al. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. *Lancet Oncol*. 2019;20(8):1124-1135. https://doi.org/10.1016/S1470-2045(19)30328-6
13. Denkert C, Seither F, Schneeweiss A, et al. 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(8):1151-1161. https://doi.org/10.1016/S1470-2045(21)00301-6
14. Tarantino P, Jin Q, Tayob N, et al. Prognostic and biologic significance of ERBB2-low expression in early-stage breast cancer. *JAMA Oncol*. 2022;8(8):1177-1183. https://doi.org/10.1001/jamaoncol.2022.2286
15. Zhang G, Ren C, Li C, et al. 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(1):142. https://doi.org/10.1186/s12916-022-02346-9
16. Agostinetto E, Rediti M, Fimereli D, et al. HER2-low breast cancer: molecular characteristics and prognosis. *Cancers (Basel)*. 2021;13(11):2824. https://doi.org/10.3390/cancers13112824
17. Kang S, Lee SH, Lee HJ, et al. 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. https://doi.org/10.1016/j.ejca.2022.08.031

18. Won HS, Ahn J, Kim Y, et al. Clinical significance of HER2-low expression in early breast cancer: a nationwide study from the Korean Breast Cancer Society. *Breast Cancer Res*. 2022;24(1):22. https://doi.org/10.1186/s13058-022-01519-x
19. Schettini F, Chic N, Brasó-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer*. 2021;7(1):1. https://doi.org/10.1038/s41523-020-00208-2
20. Domergue C, Martin E, Lemarié C, et al. Impact of HER2 status on pathological response after neoadjuvant chemotherapy in early triple-negative breast cancer. *Cancers (Basel)*. 2022;14(10):2509. https://doi.org/10.3390/cancers14102509
21. Jacot W, Maran-Gonzalez A, Massol O, et al. Prognostic value of HER2-low expression in non-metastatic triple-negative breast cancer and correlation with other biomarkers. *Cancers (Basel)*. 2021;13(23):6059. https://doi.org/10.3390/cancers13236059
22. Ergun Y, Ucar G, Akagunduz B. Comparison of HER2-zero and HER2-low in terms of clinicopathological factors and survival in early-stage breast cancer: a systematic review and meta-analysis. *Cancer Treat Rev*. 2023;115:102538. https://doi.org/10.1016/j.ctrv.2023.102538
23. de Moura Leite L, Cesca MG, Tavares MC, et al. HER2-low status and response to neoadjuvant chemotherapy in HER2 negative early breast cancer. *Breast Cancer Res Treat*. 2021;190(1):155-163. https://doi.org/10.1007/s10549-021-06365-7
24. de Nonneville A, Houvenaeghel G, Cohen M, et al. 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. https://doi.org/10.1016/j.ejca.2022.09.017
25. Jiang C, Perimbeti S, Deng L, Shapiro CL, Gandhi S. Clinical outcomes of de novo metastatic HER2-low breast cancer: a National Cancer Database Analysis. *NPJ Breast Cancer*. 2022;8(1):135. https://doi.org/10.1038/s41523-022-00498-8
26. Horisawa N, Adachi Y, Takatsuka D, et al. The frequency of low HER2 expression in breast cancer and a comparison of prognosis between patients with HER2-low and HER2-negative breast cancer by HR status. *Breast Cancer*. 2022;29(2):234-241. https://doi.org/10.1007/s12282-021-01303-3
27. Fernandez AI, Liu M, Bellizzi A, et al. Examination of low ERBB2 protein expression in breast cancer tissue. *JAMA Oncol*. 2022;8(4):1-4. https://doi.org/10.1001/jamaoncol.2021.7239