Article

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Establishing a Predictive Model to Predict Survival of de Novo Metastatic HER2-Low Breast Cancer: A National Cancer Database Analysis

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Background: Breast cancer with low human epidermal growth factor receptor (HER2) expression is increasingly considered as a distinct subtype which consists of types of HER2 immunohistochemistry (IHC) 1+ and HER2 IHC 2+/*in-situ* hybridization (ISH)-negative. We aim to assess the survival difference between HER2 IHC 1+ and HER2 IHC 2+/ISH-negative breast cancer patients with metastasis at presentation and construct a prognostic nomogram for HER2-low patients.

Method: Patients diagnosed with de novo metastatic HER2-low breast cancer from 2010 to 2015 were included and analyzed using the National Cancer Database (NCDB). Cox proportional hazards regression model and Kaplan–Meier (KM) method were used for survival analysis. Nomograms were built to predict survival.

Result: A total of 7897 patients were included in the final analysis, among which 5458 (69.1%) patients were HER2 IHC 1+ and 2439 (30.9%) were HER2 IHC 2+/ISH-negative. Although the Kaplan–Meier survival analysis showed difference in survival, this survival difference was lost in the multivariate Cox analysis (multivariate: HR (hazard ratio) = 0.97; 95% CI (confidence interval) [0.92–1.03]). A prognostic nomogram was successfully constructed for individually predicting the long-term survival rate of HER2-low patients, which exhibited an acceptable predictive capability in training (C index: 0.719) and validation cohort (C index: 0.706). This nomogram could easily divide patients into high and low-risk subgroups with distinct prognoses.

Conclusions: Our data suggest no statistical survival differences between HER2 1+ and HER2 2+ breast cancer. Additionally, a nomogram was constructed with an acceptable capacity to individually predict the long-term outcome of HER2-low metastatic breast cancer patients.

Keywords: breast cancer; HER2 low; surgery; NCDB; survival

Introduction

HER2 (human epidermal growth factor receptor)-low breast cancer is a subtype that is characterized by HER2 protein levels that are intermediate between HER2-positive (immunohistochemistry (IHC) score 3+ or 2+ with *in situ* hybridization (ISH) positive) and HER2-negative (IHC score 0) tumors. These tumors are often referred to as HER2-equivocal or HER2-low tumors. The exact threshold for defining low HER2 expression varies depending on the testing method and laboratory, but typically it involves HER2 protein levels that are 1+ or 2+ by IHC or a HER2/chromosome enumeration probe (CEP17) ratio less than 2.0 by ISH [1].

HER2-low breast cancer is increasingly considered to have distinct clinical and pathological characteristics compared to HER2-positive breast cancer [2,3]. However, the optimal treatment strategy for HER2-equivocal tumors is

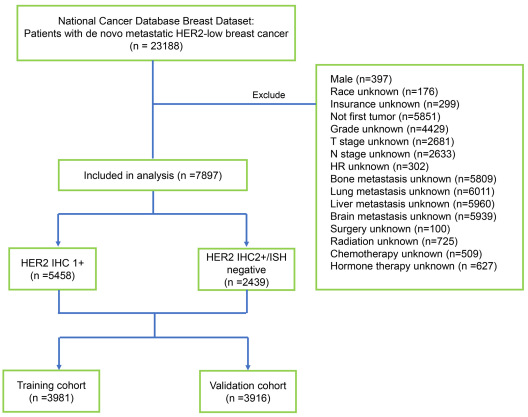

Fig. 1. The flowchart of patient selection.

still unclear, and there is an ongoing debate about whether these tumors should be treated similarly to HER2-positive or HER2-negative tumors. Moreover, there has been growing interest in developing targeted therapies for HER2-low breast cancer [4,5]. Several clinical trials are underway to evaluate the efficacy of novel HER2-targeted agents, such as antibody-drug conjugates (ADCs), in HER2-equivocal tumors [4,6,7]. These therapies may offer new treatment options for HER2-low breast cancer patients. For instance, in the DESTINY-Breast 04 trial, trastuzumab deruxtecan (T-DXd) was proven to increase the progression-free survival and overall survival of HER2-low metastatic breast cancer dramatically [8].

Data regarding the survival of metastatic breast cancer with low expression of HER2 are still lacking, especially for the survival difference between HER2 IHC 1+ and HER2 IHC 2+/ISH-negative tumors. Hence, our study compared the survival of de novo metastatic HER2 IHC 1+ and HER2 IHC 2+/ISH-negative tumors by using the National Cancer Database (NCDB). The results indicated no significant survival difference between HER2 1+ and HER2 2+ de novo metastatic breast cancer. A nomogram was also constructed to predict the long-term survival of patients with HER2-low breast cancer. This approach could help clinicians make appropriate treatment decisions and provide prognostic advice toward counseling such patients.

Methods

Database and Patients Selection

Data were extracted from the NCDB database (https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/), representing approximately 70% of newly diagnosed cancer cases in the United States and is jointly sponsored by the American Cancer Society and the American College of Surgeons. Patient inclusion criteria were as follows: (1) Patients with breast cancer diagnosed between 2010 and 2015; (2) Patients with American Joint Committee on Cancer (AJCC) M1 stage; (3) Patients with HER2 IHC 1+ and HER2 IHC 2+/ISH-negative tumor.

Patients were excluded for any of the following reasons: (1) Unknown information about bone, lung, liver and brain metastasis, (2) male patients, (3) not the first tumor, and (4) unknown information of race, insurance, histological grade, AJCC T and N stage, hormone receptor (HR), surgery, radiation, chemotherapy, and hormone therapy. Based on the exclusion and inclusion criteria, 7897 eligible patients were included (Fig. 1). Subsequently, patients were randomly divided into validation and training cohorts. A training cohort was utilized to construct the nomogram and verified in the validation cohort.

Multiple variables were extracted from the NCDB database, including demographic characteristics (race, age at diagnosis, and insurance status), disease characteristics (histological grade, histological subtype, AJCC T and N stage), and treatment characteristics (surgery, radiotherapy, chemotherapy, and hormone treatment). A categorical variable was created from the continuous variable, such as the age of diagnosis ($<$35, 35–49, 50–69, and $\geq$70). The primary outcome was overall survival (OS).

Statistical Analysis

Demographic and clinicopathological factors were summarized using descriptive statistics. Pearson χ^2 test was used to evaluate correlations between clinicopathological. The Kaplan–Meier survival curve was plotted for survival analysis, and a 2-sided log-rank test was utilized to compare the survival difference between tumors with HER2 IHC 1+ and HER2 IHC 2+/ISH-negative. Moreover, a univariate and multivariate Cox regression analysis was conducted to report hazard ratios (HR) with 95% CIs (confidence intervals). Additionally, nomograms were developed to predict OS in 1-, 3- and 5-year. Estimating the consistency between the observed outcomes and the predictions based on the nomogram was performed by plotting calibration curves.

Descriptive statistics, Pearson χ^2 test, Cox proportional hazards model, and logistic regression model were calculated using SPSS 24.0 (IBM Corp, Armonk, NY, USA). Kaplan–Meier analyses were conducted using R software (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria). A p value of < 0.05 was set as statistically significant.

Results

Baseline Characteristics

A total of 7897 cases were included in the final analysis, among which 5458 (69.1%) patients were HER2 IHC 1+ and 2439 (30.9%) were HER2 IHC 2+/ISH-negative. The baseline characteristics between the two groups were compared with the Pearson χ^2 test (Table 1). Tumors with HER2 IHC 1+ had a higher rate of poorly differentiated

Table 1. Baseline characteristics of patients with de novo metastatic HER2-low breast cancer.

Characteristics	Total cohort No. (%)	HER2 IHC 1+ No. (%)	HER2 IHC 2+/ISH-negative No. (%)	*p* value	χ^2 values
Age				0.150	5.31
<35	220 (2.8)	139 (2.5)	81 (3.3)		
35–49	1403 (17.8)	986 (18.1)	417 (17.1)		
50–69	4159 (52.7)	2857 (52.3)	1302 (53.4)		
≥70	2115 (26.8)	639 (26.2)	1476 (27.0)		
Race				0.927	0.15
White	6136 (77.7)	4246 (77.8)	1890 (77.5)		
Black	1478 (18.7)	1019 (18.7)	459 (18.8)		
Others	283 (3.6)	193 (3.5)	90 (3.7)		
Insurance status				0.188	3.34
Uninsured	448 (5.7)	298 (5.5)	150 (6.2)		
Private	3306 (41.9)	2317 (42.5)	989 (40.5)		
Public insurance	4143 (52.5)	2843 (52.1)	1300 (53.3)		
Grade				0.004	11.08
1	726 (9.2)	490 (9.0)	236 (9.7)		
2	3792 (48.0)	2565 (47.0)	1227 (50.3)		
3–4	3379 (42.8)	2403 (44.0)	2439 (40.0)		
HR				<0.001	26.53
HR–	1261 (16.0)	949 (17.4)	312 (12.8)		
HR+	6636 (84.0)	4509 (82.6)	2127 (87.2)		
T stage				0.005	12.89
T0–1	1065 (13.5)	772 (14.1)	293 (12.0)		
T2	2611 (33.1)	1823 (33.4)	788 (32.3)		
T3	1381 (17.5)	911 (16.7)	470 (19.3)		
T4	2840 (36.0)	1952 (35.8)	888 (36.4)		
N stage				0.116	5.92
N0	1899 (24.0)	1355 (24.8)	544 (22.3)		
N1	3729 (47.2)	2554 (46.8)	1175 (48.2)		
N2	1088 (13.8)	744 (13.6)	344 (14.1)		
N3	1181 (15.0)	805 (14.7)	376 (15.4)		
Bone metastasis				0.579	0.31
No	2330 (29.5)	1600 (29.3)	730 (29.9)		
Yes	5567 (70.5)	3858 (70.7)	1709 (70.1)		
Brain				0.326	0.97
No	7389 (93.6)	5097 (93.4)	2292 (94.0)		
Yes	508 (6.4)	361 (6.6)	147 (6.0)		
Liver				0.257	1.29
No	6351 (80.4)	4371 (80.1)	1980 (81.2)		
Yes	1546 (19.6)	1087 (19.9)	459 (18.8)		
Lung				0.525	0.40
No	5449 (69.0)	3754 (68.8)	1695 (69.5)		
Yes	2448 (31.0)	1704 (5458)	744 (30.5)		
Surgery				0.405	1.81
No	5378 (68.1)	3715 (68.1)	1663 (68.2)		
Lumpectomy	734 (9.3)	522 (9.6)	212 (8.7)		
Mastectomy	1785 (22.6)	1221 (22.4)	564 (23.1)		
Radiotherapy				0.173	1.86
No	4880 (61.8)	3400 (62.3)	1480 (60.7)		
Yes	3017 (38.2)	2058 (37.7)	959 (39.3)		
Chemotherapy				0.573	0.32
No	3822 (48.4)	2630 (48.2)	1192 (48.9)		
Yes	4075 (51.6)	2828 (51.8)	1247 (51.1)		

Table 1. Continued.

Hormone therapy				<0.001	27.80
No	2579 (32.7)	1884 (34.5)	695 (28.5)		
Yes	5318 (67.3)	3574 (65.5)	1744 (71.5)		

Abbreviations: ISH, *in situ* hybridization; IHC, immunohistochemistry; HR, positive hormone receptors; HER2, human epidermal growth factor receptor 2.

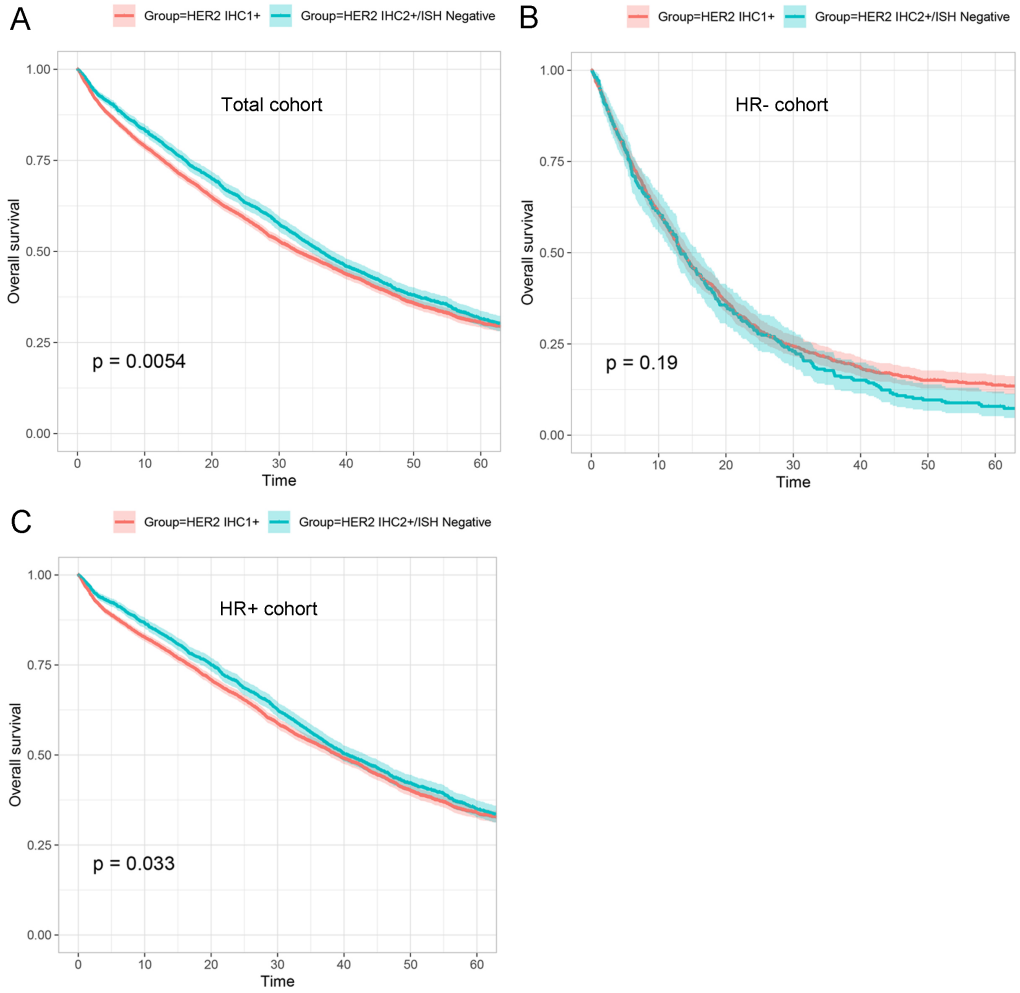

Fig. 2. Kaplan–Meier curve of OS for breast cancer patients between HER2 1+ and HER2 2+/ISH-negative de novo metastatic breast cancer. (A) Total cohort. (B) HR-negative cohort. (C) HR-positive cohort.

grade (44.0% vs. 40.0%, $p < 0.001$), HR– (17.4% vs. 12.8%, $p < 0.001$). Moreover, patients with HER2 IHC 2+/ISH-negative tumors were more likely to receive hormone therapy (71.5% vs. 65.5%, $p < 0.001$). Detailed clinicopathological information is shown in Table 1.

Survival Analyses

The overall survival of patients with HER2 IHC 1+ or HER2 IHC 2+/ISH-negative tumors was compared by the Kaplan–Meier method. As shown in Fig. 2A, patients with HER2 IHC 2+/ISH-negative tumors had a superior OS compared to those with HER2 IHC 1+ tumors ($p = 0.005$). Subgroup analysis was further conducted by HR status. The survival difference has remained in the HR+ cohort (Fig. 2C). However, in HR– cohort, no survival difference was found between the two groups (Fig. 2B). The Cox regression model was also constructed to further assess the survival of patients with HER2 IHC 1+ or HER2 IHC 2+/ISH-negative tumors. Although univariate analysis showed similar results with the Kaplan–Meier method, the survival advantage of HER2 IHC 2+/ISH-negative patients was lost in the total and the HR+ cohorts (Table 2).

Subsequently, the patient cohort was randomly divided into validation and training cohorts (Fig. 1). The two groups had no statistically significant differences regarding baseline characteristics (Table 3). Then, univari-

Table 2. Univariate and multivariate analysis for overall survival (OS) among patients with de novo metastatic HER2-low breast cancer.

	Univariate analysis					Multivariate analysis				
	HR (95% CI)	*p* value	Wald χ^2	β	SE	HR (95% CI)	*p* value	Wald χ^2	β	SE
All patients										
HER2 IHC 1+	Reference					Reference				
HER2 IHC 2+/ISH-negative	0.92 (0.87–0.98)	0.005	7.73	–0.08	0.03	0.97 (0.92–1.03)	0.339	0.81	–0.03	0.03
HR– patients										
HER2 IHC 1+	Reference					Reference				
HER2 IHC 2+/ISH-negative	1.10 (0.96–1.26)	0.190	1.72	0.092	0.07	1.09 (0.94–1.25)	0.249	1.33	0.08	0.07
HR+ patients										
HER2 IHC 1+	Reference					Reference				
HER2 IHC 2+/ISH-negative	0.93 (0.87–0.99)	0.033	4.55	–0.07	0.03	0.95 (0.89–1.02)	0.149	1.90	–0.05	0.03

Abbreviations: CI, confidence interval; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; HR, positive hormone receptors; SE, standard error.

ate and multivariate Cox regression analysis was conducted to screen factors significantly related to OS of newly diagnosed metastatic HER2-low breast cancer (Table 4). As a result, the multivariable analysis indicated that patients with age older than 70 years (vs. age <35; HR = 1.90; 95% CI [1.42–2.53]; $p < 0.001$), black race (vs. white; HR = 1.15; 95% CI [1.04–1.27]; $p = 0.006$), grade 2 (vs. grade 1; HR = 1.31; 95% CI [1.12–1.53]; $p = 0.001$), grade 3–4 (vs. grade 1; HR = 1.70; 95% CI [1.42–2.00]; $p < 0.001$), T4 stage (vs. T0–1; HR = 1.24; 95% CI [1.08–1.41]; $p = 0.002$), bone metastasis (vs. no metastasis; HR = 1.33; 95% CI [1.21–1.46]; $p < 0.001$), brain metastasis (vs. no metastasis; HR = 2.01; 95% CI [1.73–2.34]; $p < 0.001$), lung metastasis (vs. no metastasis; HR = 1.15; 95% CI [1.05–1.25]; $p = 0.002$) and liver metastasis (vs. no metastasis; HR = 1.68; 95% CI [1.53–1.85]; $p < 0.001$) were dramatically related with decreased OS. On the contrary, patients with received private insurance (vs. uninsured; HR = 0.73; 95% CI [0.61–0.87]; $p = 0.001$), HR+ (vs. HR–; HR = 0.63; 95% CI [0.55–0.72]; $p < 0.001$), lumpectomy (vs. no surgery; HR = 0.62; 95% CI [0.53–0.73]; $p < 0.001$), mastectomy (vs. no surgery; HR = 0.66; 95% CI [0.59–0.73]; $p < 0.001$), chemotherapy (vs. no chemotherapy; HR = 0.67; 95% CI [0.61–0.74]; $p < 0.001$), and hormone therapy (vs. no hormone therapy; HR = 0.50; 95% CI [0.45–0.56]; $p < 0.001$) were dramatically related with increased OS.

Nomogram and Stratifying Risk

In order to better predict the survival rate of newly diagnosed metastatic HER2-low breast cancer patients, a prognostic nomogram was constructed by including several independent prognostic factors (age, race, insurance status, grade, HR, T stage, surgery, chemotherapy, hormone therapy, and metastasis status of bone, lung, liver, and brain). As shown in Fig. 3, a total point could be calculated for individual breast patients according to their point scale in the nomogram. In this way, we could forecast the 1-, 3-, and 5-year survival rates. For example, the clinicopathological features of randomly selected patients resulted in a total point score of 706, resulting in the 1-, 3-, and 5-year survival rates of 96.6%, 90.6%, and 86.3% for OS, respectively. A higher score was generally associated with a worse prognosis for patients. The Harrell's concordance index (C-index) for the OS prediction nomogram was 0.719 in the training cohort and 0.706 in the validation cohort, respectively.

Moreover, a plot of the calibration curves revealed good consistency between the predicted survival probability by the nomogram and the observed survival probability (**Supplementary Fig. 1**). Based on the median risk score calculated by the nomogram, patients were further divided into low- and high-risk groups. A significant difference in survival between low- and high-risk patients is shown in Fig. 4.

Discussion

The prognosis of HER2-low breast cancer is generally better than that of HER2-positive breast cancer but worse than that of HER2-negative patients. Several studies have shown that HER2-equivocal tumors have a 5-year overall survival rate of approximately 80%, which is intermediate between the 5-year overall survival rates of patients with HER2-negative tumors (approximately 90%) and HER2-positive tumors (approximately 70%) [9,10].

The improved prognosis of HER2-equivocal tumors may be associated with the fact that these tumors tend to be more hormone receptor-positive and less aggressive than HER2-positive tumors [11]. Hormone receptor-positive breast tumors are generally related to a better prognosis than

Table 3. Baseline characteristics of training and validation cohort.

Characteristics	Training cohort No. (%)	Validation cohort No. (%)	*p* value	χ^2 values
Age			0.282	3.82
<35	99 (2.5)	121 (3.1)		
35–49	700 (17.6)	703 (18.0)		
50–69	2092 (52.5)	2067 (52.8)		
≥70	1090 (27.4)	1025 (26.2)		
Race			0.725	0.64
White	3108 (78.1)	3028 (77.3)		
Black	732 (18.4)	746 (19.1)		
Others	141 (3.5)	142 (3.6)		
Insurance status			0.298	0.30
Uninsured	212 (5.3)	236 (6.0)		
Private	1656 (41.6)	1650 (42.1)		
Public insurance	2113 (53.1)	2030 (51.8)		
Grade			0.331	2.21
1	347 (8.7)	379 (9.7)		
2	1925 (48.4)	1867 (47.7)		
3–4	1709 (42.9)	1670 (42.6)		
HR			0.593	0.29
HR–	627 (15.7)	634 (16.2)		
HR+	3354 (84.3)	3282 (83.8)		
HER2			0.680	0.17
HER2 IHC 1+	2743 (68.9)	2715 (69.3)		
HER2 IHC 2+/ISH-negative	1238 (31.1)	1201 (30.7)		
T stage			0.851	0.79
T0–1	528 (13.3)	537 (13.7)		
T2	1330 (33.4)	1281 (32.7)		
T3	688 (17.3)	693 (17.7)		
T4	1435 (36.0)	1405 (35.9)		
N stage			0.142	5.43
N0	1001 (25.1)	898 (22.9)		
N1	1858 (46.7)	1871 (47.8)		
N2	535 (13.4)	553 (14.1)		
N3	587 (14.7)	594 (15.2)		
Bone metastasis			0.821	0.05
No	1170 (29.4)	1160 (29.6)		
Yes	2811 (70.6)	2756 (70.4)		
Brain			0.355	0.86
No	3735 (93.8)	3654 (93.3)		
Yes	246 (6.2)	262 (6.7)		
Liver			0.837	0.04
No	3198 (80.3)	3153 (80.5)		
Yes	783 (19.7)	763 (19.5)		
Lung			0.557	0.35
No	2759 (69.3)	2690 (68.7)		
Yes	1222 (30.7)	1226 (31.3)		
Surgery			0.529	1.27
No	2728 (68.5)	2650 (67.7)		
Lumpectomy	374 (9.4)	360 (9.2)		
Mastectomy	879 (22.1)	906 (23.1)		
Radiotherapy			0.960	0.01
No	2459 (61.8)	2421 (61.8)		
Yes	1522 (38.2)	1495 (38.2)		

Table 3. Continued.

Chemotherapy			0.411	0.68
No	1945 (48.9)	1877 (47.9)		
Yes	2036 (51.1)	2039 (52.1)		
Hormone therapy			0.890	0.02
No	1303 (32.7)	1276 (32.6)		
Yes	2678 (67.3)	2640 (67.4)		

Abbreviations: ISH, *in situ* hybridization; IHC, immunohistochemistry; HR, positive hormone receptors; HER2, human epidermal growth factor receptor 2.

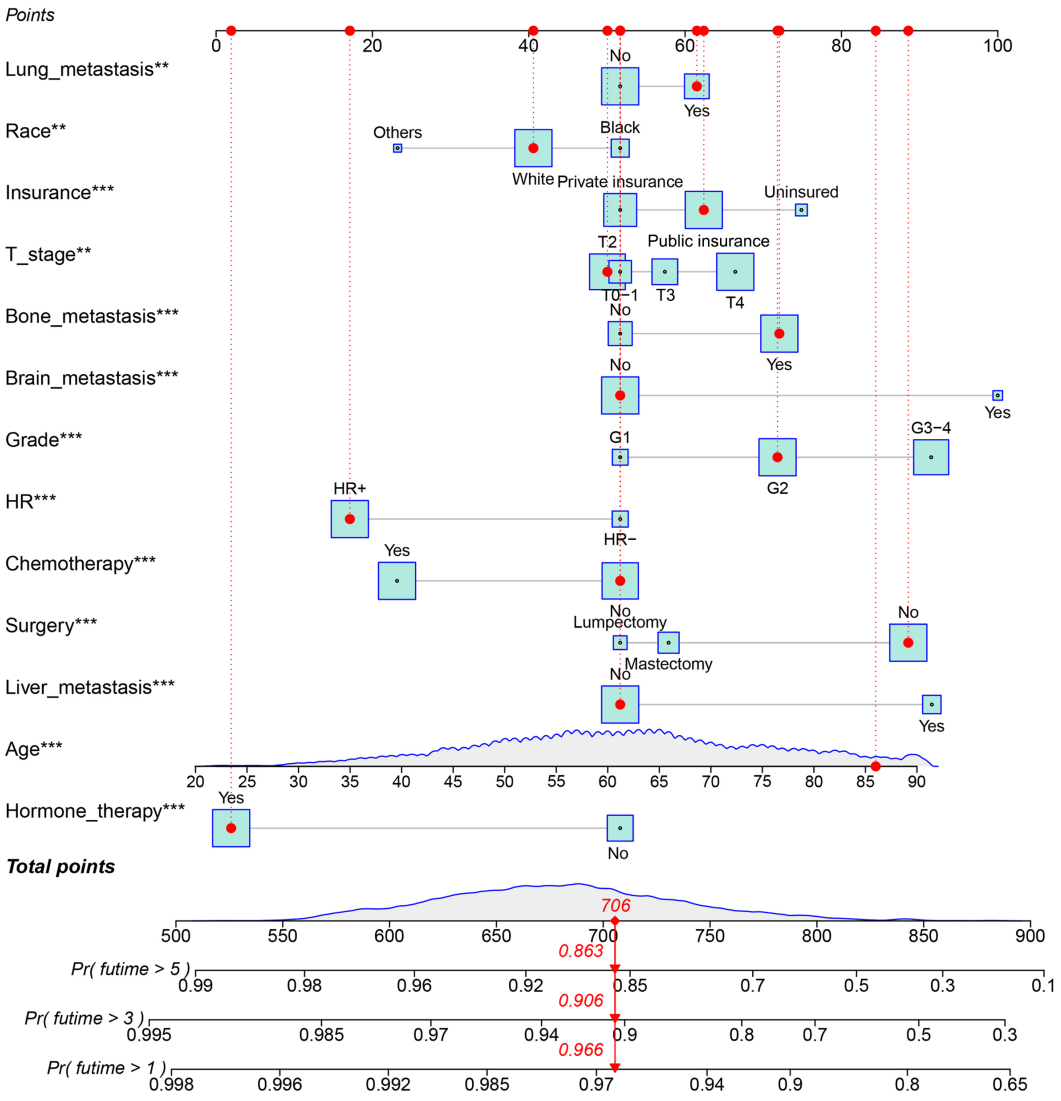

Fig. 3. Nomogram for predicting overall survival probability of patients with de novo metastatic HER2-low breast cancer. $^{**}p < 0.01$, $^{***}p < 0.001$.

hormone receptor-negative tumors [12,13], as these tumors tend to grow more slowly and respond better to hormonal therapies. In addition, HER2-equivocal tumors tend to have lower proliferation rates than HER2-positive tumors, which may contribute to their improved prognosis [14,15]. However, little literature has focused on differences within HER2-low breast cancers, especially regarding the survival difference between HER2 IHC 1+ and HER2 IHC 2+/ISH-negative breast tumors.

A previously published study reported no difference in complete pathological response and survival between HER2 IHC 1+ and IHC 2+/ISH-negative tumors [2]. However, Cherifi *et al.* [16] found a better OS and DFS (disease free survival) for HER2 IHC 2+ breast cancer pa-

Table 4. Cox analysis for overall survival (OS) of patients with de novo metastatic HER2-low breast cancer.

Variables	Univariate analysis		Wald χ^2	β	SE	Multivariate analysis		Wald χ^2	β	SE
	HR (95% CI)	*p* value				HR (95% CI)	*p* value			
Age		<0.001	171.30				<0.001	81.86		
<35	Reference					Reference				
35–49	0.99 (0.74–1.31)	0.933	0.01	–0.01	0.15	1.06 (0.80–1.41)	0.684	0.18	0.06	0.15
50–69	1.28 (0.98–1.68)	0.074	3.20	0.25	0.14	1.28 (0.97–1.69)	0.079	3.14	0.25	0.14
≥70	2.01 (1.53–2.65)	<0.001	24.79	0.70	0.14	1.90 (1.42–2.53)	<0.001	19.24	0.64	0.15
Race		<0.001	29.44				0.001	13.71		
White	Reference					Reference				
Black	1.25 (1.13–1.37)	<0.001	19.92	0.22	0.05	1.15 (1.04–1.27)	0.006	7.54	0.14	0.05
Others	0.71 (0.56–0.91)	0.007	7.35	–0.34	0.12	0.76 (0.59–0.97)	0.026	4.93	–0.28	0.13
Insurance status		<0.001	127.63				<0.001	20.43		
Uninsured	Reference					Reference				
Private insurance	0.60 (0.51–0.72)	<0.001	32.61	–0.51	0.09	0.73 (0.61–0.87)	0.001	11.81	–0.31	0.09
Public insurance	0.95 (0.80–1.13)	0.550	0.36	–0.05	0.09	0.88 (0.73–1.05)	0.142	2.10	–0.13	0.09
Grade		<0.001	118.03				<0.001	58.54		
1	Reference					Reference				
2	1.30 (1.11–1.52)	0.001	10.75	0.26	0.08	1.31 (1.12–1.53)	0.001	11.43	0.27	0.08
3–4	1.89 (1.61–2.20)	<0.001	63.97	0.63	0.08	1.70 (1.45–2.00)	<0.001	41.86	0.53	0.08
HR										
HR–	Reference					Reference				
HR+	0.44 (0.40–0.48)	<0.001	278.89	–0.83	0.05	0.63 (0.55–0.72)	<0.001	49.35	–0.47	0.07
HER2										
HER2 IHC 1+	Reference					NA				
HER2 IHC 2+	0.96 (0.88–1.04)	0.278	1.18	–0.05	0.04					
T stage		<0.001	80.57				0.001	23.02	0.02	0.04
T0–1	Reference					Reference				
T2	0.96 (0.84–1.09)	0.563	0.38	–0.04	0.07	0.98 (0.86–1.12)	0.758	0.11	–0.02	0.07
T3	1.12 (0.97–1.29)	0.117	2.40	0.11	0.07	1.08 (0.93–1.25)	0.341	0.86	0.07	0.08
T4	1.43 (1.26–1.62)	<0.001	31.24	0.36	0.06	1.24 (1.08–1.41)	0.002	9.33	0.21	0.07
N stage		0.046	7.98				0.621	1.78		
N0	Reference					Reference				
N1	1.05 (0.95–1.15)	0.348	0.88	0.05	0.05	0.99 (0.90–1.10)	0.876	0.02	–0.01	0.05
N2	1.11 (0.97–1.26)	0.124	2.37	0.10	0.07	0.96 (0.84–1.10)	0.570	0.33	–0.04	0.07
N3	1.19 (1.05–1.34)	0.008	7.10	0.17	0.06	1.05 (0.92–1.21)	0.435	0.60	0.05	0.07
Bone metastasis										
No	Reference					Reference				
Yes	1.22 (1.12–1.34)	<0.001	0.44	–0.03	0.04	1.33 (1.21–1.46)	<0.001	35.52	0.29	0.05
Brain										
No	Reference					Reference				
Yes	2.24 (1.94–2.58)	<0.001	121.29	0.81	0.07	2.01 (1.73–2.34)	<0.001	82.06	0.70	0.08
Liver										
No	Reference					Reference				
Yes	1.80 (1.64–1.98)	<0.001	161.74	0.59	0.05	1.68 (1.53–1.85)	<0.001	115.22	0.52	0.05
Lung										
No	Reference					Reference				
Yes	1.51 (1.40–1.64)	<0.001	99.86	0.41	0.04	1.15 (1.05–1.25)	0.002	9.77	0.14	0.04
Surgery			192.55					78.98		
No	Reference					Reference				
Lumpectomy	0.48 (0.41–0.56)	<0.001	91.30	–0.74	0.08	0.62 (0.53–0.73)	<0.001	34.74	–0.48	0.08
Mastectomy	0.57 (0.51–0.62)	<0.001	128.44	–0.57	0.05	0.66 (0.59–0.73)	<0.001	59.04	–0.42	0.05

Table 4. Continued.

Radiotherapy										
No	Reference					Reference				
Yes	0.80 (0.73–0.86)	<0.001	31.33	–0.23	0.04	0.92 (0.85–1.00)	0.062	3.54	–0.08	0.04
Chemotherapy										
No	Reference					Reference				
Yes	0.81 (0.75–0.88)	<0.001	28.73	–0.21	0.04	0.67 (0.61–0.74)	<0.001	71.49	–0.40	0.05
Hormone therapy										
No	Reference					Reference				
Yes	0.46 (0.43–0.50)	<0.001	361.07	–0.77	0.04	0.50 (0.45–0.56)	<0.001	156.00	–0.69	0.06

Abbreviations: CI, confidence interval; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; HR, positive hormone receptors; SE, standard error.

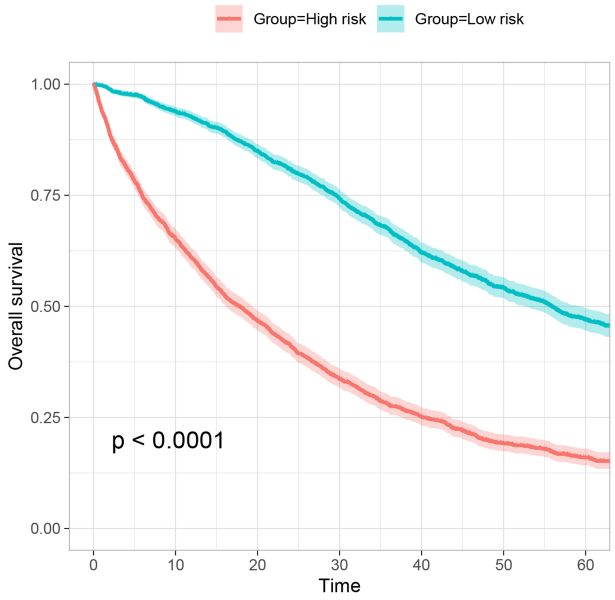

Fig. 4. Kaplan–Meier curve of OS for de novo metastatic HER2-low breast cancer patients with high or low risk stratified by nomogram.

tients than for HER2 IHC 1+, independent of the HR status. In our study, the overall survival of metastatic breast tumors with HER2 IHC 1+ or HER2 IHC 2+/ISH-negative tumors was compared by the Kaplan–Meier and Cox regression analysis. Although the Kaplan–Meier method and univariate analysis showed a superior OS in HER2 IHC 2+/ISH-negative tumors compared with those with HER2 IHC 1+ tumors, the statistical differences were lost in multivariate Cox regression analysis. Hence, our data suggest no survival difference between HER2 1+ and HER2 2+ breast cancer. This may be due to the fact that tumors with HER2 IHC 2+/ISH-negative were more likely to have well-differentiated grade and HR-positive, which tend to have a good effect on endocrine therapy. In addition, a cross-talk between hormone receptor signaling and HER2 signaling may also contribute to treatment resistance in HR-positive breast cancer [17], which may affect the prognosis of patients.

It is also meaningful to identify independent prognostic factors toward newly diagnosed metastatic HER2-low breast cancer patients. As a result, several independent prognostic factors were identified, including age, race, insurance status, grade, HR status, T stage, surgery, chemotherapy, hormone therapy, and metastasis status of bone, liver, lung and brain. It is well known that nomograms would be useful in informing clinical decision-making and predicting patient prognosis [18]. Therefore, a prognostic nomogram was constructed by including independent prognostic factors. This nomogram could easily divide patients into low-risk and high-risk groups, which could help surgeons make appropriate treatment decisions. In the training and validation set, our nomogram exhibited an acceptable predictive capability with C-index above 0.7, which was comparable to many well-recommended nomograms [19,20].

This study may inevitably have several limitations. For example, detailed information, such as the extent of distant metastasis, concomitant disease, and residues of tumor resection (R0, R1, or R2), are not available in the current database. In addition, selection bias is inherent in retrospective studies. More prospective investigation with large sample size is still warranted to validate our results.

Conclusions

The results indicated that there was no significant survival difference between HER2 1+ and HER2 2+ de novo metastatic breast cancer. Additionally, this study constructed a nomogram with an acceptable capacity to individually predict the long-term survival of patients with de novo HER2-low metastatic breast cancer.

Abbreviations

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NCDB, National Cancer Database; KM, Kaplan–Meier; CEP17, chromosome enumeration prob 17; ADCs, antibody-drug conjugates; T-DXd, trastuzumab deruxtecan; AJCC, American Joint Committee on Cancer; HR, hormone receptor; OS, overall survival.

Availability of Data and Materials

The data generated and/or analysed during the current study are available in the NCDB database (https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/).

Author Contributions

MYL, ML and LYD—designed the research study; MYL, ML, LZ, HJL, AM, KY, HHL and LYD—analyzed the data; MYL, ML, KY and LYD—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335176.29.

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