A Novel Prognostic Nomogram for the 2-year Survival in Human Epidermal Growth Factor Receptor 2 Positive Breast Cancer Patients

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Abstract

Background: Targeted therapies have largely improved prognosis of human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Yet, disease can still progress rapidly for some patients in the first two years after diagnosis. Our study aimed to establish a nomogram model to predict the 2-year breast cancer-specific survival (BCSS) in early HER2-positive breast cancer patients.

Methods: A total of 32,481 HER2-positive patients derived from Surveillance, Epidemiology, and End Results (SEER) database were included in the construction of nomogram. Concordance index (C-index) and calibration curve were used to evaluate the discrimination ability and predictive accuracy. We tested the model in 804 patients from Shanghai Jiao Tong University Breast Cancer Data Base (SJTU-BCDB).

Results: Age, estrogen receptor (ER) status, progesterone receptor (PR) status, histologic type, T stage and N stage were selected to construct the nomogram according to multivariable analysis. The 2-year BCSS rate was 95% and 60% for patients at low risk (<8 points) and high risk (>13 points) respectively. The C-index of model derived from SEER database is 0.81 (95%CI 0.79-0.83). Sensitivity analysis was performed in patients after breast surgeries with the C-index of 0.81 (95%CI, 0.79-0.83). Validation in 804 patients from SJTU-BCDB showed respective C-index of 0.77 (95%CI, 0.62-0.92) in total population, 0.67 (95%CI 0.44-0.90) and 0.90 (95%CI 0.81-0.90) in patients who received anti-HER2 therapy or not.

Discussion: The novel nomogram can predict the 2-year survival outcome in HER2-positive patients independent of receiving anti-HER2 therapy or not and allow clinicians to adjust therapeutic strategies for patients with higher risk.

1. Background

Breast cancer is the most common type of malignant tumor among women worldwide. Human epidermal growth factor receptor 2 (HER2) was acknowledged to be one of the important predictors for breast cancer patients. HER2 positivity, defined as HER2 overexpression or amplification, is associated with aggressive disease progression and poor clinical prognosis[1] and HER2 positive tumors accounts for 15-20% of breast cancer[2]. The emergence of several anti-HER2 agents has markedly improved the survival outcome of HER2 positive breast cancer patients[3]. Trastuzumab, a monoclonal antibody targeting against HER2 receptor[4], was recommended to be used regularly combined with other necessary adjuvant therapies in HER2-positive diseases because of its validated therapeutic effect in a series of clinical trials[3,5]

However, survival outcomes diverge in patients receiving trastuzumab. Treatment failures are common in HER2 positive breast cancer, especially in the early phase of treatment. Evidence showed that cumulative breast cancer progression rate could come up to 10-15% in the first two years under trastuzumab treatment and then reach a plateau of 20-25% gradually in the following years[3], leading to more attention on insufficient primary treatment and drug resistance in early.

Following the approval of trastuzumab, more anti-HER2 compounds, such as pertuzumab, lapatinib, neratinib and trastuzumab-DM1 (T-DM1) [6–9], came into public for the intensified treatment of HER2 positive breast cancer patients. Although these new drugs provided more available options, how to weigh against benefit, toxicity and cost remained difficult when clinicians made therapeutic decisions. Here, we performed a retrospective study and aimed to provide a new tool to predict the 2-year survival in non-metastatic HER2 positive breast cancer patients, which may assist clinicians in selection between moderate and aggressive therapeutic strategies.

2. Methods

2.1 Data Resources and Patients Selection

A total of 32,481 breast cancer patients obtained from Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2016 were analyzed retrospectively and enrolled in the construction of a nomogram model. Cases with HER2-positive non-metastatic invasive breast cancer were included. Exclusion criteria were other malignant tumor history, occult breast cancer and incomplete follow-up information. Selected by the same inclusion and exclusion criteria, 804 patients from prospectively-maintained Shanghai Jiao Tong University Breast Cancer Data Base (SJTU-BCDB) between 2009 and 2016 were assigned to the validation group. The validation group was further divided into trastuzumab-treated and untreated subgroups.

2.2 Statistical Analysis

Breast cancer-specific survival (BCSS) and overall survival (OS) with corresponding 95% confidence interval (CI) was estimated by Kaplan–Meier method. The 2-year BCSS was selected as the primary outcome based on which the nomogram was constructed. To identify potential predictors, we performed univariate and multivariate Cox proportional hazards model. Factors with p-value >0.05 were excluded. The package of *rms* on R Studio was used to construct the nomogram model. The discrimination ability and calibration of the nomogram was measured by Concordance index (C-index) and calibration plot respectively. Sensitivity analysis was performed in patients who received breast surgeries. External validation was performed in patients from SJTU-BCDB. All tests were performed using R Studio version 1.2.5019 based on R version 3.6.1.

3. Results

3.1 Baseline Characteristics

Clinicopathologic features of primary cohort and validation cohort were presented in Table 1. A total of 665 BCSS events happened in primary cohort and 9 happened in validation cohort. 1152 patients in primary set and 10 patients in validation set developed the 2-year OS events respectively. About 5% (n=1,740) of patients in primary cohort didn’t receive any surgery while all patients in validation cohort underwent breast operation.

Table 1
Basic Characteristics of Patients in Primary Cohort and Validation Cohort

Characteristics	Primary Cohort (n=32,481)	Validation Cohort (n=804)
Age(years)		
<60	19,420(59.8%)	582(72.4%)
≥60	13,061(40.2%)	222(27.6%)
Subtype		
HR+	22,987(70.8%)	389(48.4%)
HR-	9,494(29.2%)	415(51.6%)
Grade		
I	1,593(4.9%)	9(1.0%)
II	11,727(36.1%)	382(47.5%)
III	19,161(59.0%)	413(51.5%)
Pathology		
IDC/ILC/mixed	30,810(94.9%)	765(95.1%)
others	1,671(5.1%)	39(4.9%)
AJCC T stage		
1	15,972(49.2%)	393(48.9%)
2	12,595(38.8%)	389(48.4%)
3	2,599(8.0%)	21(2.6%)
4	1,315(4.0%)	1(0.1%)
AJCC N stage		
0	19,421(59.8%)	472(58.7%)
1	9,511(29.3%)	195(24.3%)
2	2,225(6.9%)	76(9.5%)
3	1,324(4.0%)	61(7.5%)

Abbreviations: HR, hormone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; AJCC, American Joint Committee on Cancer.

Characteristics	Primary Cohort (n=32,481)	Validation Cohort (n=804)
Surgery		
No Surgery	1,740(5.4%)	0(0)
Lumpectomy	14,804(45.6%)	175(21.8%)
Mastectomy	15,937(49.0%)	629(78.2%)

Abbreviations: HR, hormone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; AJCC, American Joint Committee on Cancer.

3.2 Survival Outcome and Multivariable Analysis of Predictors

The 2-year BCSS and OS in primary cohort was 97.7% (95% CI 97.6-97.9%) and 96.1% (95%CI 95.9-96.3%) respectively. Results of univariate analysis for the 2-year BCSS were presented in Table 2. Results of backward stepwise regression analysis showed that old age (≥60 years, hazard ratio=2.94, 95%CI, 2.50-3.45) might be independent unfavorable risk factors of the 2-year BCSS. Contrarily, estrogen receptor positivity (hazard ratio=0.44, 95%CI 0.38-0.52) and progesterone receptor positivity (hazard ratio=0.44, 95%CI, 0.38-0.52) were associated with improved the 2-year BCSS. The invasive lobular carcinoma (ILC) or invasive ductal carcinoma (IDC) contained pathologic types were related to rhe worse BCSS compared with other types, but showed no significant difference compared with each other. Thus, they were merged into one category in the construction of nomogram. Patients with higher T stage and N stage had worse survival outcome as shown in Table 2. In addition, analysis of potential prognostic factors for the 2-year OS showed similar outcomes (Table 3).

Table 2
Predictors of the 2-year BCSS in Univariate and Multivariate Cox Regression Analysis in HER2+ Patients

	Univariant analysis		Multivariant analysis	
Characteristics	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)		<.001		<.001
<60	1.00		1.00	
≥60	2.94(2.50-3.45)		3.30(2.81-3.88)	
ER		<.001		<.001
Negative	1.00		1.00	
Positive	0.44(0.38-0.52)		0.70(0.58-0.85)	
PR		<.001		<.001
Negative	1.00		1.00	
Positive	0.44(0.38-0.52)		0.69(0.56-0.85)	
Grade				
I	1.00	0.003	1.00	0.060
II	2.88(1.42-5.85)	<0.001	1.98(0.97-4.03)	0.012
III	5.13(2.55-10.32)		2.48(1.22-5.03)	
Pathology				
IDC/ILC/mixed	1.00	0.267	1.00	0.020
others	0.81(0.55-1.18)		0.64(0.44-0.93)	
AJCC T stage				
1	1.00	<.001	1.00	<.001
2	3.63(2.91-4.53)	<.001	2.85(2.27-3.59)	<.001
3	7.01(5.40-9.11)	<.001	4.99(3.77-6.60)	<.001
4	17.82(13.86-22.91)		9.56(7.25-12.61)	

Abbreviations: BCSS, breast cancer-specific survival; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; AJCC, American Joint Committee on Cancer.

	Univariant analysis		Multivariant analysis	
AJCC N stage	1.00	<.001	1.00	<.001
0	2.54(2.11-3.05)	<.001	1.67(1.38-2.04)	<.001
1	4.19(3.29-5.32)	<.001	2.24(1.74-2.89)	<.001
2	8.02(6.36-10.11)		3.37(2.62-4.34)	
3				

Abbreviations: BCSS, breast cancer-specific survival; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; AJCC, American Joint Committee on Cancer.

Table 3
Predictors of the 2-year OS in Univariate and Multivariate Cox Regression Analysis in HER2+ Patients

	Univariant analysis		Multivariant analysis	
Characteristics	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)		<.001		<.001
<60	1.00		1.00	
≥60	3.99(3.51-4.54)		4.28(3.75-4.87)	
ER		<.001		<.001
Negative	1.00		1.00	
Positive	0.57(0.51-0.64)		0.74(0.64-0.86)	
PR		<.001		
Negative	1.00		1.00	0.004
Positive	0.58(0.51-0.65)		0.80(0.69-0.93)	
Grade				
I	1.00	0.262		
II	1.21(0.87-1.70)	0.001		
III	1.72(1.24-2.38)			
Pathology		0.097		0.002
IDC/ILC/mixed	1.00		1.00	
others	0.78(0.58-1.05)		0.64(0.47-0.85)	
AJCC T stage				
1	1.00	<.001	1.00	<.001
2	2.27(1.96-2.62)	<.001	2.16(1.78-2.41)	<.001
3	3.49(2.87-4.23)	<.001	3.35(2.30-3.47)	<.001
4	9.27(7.75-11.10)		6.80(5.56-8.31)	

Abbreviations: OS, overall survival; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; AJCC, American Joint Committee on Cancer.

	Univariant analysis		Multivariant analysis	
AJCC N stage				
0	1.00	<.001	1.00	0.011
1	1.57(1.37-1.79)	<.001	1.20(1.04-1.23)	<.001
2	2.38(1.97-2.88)	<.001	1.52(1.25-1.86)	<.001
3	4.19(3.48-5.06)		2.19(1.79-2.69)	

Abbreviations: OS, overall survival; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; AJCC, American Joint Committee on Cancer.

3.3 Nomogram Construction

According to the multivariable cox regression model, we constructed a prognostic nomogram using age, estrogen receptor (ER) status, progesterone receptor (PR) status, histologic type, T stage and N stage (Figure 1). For an individual patient, each predictor is assigned with a specific score according to the first row of the nomogram. The total points of six predictors can be calculated to predict the probability of the 2-year BCSS by locating points in the seventh row. In our nomogram, 89.2% of patients had total scores less than eight and the probability of the 2-year BCSS were 95%. A total score of eight to thirteen was associated with a moderate the 2-year BCSS (range 60%-80%). Twenty-nine patients had total scores more than thirteen, and they were at high risk with the 2-year BCSS of less than 60%. Statistical difference was observed among the three subgroups (log-rank $p < 0.001$).

3.4 Internal and External Validation

Internal validation showed a C-index of 0.81 (95%CI 0.79-0.83) for the 2-year BCSS prediction. To avoid potential disturbance of breast surgery, sensitivity analysis was performed in patients who received operation. A C-index of 0.81 (95%CI 0.79-0.83) supported the universality of the novel nomogram in HER2 positive breast cancer patients with or without breast surgery (Figure 2). The calibration plots for predicting the 2-year BCSS in primary cohort and sensitivity analysis showed good consistency between predicted probability and observed probability.

To evaluate the external applicability of the nomogram model, we validated it in the independent data derived from SJTU-BCDB. The 2-year BCSS was 98.9% (98.2%-99.6%) in the validation cohort. The C-index of the nomogram for the 2-year BCSS prediction was 0.81 (95%CI 0.79-0.83). In patients with or without receiving anti-HER2 therapy, the C-index of the nomogram were 0.67 (95%CI 0.44-0.90) and 0.90 (95%CI 0.81-0.90) respectively.

4. Conclusions

In the last two decades, the introduction of anti-HER2 agents had revolutionized the treatment of HER2 positive breast cancer patients impressively[10]. Besides trastuzumab, addition or substitution of new novel anti-HER2 regimens were common in clinical practice, accompanied with increased cost and toxicity[11]. Therefore, it is important for clinicians to identify HER2vpositive patients at high risk of recurrence or death and monitor therapeutic strategies.

Our study discovered prognostic factors for the 2-year survival outcome of HER2 positive breast cancer patients. Based on the factors, we built a prognostic model. Emerging evidence indicated that the first two years were particularly important in HER2-positive breast cancer treatment. Although trastuzumab plus standard chemotherapy for early-stage HER2 positive breast cancer was recommended by National Comprehensive Cancer Network guideline[12], new recurrences could be observed during or within 12 months after 1-year adjuvant trastuzumab treatment, which was defined as trastuzumab resistance[13,14]. In clinical trials, the results showed that approximately 10-15% of early HER2 positive breast cancer patients receiving trastuzumab treatment experienced disease progression in the first two years and then the rate increased slowly and finally reached a plateau of 20-25% in the following years[3,5]. Different from HER2 positive subtype, the results of clinical trials showed that for triple-negative breast cancer, the DFS and OS rates remained high in the first 12 months and then kept decreasing slowly in the following years[15,16]. Comparatively, patients with HR+/HER2- had high 5-year DFS or BCSS rates[17,18] though recurrences can occur even several decades later after primary diagnosis[18]. These data called for more attention to the prognosis in the first two years of the treatment for HER2-positive early breast cancer patients.

Therefore, we chose to analyzed potential predictive factors for the 2-year BCSS in HER2 positive early breast cancer. Age, ER status, PR status, histologic type, T stage and N stage were found significantly associated with HER2 positive breast cancer prognosis. ER and PR positivity were associated with better BCSS, which was in agreement with previous retrospective studies[19,20]. The favorable effects of ER or PR positivity on the survival outcome of HER2 positive breast cancer patients were also observed when the OS or DFS rates were compared between HR positive and HR negative subgroups in clinical trials[3,5,6,8]. The histologic grade was commonly recommended as a predictor for breast cancer prognosis[21]. However, our study showed that it might be less valuable when predicting the very early survival outcome of HER2 positive subtype. The majority of HER2 positive tumors presented with histologic grades II/III and we didn't find statistically important impact of tumor grade on survival outcome of HER2 positive patients. This was also concordant with previous knowledge[20]. The effect of different pathologic types on the short-term survival outcome was generally overlooked before. Here, we found it necessary to classify the histologic type into two categories to improve the predictive ability.

Nomogram is a well-developed graphical model for cancer prognosis[22]. It emphasizes the magnitude of the effect of each predictor and makes the integration more convenient to read and use. Data source of our nomogram was derived from SEER database which covered about 34.6% of the U.S. population[23], making the model more applicable. All of the predictors in our nomogram model were basic

clinicopathologic characteristics which could be collected easily during the process of diagnosis and treatment, so that it would be used conveniently in clinical practice. According to the nomogram, patients at high risk had increasing chances experiencing BCSS events and therapeutic escalation, including concomitant trastuzumab and pertuzumab[6] or sequential trastuzumab and neratinib[7,24]. On the other hand, patients with low scores were less risky. Proper de-escalated therapy, such as strategies in the APT trial, could lighten the financial burdens for patients and avoid adverse effects without therapeutic effect compromise[25].

We should admit that there were some limitations of the nomogram model. We could not obtain the details about whether patients derived from SEER database received anti-HER2 treatment and our model was based on the whole population without regard to anti-HER2 drug use. To solve this problem, we validated our model in patients from SJTU-BCDB. Although the number of the 2-year NCSS events was small in validation cohort, the nomogram model still showed good predictive ability. In addition, because the validation was based on one single institution in China, whether the nomogram could be generally applied should be further investigated.

In conclusion, we constructed a novel nomogram with great potential to help clinicians with making therapeutic strategies for non-metastatic HER2 positive breast cancer patients. Still, our model needed to be tested in various populations to gain greater reliance.

Declarations

Ethics approval and consent to participate: All the experiment protocol for involving human data was in accordance with the international guidelines.

Consent for publication: NA

Availability of data and materials: The data from SEER database (https://seer.cancer.gov/data/) and SJTU-BCDB (http://bcdb.mdt.team:8080/) was open upon request. We had the administrative permission to access and use the data from these two database.

Competing interest: The authors declare that they have no conflicts of interest.

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Authors' contributions: LZ, JY and MC made study design. DL, Weilin C, Weiguo C, and KS participated in data acquisition. JW and MC conducted statistical analysis and manuscript preparation. KS and LZ helped to review the manuscript. All authors read and approved the final manuscript.

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Figures

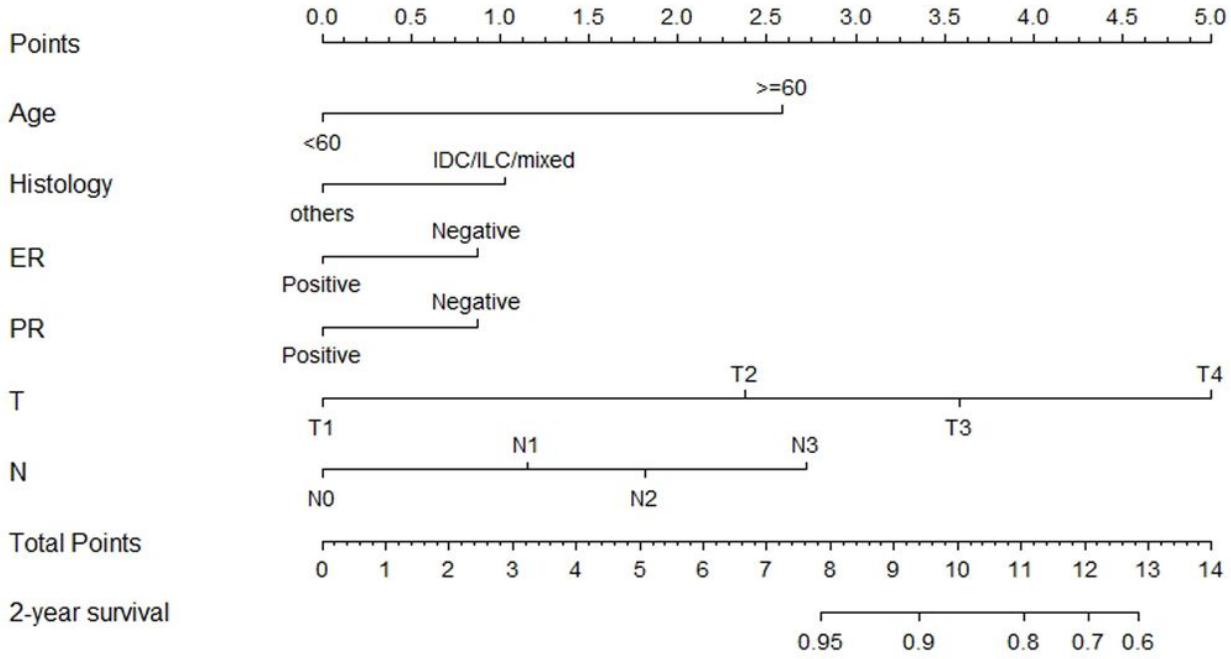

Figure 1

Nomogram of predictors for the 2-year breast cancer-specific survival in HER2 positive patients. Abbreviations: HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; IDL, invasive ductal cancer; ILC, invasive lobular cancer; T, AJCC tumor size stage; N, AJCC lymph node stage.

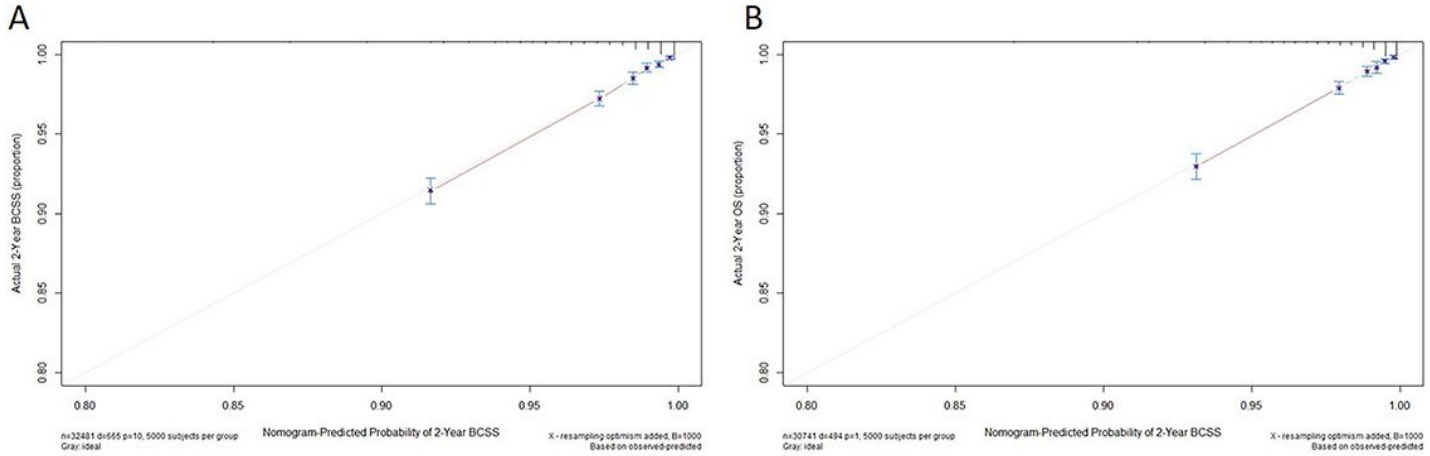

Figure 2

Calibration curve for nomogram in primary cohort (A) and in patients who received breast surgeries (B). Abbreviations: BCSS, breast cancer-specific survival.