Original Article

Development of a prognostic nomogram for lymph node positive HR$^+$/HER2$^-$ breast cancer patients: a study of SEER database and a Chinese cohort

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Background: The hormone receptor$^+$/human epidermal growth factor receptor 2$^-$ (HR$^+$/HER2$^-$) breast cancer (BC) patients account for the largest proportion in all patients and are still at high risk of long-range recurrence. This current study aimed to construct a prognostic nomogram to predict 3-year and 5-year BC-specific survival (BCSS) in HR$^+$/HER2$^-$ BC patients with axillary lymph node metastasis.

Methods: A total of 25,338 HR$^+$/HER2$^-$ patients with axillary lymph node-positive BC were enrolled from the Surveillance, Epidemiology and End Results (SEER) database and randomly divided into the training (n=17,738) and validation (n=7,600) cohorts using a ratio of 7:3. Univariate and multivariable Cox regression hazards were used to build a prognostic nomogram based on the training cohort. The nomogram was validated with two independent cohorts. Receiver operating characteristic (ROC) curves and calibration plots were used to evaluate the performance of the model, and Kaplan-Meier survival analyses were applied to test the clinical utility of the risk stratification system.

Results: Twelve factors including age, race, marital status, grade, T stage, N stage, radiotherapy, chemotherapy, and metastasis to the bone, brain, lung and liver were identified and incorporated to construct the nomogram (P<0.001). The area under the ROC curve (AUC) values at 3- and 5-year in the training and internal validation sets were 0.800, 0.800, 0.831 and 0.819, respectively, while those of the external set were 0.765 and 0.735, indicating a satisfactory discrimination with our nomogram. The calibration curves showed highly consistent results for the actual and predicted survival probabilities. Furthermore, patients were divided into three risk groups according to the total scores of the nomogram. The risk stratification system accurately differentiated between patients with different BCSS rates.

Conclusions: We constructed the first nomogram and corresponding risk stratification system to predict the 3-year and 5-year BCSS for HR$^+$/HER2$^-$ patients with lymph node-positive BC, indicating a satisfactory accuracy and clinical application.

Keywords: HR$^+$/HER2$^-$ breast cancer (HR$^+$/HER2$^-$ BC); lymph node-positive; nomogram; breast cancer-specific survival (BCSS); Surveillance, Epidemiology and End Results (SEER)

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Introduction

Breast cancer (BC) has become the most commonly diagnosed cancer and the leading cause of cancer-related deaths in women. Since 2020, it has surpassed lung cancer as the world's leading diagnosed cancer, with 2.26 million new cases worldwide (1). BC manifests a high degree of heterogeneity at both clinical and molecular levels, and stratifying BC into different subtypes has proved to be an effective strategy to overcome heterogeneity (2). Estrogen receptor, progesterone receptor, human epidermal growth factor receptor (HER)2, and Ki-67 are used to define molecular subtypes (3). The molecular subtypes are closely related to BC prognosis. Patients with hormone receptor positive (HR^+) tumors are the most common and generally have a better prognosis owing to their sensitivity to endocrine therapy. However, patients with HR^+ BC are still at high risk of long-range recurrence and cancer-specific death compared with other subtypes (4,5). To reduce the rate of late recurrence, it is necessary to improve the management of patients in this group.

Given the biological heterogeneity of BC, current tumor node metastasis (TNM) staging system, even with its ability to incorporate molecular subtype information, is still inadequate to fully meet the corresponding clinical needs. Moreover, other clinical factors such as age, race, adjuvant therapy, and genetic background, may influence the prognosis. In recent years, genetic testing has been gradually selected as a tool to assess the risk of BC recurrence and make chemotherapy decisions, which mainly includes Oncotype DX recurrence score, Prediction Analysis of Microarray 50 (PAM50) recurrence score, MammaPrint (70 gene test), and breast cancer index (BCI). Axillary lymph node metastasis is an important prognostic factor that affects the recurrence and survival of invasive BC (6). However, most genetic tests are performed in populations with negative lymph nodes or a small number of lymph nodes with metastasis. Studies have found that these test results are often inconsistent, and that the correlation between these scores and the lymph node status is not strong (7-9). Therefore, there is a current demand to identify more specific prognostic factors to predict the prognosis of BC patients individually and guide clinical practice.

In the current study, we evaluated the prognostic value of clinical factors for $HR^+/HER2^-$ patients with lymph node metastasis. We selected the nomogram as the presentation form of the prediction model, which has been proved to be superior to the traditional TNM staging system, and has obvious advantages in predicting tumor recurrence, prognosis and outcome (10). On the basis of multivariate Cox proportional hazards regression, the nomogram assigns different scores of each influencing factor according to the contribution degree to the outcome variable. Each score is added to get the total score. Finally, the predicted value of the outcome event of the individual is calculated through the function conversion relationship between the total score and the probability of the outcome event. No previous nomogram has been established and validated to show the survival of patients with $HR^+/HER2^-$ and lymph node-positive BC. We extracted data from the Surveillance, Epidemiology and End Results (SEER) database, which is the most comprehensive cancer database including particular patient information of the United States population. We also collected a patient cohort to externally validate our nomogram, thus helping us confirm whether the nomogram was generalisable to another cohort. We

Highlight box

Key findings

- We constructed a novel nomogram for breast cancer (BC)-specific survival and risk stratification in hormone receptor$^+$/human epidermal growth factor receptor 2$^-$ ($HR^+/HER2^-$) BC patients with axillary lymph node metastasis.

What is known and what is new?

- Patients with HR^+ BC are still at high risk of long-range recurrence and cancer-specific death compared with other subtypes. To reduce the rate of late recurrence, it is necessary to improve the management of patients in this group.
- Our nomogram takes account of the different factors to assist clinicians to identify women at high risk and decide on the best treatment options postoperatively for each patient.

What is the implication, and what should change now?

- The manifestation of the nomogram provides a more intuitive approach to assist clinicians to identify high-risk populations and a reference for postoperative treatments to some extent.

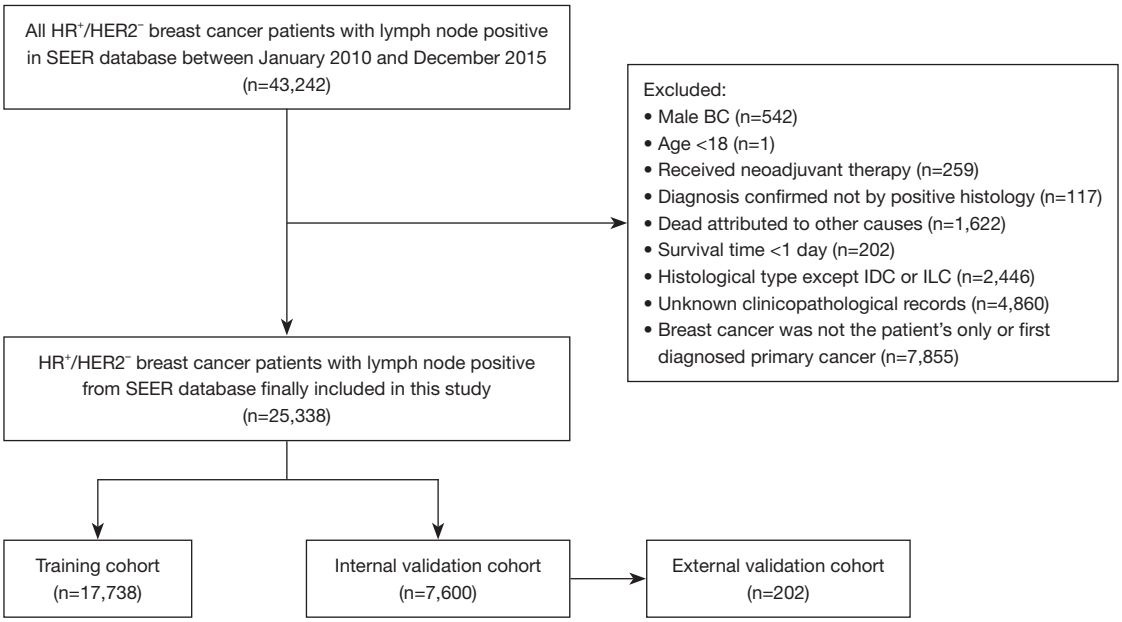

Figure 1 The flowchart of patients identified in this study. HR, hormone receptor; HER2, human epidermal growth factor receptor 2; SEER, Surveillance, Epidemiology and End Results; BC, breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

present this article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-177/rc).

Methods

Patient selection and data acquisition

SEER is a cancer database that collects disease information and survival outcomes for patients with cancer, and was established by the National Cancer Institute. In this study, we used SEER*Stat 8.3.5 to download and extract data on BC patients diagnosed between 2010 and 2015.

The inclusion criteria were as follows: (I) diagnosis confirmed only by positive histology; (II) patients actively followed up with complete survival information and survival time of at least one day; (III) patient's only or first diagnosed primary cancer being BC; (IV) subtype of BC being HR^+ and $HER2^-$; and (V) histological type being invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), or mixed.

The following patients were excluded: (I) men; (II) age of diagnosis <18; (III) neoadjuvant therapy received; (IV) missing-information on race, marital status at diagnosis, tumor location, histological type, grade, American Joint Committee on Cancer (AJCC) T, N and M stage, metastasis site, radiotherapy, chemotherapy, living status, subtype or number of positive lymph nodes. A total of 25,338 patients were included in this study (*Figure 1*).

The enrolled patients were randomly divided into the training cohort and internal validation cohort with a ratio of 7:3. The training cohort was used to determine the independent prognostic factors of patients and establish a prognostic nomogram prediction model. The internal validation set was used to verify the nomogram-prediction model.

To verify our nomogram, we included 202 patients diagnosed with BC in 2010–2015 from the First Hospital of China Medical University as the external validation cohort. Patients were enrolled according to the inclusion and exclusion criteria used in the training cohort. The last follow-up was in January 2021. The experimental protocol was approved by the Research Ethics Committee of the First Hospital, China Medical University (No. 2020-203) in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and the written informed consent was obtained from all subjects.

Variable collection

The variables selected in this study included age at diagnosis, race, marital status, tumor location, histological type, histological grade, AJCC T status, AJCC N status, AJCC M status, metastatic site (lung, liver, brain, bone), treatment information (radiotherapy, chemotherapy), and ER, PR and HER2 expression. Breast cancer-specific survival (BCSS), defined as the interval from diagnosis to BC-specific death, was used as the primary endpoint.

Statistical analysis

First, the significant influencing factors were screened out through univariate Cox analysis (P<0.05), and subsequently included in the multivariate Cox analysis. The nomogram was constructed based on the results of the multivariate Cox proportional hazards regression. (P<0.05).

The nomogram prediction model was constructed using R software. Receiver operating characteristic (ROC) curves and area under the curve (AUC)/concordance (C) index (C-index) were used to quantitatively evaluate the model efficacy and predictive ability. A calibration curve was used to verify the prediction model and evaluate the performance of the nomogram. We calculated the total scores of patients using the "survival", "rms", "nomogram Ex", and "nomogram Formula" package of R studio and established a risk stratification system according to X-Tile software. The patients were divided into low-, medium-, and high-risk subgroups with significantly different BCSS. Kaplan-Meier curves were used to show the survival for different risk groups.

SPSS 23.0 and R software 4.0.3 were used for statistical analysis, and R software 4.0.3 was used for model visualization and verification. Statistical significance was set at P<0.05 in a two-tailed test.

Results

Clinicopathologic characteristics

A total of 25,338 patients that met the inclusion and exclusion criteria were finally enrolled from the SEER database, and were randomly divided into a training cohort (n=17,738) and an internal validation cohort (n=7,600) (*Figure 1*). *Table 1* shows the detailed demographic and clinicopathological characteristics of all patients.

The median age of all cases was 57, with the largest proportion of patients aged 50–59 accounting for 27.5% of all patients. The median follow-up period was 45 months. The 3- and 5-year BCSS rates were 94.8% and 92.2%, respectively. The most common histological type was IDC, with the highest proportion of patients belonging to the grade II category. In the AJCC T staging system, the largest number of patients belonged to the T2 staging category. In the AJCC N staging system, the largest proportion of patients belonged to the N1 category (75%). Bone metastasis was the most common (3.09%, n=784), lung metastasis rate was 0.84% (n=212), liver metastasis rate was 0.78% (n=197), with the brain metastasis rate being the lowest at 0.075% (n=19).

Univariate and multivariable Cox analysis and the construction of nomogram

The hazard ratio (HR) results of the univariate and multivariable Cox proportional hazards regressions are shown in *Table 2*. Univariate Cox regression analysis showed that three general conditions: age (P<0.001), race (P<0.001), marital status (P<0.001) and nine clinical conditions: histological grade (P<0.001), AJCC T stage (P<0.001), AJCC N stage (P<0.001), radiotherapy (P<0.001), chemotherapy (P<0.001), bone metastasis (P<0.001), liver metastasis (P<0.001), lung metastasis (P<0.001), brain metastasis (P<0.001) were related variables of BCSS. Location (P=0.653) and histological type (P=0.344) were not included in the multivariable Cox regression analysis.

In multivariate Cox regression analysis, the older age [age ≥80; HR =1.592; 95% confidence interval (CI): 0.953–2.659; P=0.076], black race (P<0.001), unmarried status (HR =1.171; 95% CI: 1.053–1.302; P=0.003), histology grade III (HR =3.292; 95% CI: 2.684–4.038; P<0.001), AJCC T4 stage (HR =5.255; 95% CI: 4.330–6.376; P<0.001), AJCC N3 stage (HR =2.614; 95% CI: 2.295–2.977; P<0.001), AJCC M1 stage (HR =3.096; 95% CI: 2.468–3.883; P<0.001), not receiving chemotherapy and radiotherapy (P<0.001), bone metastasis (HR =3.504; 95% CI: 2.980–4.119; P<0.001), brain metastasis (HR =4.682; 95% CI: 2.576–8.510; P<0.001), liver metastasis (HR =3.146; 95% CI: 2.429–4.074; P<0.001) and lung metastasis (HR =1.501; 95% CI: 1.156–1.950; P=0.002) were independently associated with BCSS rate. These variables were used to construct the nomogram (*Figure 2*).

Development and validation of the prognostic nomogram

According to the results of multivariable Cox regression

Table 1 Clinicopathological features of breast cancer patients in the training and internal validation groups

Variables	Total	Training cohort (n=17,738)	Validation cohort (n=7,600)
Age (year)			
20–29	175	122	53
30–39	1,661	1,154	507
40–49	5,783	4,052	1,731
50–59	6,974	4,924	2,050
60–69	6,262	4,357	1,905
70–79	3,262	2,304	958
≥80	1,221	825	396
Race			
Black	2,389	1,689	700
White	19,778	13,814	5,964
Other	3,171	2,235	936
Marital status			
Married	15,287	10,781	4,506
Unmarried	10,051	6,957	3,094
Location			
Left	12,574	8,868	3,706
Right	12,764	8,870	3,894
Histological type			
Infiltrating duct carcinoma	19,331	13,530	5,801
Infiltrating lobular carcinoma	3,641	2,555	1,086
Mixed	2,366	1,653	713
Histological grade			
I	4,500	3,137	1,363
II	13,569	9,515	4,054
III	7,222	5,053	2,169
IV	47	33	14
T stage			
T1	9,581	6,781	2,800
T2	11,414	7,950	3,464
T3	3,285	2,272	1,013
T4	1,058	735	323
N stage			
N1	19,014	13,314	5,700
N2	4,149	2,896	1,253
N3	2,175	1,528	647
M stage			
M0	24,214	16,943	7,271
M1	1,124	795	329
Radiotherapy			
Yes	14,976	10,474	4,502
No/unknown	10,362	7,264	3,098
Chemotherapy			
Yes	16,839	11,772	5,067
No/unknown	8,499	5,966	2,533
Bone metastasis			
Yes	784	551	233
No	24,554	17,187	7,367
Brain metastasis			
Yes	19	15	4
No	25,319	17,723	7,596
Liver metastasis			
Yes	197	141	56
No	25,141	17,597	7,544
Lung metastasis			
Yes	212	154	58
No	25,126	17,584	7,542

analysis, we used the R software to construct nomogram models of patients' 3- and 5-year BCSS.

The ROC curve showed that the AUC values of the 3- and 5-year BCSS in the training cohort were 0.800 and 0.800 (*Figure 3A*,*3B*). The AUC values at 3- and 5-year BCSS were 0.831 and 0.819 for the internal validation set (*Figure 3C*,*3D*) and those for the external validation set were 0.765 and 0.735 respectively (*Figure 3E*,*3F*), demonstrating that our model had satisfactory discrimination. The calibration curves also showed that the actual observed

Table 2 Univariate and multivariate Cox regression analysis of HR+/HER2− and lymph node-positive breast cancer patients in the training cohort

Variables	Univariate Cox			Multivariate Cox		
	HR	95% CI	P	HR	95% CI	P
Age (year)			<0.001			<0.001
20–29		Reference			Reference	
30–39	0.601	0.361–1.001	0.050	0.673	0.404–1.124	0.130
40–49	0.359	0.220–0.587	<0.001	0.481	0.294–0.789	0.004
50–59	0.457	0.281–0.743	0.002	0.654	0.402–1.068	0.090
60–69	0.443	0.272–0.722	0.001	0.659	0.403–1.078	0.097
70–79	0.707	0.433–1.155	0.166	1.061	0.645–1.744	0.820
≥80	1.336	0.812–2.201	0.255	1.592	0.953–2.659	0.076
Race			<0.001			<0.001
Black		Reference			Reference	
White	0.511	0.444–0.587	<0.001	0.617	0.534–0.713	<0.001
Other	0.444	0.362–0.546	<0.001	0.529	0.429–0.651	<0.001
Marital status			<0.001			
Married		Reference				
Unmarried	1.633	1.476–1.807	<0.001	1.171	1.053–1.302	0.003
Location			0.653			
Left		Reference				
Right	0.977	0.882–1.082				
Histological type			0.344			
Infiltrating duct carcinoma		Reference				
Infiltrating lobular carcinoma	1.122	0.920–1.367				
Mixed	1.390	1.109–1.744				
Histological grade			<0.001			<0.001
I		Reference			Reference	
II	1.896	1.548–2.323	<0.001	1.509	1.230–1.851	<0.001
III	4.691	3.842–5.729	<0.001	3.292	2.684–4.038	<0.001
IV	2.665	0.983–7.227	0.054	1.958	0.720–5.322	0.188
T stage			<0.001			<0.001
T1		Reference			Reference	
T2	2.470	2.133–2.860	<0.001	1.760	1.514–2.046	<0.001
T3	4.571	3.874–5.394	<0.001	2.779	2.334–3.310	<0.001
T4	13.286	11.136–15.851	<0.001	5.255	4.330–6.376	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate Cox			Multivariate Cox		
	HR	95% CI	P	HR	95% CI	P
N stage			<0.001			<0.001
N1		Reference			Reference	
N2	2.007	1.767–2.280	<0.001	1.544	1.353–1.761	<0.001
N3	4.476	3.958–5.062	<0.001	2.614	2.295–2.977	<0.001
M stage			<0.001			<0.001
M0		Reference			Reference	
M1	10.390	9.237–11.690	<0.001	3.096	2.468–3.883	<0.001
Radiotherapy			<0.001			<0.001
No/unknown		Reference			Reference	
Yes	0.590	0.530–0.650	<0.001	0.659	0.593–0.733	<0.001
Chemotherapy			<0.001			<0.001
No/unknown		Reference			Reference	
Yes	0.810	0.730–0.900	<0.001	0.879	0.776–0.995	0.042
Bone metastasis			<0.001			
No		Reference				
Yes	9.700	8.500–11.000	<0.001	3.504	2.980–4.119	<0.001
Brain metastasis			<0.001			
No		Reference				
Yes	30.000	17.000–53.000	<0.001	4.682	2.576–8.510	<0.001
Liver metastasis			<0.001			
No		Reference				
Yes	16.000	13.000–20.000	<0.001	3.146	2.429–4.074	<0.001
Lung metastasis			<0.001			
No		Reference				
Yes	12.140	9.759–15.110	<0.001	1.501	1.156–1.950	0.002

HR, hormone receptor; HER, human epidermal growth factor receptor; HR, hazard ratio; CI, confidence interval.

results were in good agreement with the predicted results in the training and validation cohorts (*Figure 4*).

Risk stratification system

The corresponding score for this variable can be obtained by referring to the standard scale above each variable. The total score was obtained by adding the scores of all factors, and the corresponding value of the total score was the 3/5-year BCSS rate of the target population. The total points for all patients in both cohorts were calculated based on the predicted nomogram score. The cutoff value of the survival data was determined using the X-Tile software. According to the cutoff value, patients were divided into low- (total scores ≤243.27), medium- (243.27 < total scores <301.52), and high-risk (total scores ≥301.52) groups. However, in the external validation cohorts, the total number of scores in this cohort did not cover all three

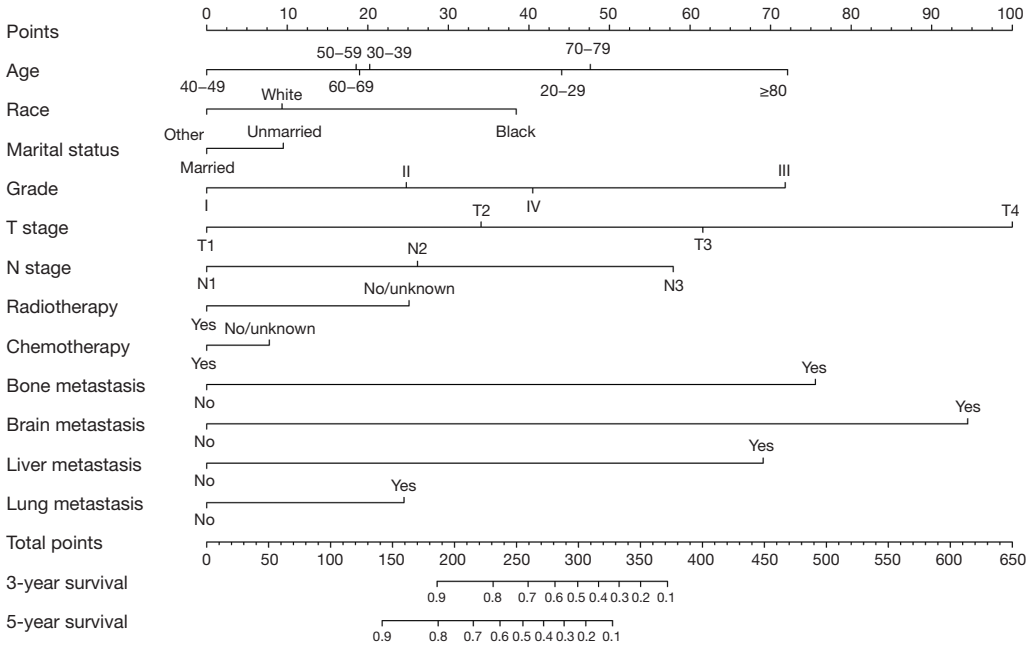

Figure 2 The nomogram for predicting the breast cancer-specific survival for HR+/HER2− patients with lymph node metastasis. HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

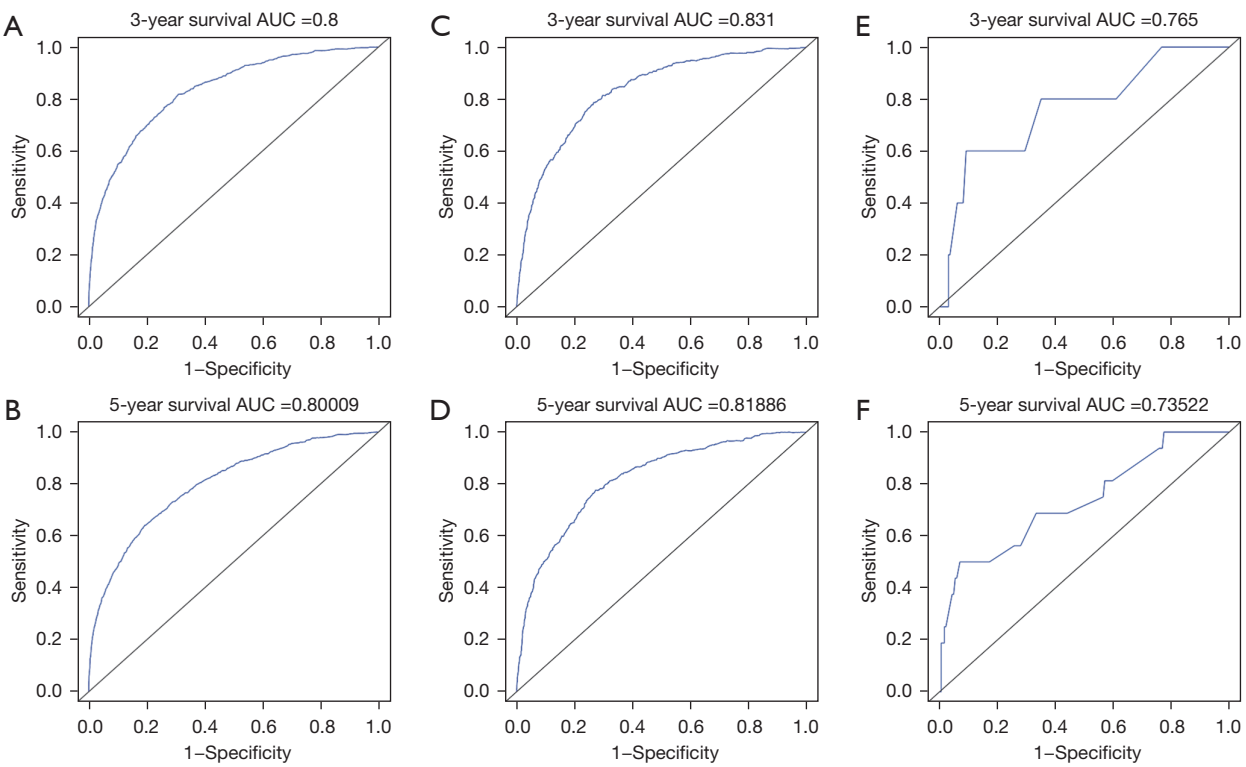

Figure 3 The ROC curves for the 3- and 5-year BCSS. (A) Prediction of 3-year BCSS in the training cohort; (B) prediction of 5-year BCSS in the training cohort; (C) prediction of 3-year BCSS in the internal validation cohort; (D) prediction of 5-year BCSS in the internal validation cohort; (E) prediction of 3-year BCSS in the external validation cohort; (F) prediction of 5-year BCSS in the external validation cohort. AUC, area under the curve; ROC, receiver operating characteristic; BCSS, breast cancer-specific survival.

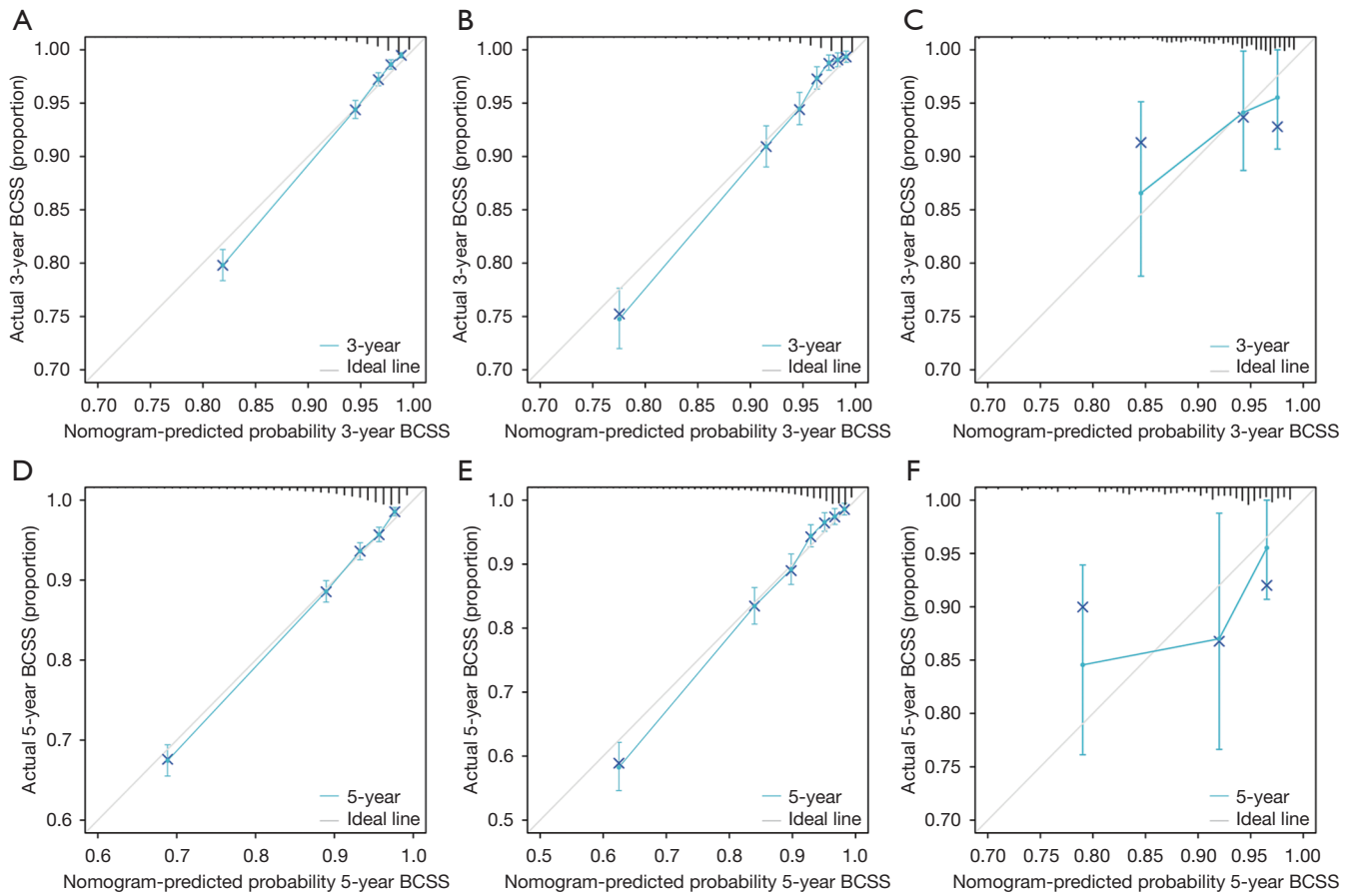

Figure 4 The calibration curves for predicting BCSS. (A) Prediction of 3-year BCSS in the training cohort; (B) prediction of 3-year BCSS in the internal validation cohort; (C) prediction of 3-year BCSS in the external validation cohort; (D) prediction of 5-year BCSS in the training cohort; (E) prediction of 5-year BCSS in the internal validation cohort; (F) prediction of 5-year BCSS in the external validation cohort. BCSS, breast cancer-specific survival.

risk groups, which was probably due to the low number of patients. Therefore, we validated our risk stratification system using only the internal validation cohort.

In both the training and internal validation cohorts, the 3-year BCSS of the low-, medium- and high-risk groups were 98.4%, 92.8% and 72.8%, respectively, and the 5-year BCSS were 96.6%,87.3% and 62.4%, respectively. The results of the Kaplan-Meier survival analysis are shown in *Figure 5* (P<0.0001).

Discussion

Lymph node status is a key indicator of patient prognosis (11,12). Patients with HR^+ BC have a better prognosis than those with the other two subtypes [HER2 positive and triple-negative breast cancer (TNBC)] (2). The HR^+/$HER2^-$ subtype patients account for the highest proportion among all molecular subtypes, and its annual incidence is predicted to increase by 2% over the next 3 years (13,14). Nevertheless, HR^+/$HER2^-$ patients with lymph node metastasis have not drawn much attention in clinical treatment. Consequently, this leads to incorrect judgment of the prognosis and under- or over-treatment in this group.

To resolve this issue, we developed a nomogram to predict the survival of HR^+/$HER2^-$ patients with lymph node metastasis. A nomogram was applied as an integrated statistical model based on multivariable analysis, which demonstrated good accuracy. Studies have shown that nomograms have advantages in terms of assessing the cancer risk, selecting therapies and medicines, and predicting survival outcomes in various types of cancer (10,15).

We constructed the first nomogram based on the Cox

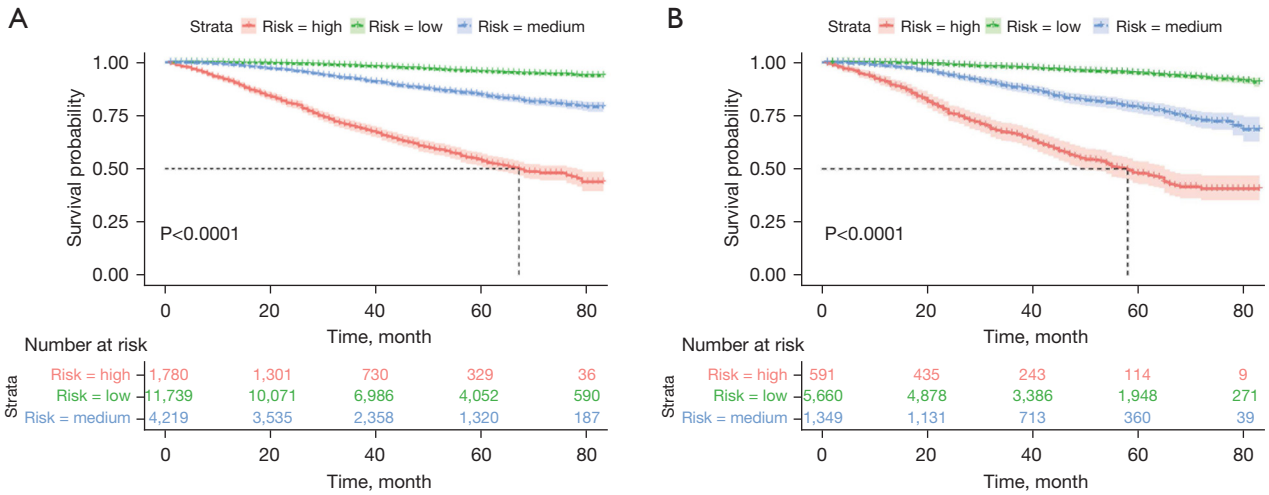

Figure 5 Survival curves of nomogram-based risk stratification. (A) Training cohort; (B) internal validation cohort.

proportional hazards model of HR+/HER2− and lymph node-positive patients. Due to the large number of this subtype of patients, the nomogram may be widely used in clinical practice in the future. Through the patient information easily obtained in clinical work, the 3-year and 5-year survival rates of patients can be easily and quickly estimated. Beyond that, a certain degree of support can be provided for identifying high-risk patients and deciding whether to prolong the endocrine therapy of patients.

The nomogram was internally validated, and its performance was evaluated using the C-index and calibration curve. According to previous studies, the C-index was between 0.6 and 0.8, indicating that our nomogram had a high predictive value on prognosis. In this study, the calibration curve showed the best consistency in predicting BCSS, thereby ensuring the reliability of the established nomogram. In conclusion, our nomogram provides an accurate estimate of patient outcome. This was an original study in which a visual predictive model was constructed to improve survival in HR+/HER2− patients and provide useful information.

Compelling evidence have shown that young age is an independent negative predictor of BC survival (16,17) and is associated with the risk of the occurrence of contralateral BC and local recurrence (18). Previous studies have also shown that elderly patients with BC have higher mortality rates, which may be because elderly patients appear to be at greater risk of developing chemotherapy-related cardiotoxicity than their younger counterparts and could not tolerate intensive standard chemotherapy (19). In addition, elderly patients are more likely to suffer from other chronic diseases (e.g., diabetes), which could also affect the survival. Similar to prior findings (20), patients aged ≥70 and ≤30 were at a higher risk of poor survival in our nomogram.

Radiotherapy is a vital adjuvant treatment for patients with lymph node metastasis. Different subtypes of BC possess differential radiosensitivity, aggressiveness, and malignancy, consequently different outcomes after radiotherapy. It has been shown that luminal A BC has the most favorable clinical benefits after receiving radiotherapy compared to the subtypes of HER2+ and TNBC (21,22). In addition, when considering the cause of the radiosensitivity disparity, TNBC and HER2+ BC are more aggressive compared with luminal BC because of the tumor itself. In our study, radiotherapy did not have a strong effect on the BCSS rate.

Chemotherapy is also an important and common treatment option for BC. In this Chinese cohort, 202 patients received chemotherapy but it was not an important prognostic factor in the present study. Moreover, chemotherapy had the least effect on the current nomogram. Whether chemotherapy is required for HR+/HER2− BC patients in the early stage has always been a controversial issue. Most current guidelines recommend that this requirement is determined through gene testing, e.g., Oncotype DX or MammaPrint. However, gene testing has its limitations and defects. In the past few years, several

retrospective analyses have shown that the results varied when chemotherapy was considered necessary for these BC patients (23-25). The DBCG77B trial reported that not all patients could benefit from adjuvant chemotherapy, even among high-risk populations (26). In the TAILORx study, the risk grouping criteria were redefined (27), which indicated that it was essential to categorize patients more accurately to implement precise treatment. Although the patients included in this study had a high risk for lymph node metastasis, our results could not prove the degree of benefit of chemotherapy in $HR^+/HER2^-$ BC patients with lymph node metastasis. Our study focused on survival after treatment. For HR^+ patients, endocrine therapy was critical, but the information of endocrine therapy was not included in SEER database. However, our nomogram revealed that the included patients benefitted from endocrine therapy to a large extent.

In our study, distant metastases of bone, brain and liver, T stage, and histological grade had a great impact on prognosis, while lymph node grade did not have great weight, which is somewhat contradictory to the current clinical consensus. According to the current consensus, higher degree of lymph nodes metastasis would indicate greater risk of recurrence. It is worth considering whether the degree of lymph node metastasis is equivalent to the degree of recurrence risk when other factors are different. However, this question warrants further research.

Using Cox regression analysis, tumor location and histological type were excluded from our model, and the same conclusion was reached as in the previous model (20). Our model included specific distant metastasis of brain, bone, liver and lung metastasis, while the AJCC M stage contained the similar information of the condition of distant metastasis. Because our nomogram needed to calculate the survival rate by combining the corresponding scores of different influencing factors, the AJCC M stage was not included to avoid duplicate calculation. Our nomogram showed that patients with brain metastasis had the highest risk of death compared to those with bone, liver, and lung metastases.

However, several limitations of this study merit attention. First, as this was a retrospective study, selection bias was inevitable. Moreover, because of the lack of data, the effects of endocrine therapy, specific radiotherapy and chemotherapy regimens, and family history could not be fully studied. In addition, because of the small number of patients included in the external validation set, the application of our nomogram to the risk group in the Chinese patient cohort could not be verified. We will attempt to collect prospective data and add more prospective validation in future studies to improve the accuracy and integrity of the nomogram.

Conclusions

We constructed a novel nomogram for BCSS and risk stratification in $HR^+/HER2^-$ BC patients with axillary lymph node metastasis. Our analysis identified 12 factors including age, race, marital status, histological grade, T stage, N stage, radiotherapy, chemotherapy, metastasis of bone, liver, lung and brain, to predict BCSS. Despite some limitations, our population-based study provides several influential survival factors and guidance for further prospective studies on $HR^+/HER2^-$ and lymph node-positive BC. The manifestation of the nomogram provides a more intuitive approach to assist clinicians to identify high-risk populations and a reference for postoperative treatments to some extent.

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Footnote

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uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-177/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The experimental protocol was approved by the Research Ethics Committee of the First Hospital, China Medical University (No. 2020-203) in accordance with the principles of the Declaration of Helsinki (as revised in 2013) and the written informed consent was obtained from all subjects.

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