Original Article

Prognostic factors for hormone receptor-positive breast cancer with liver metastasis and establishment of novel nomograms for prediction: a SEER-based study

Zheng Xu[1,2], Yong Chen[1,2], Yi Dai[1,2], Yuxingzi Chen[1,2], Jinhua Ding[1]

[1]Department of Thyroid and Breast Surgery, The Affiliated Lihuili Hospital, Ningbo University, Ningbo, China; [2]Health Science Center, Ningbo University, Ningbo, China

Contributions: (I) Conception and design: Z Xu, J Ding; (II) Administrative support: J Ding; (III) Provision of study materials or patients: Z Xu, Yong Chen, Y Dai; (IV) Collection and assembly of data: Z Xu, Yuxingzi Chen; (V) Data analysis and interpretation: Z Xu, J Ding; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jinhua Ding, MD, PhD. Department of Thyroid and Breast Surgery, The Affiliated Lihuili Hospital, Ningbo University, No. 1111 Jiangnan Road, Gaoxin District, Ningbo 315000, China. Email: cookie800128@sina.com.

Background: The prognosis of patients with hormone receptor (HR)-positive breast cancer with liver metastasis (BCLM) remains dismal and varies widely from person to person. Thus, we sought to construct nomograms to predict overall survival (OS) and breast cancer-specific survival (BCSS) in patients with HR-positive BCLM using data from the Surveillance, Epidemiology and End Results (SEER) database.

Methods: The data of patients with BCLM, who had received HR-positive diagnoses between 2010 and 2016, were collected from the SEER database. A Cox proportional hazards model was used to evaluate and identify the independent risk factors for OS and BCSS. Subsequently, two new nomograms were developed. Finally, the receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) results were evaluated.

Results: The data of 1,780 patients diagnosed between 2010 and 2015 were used to build the nomogram models. Using both univariate and multivariate Cox regression analyses, nine variables, including age, marital status, grade, human epidermal growth factor receptor 2 (HER2) status, chemotherapy, surgery, bone metastasis, lung metastasis, and brain metastasis, were found to be significantly associated with OS. Conversely, 10 variables, including age, marital status, T stage, grade, HER2 status, chemotherapy, surgery, bone metastasis, lung metastasis, and brain metastasis, were identified as independent risk factors for BCSS. Using the risk factors listed above, we created 1-, 2-, and 3-year survival nomograms for OS and BCSS, respectively. Subsequently, the data of 312 patients, who had been diagnosed in 2016, were used for the external validation. These results, including the ROC curve, calibration curve, and DCA results, showed that our nomogram had strong predictive power.

Conclusions: Nomograms can effectively and reliably predict a patient's prognosis and could be useful in clinical decision making. The nomograms had strong discrimination, calibration, and clinical values. More aggressive treatment and closer monitoring should be considered when treating high-risk individuals.

Keywords: Breast cancer (BC); hormone receptor-positive (HR-positive); liver metastasis; nomogram; prognosis factors

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Introduction

According to the Cancer Statistics 2022 report, breast cancer (BC) is the leading malignancy and primary cause of mortality in women (1). It was estimated that approximately 290,560 American women would be diagnosed with BC in 2022 and 43,000 would die from it (1). Distant metastasis (rather than the primary tumor) is the most frequently lethal to patients with BC (2). Common sites of BC metastasis include the bone, lungs, and liver, among which, the liver is the third most common site (3). Previous studies have shown that more than 30% of patients with BC develop non-lymph node metastasis (4,5). Compared to those with bone and lung metastases, BC patients with liver metastasis have a worse prognosis and a median survival time of only 14 to 16 months, regardless of whether systemic therapy is administered for primary/metastatic sites, which may be related to endocrine therapy resistance and the failure of chemotherapy (6,7). Further, when BC with liver metastasis (BCLM) initially appears, it may result in digestive symptoms, including nausea and anorexia, as well as signs and symptoms of cachexia, including severe hepatomegaly, jaundice, and ascites, which have significant negative effects on the quality of life of patients (8,9).

Thus, a unique predictive diagnostic tool for BCLM urgently needs to be established for clinical practice. The tumor-node-metastasis (TNM) staging system is one of the most widely used conventional prediction tools; however, it has certain drawbacks that prevent it from adequately covering cancer biology and quantifying the prognosis of patients with distant metastatic disease (10). In addition, while some studies have attempted to simulate the prognosis of BCLM patients, they have failed to sufficiently focus on the molecular type (7,11).

Hormone receptor (HR) status, which includes the estrogen receptor (ER) and progesterone receptor, is a vital prognostic factor, and the HR-positive subtype is the most common type of BC (12,13). The prognosis of BC patients varies depending on their HR status; patients with the HR-positive/human epidermal growth factor receptor 2 (HER2)-positive subtype have a better prognosis than those with the HR-negative/HER2-negative subtype (14). To the best of our knowledge, no previous study exists on the prognostic prediction of patients with HR-positive BCLM.

Nomograms can be used to help construct prognostic models to aid in clinical decision making. A nomogram is a solid instrument for quantifying the risk of variables in prognostic models and is broadly used in prognostic analysis in oncology (15). In this study, we identified a representative cohort from the Surveillance, Epidemiology and End Results (SEER) population-based national registration database to evaluate the prognosis of HR-positive *de novo* liver metastatic BC, and using a large sample size, we established and validated two nomograms to predict overall survival (OS) and breast cancer-specific survival (BCSS). We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-874/rc).

Highlight box

Key findings

- We established two nomogram models to make personalized predictions for patients with hormone receptor (HR)-positive breast cancer with liver metastasis (BCLM) that exhibited ideal accuracy and calibration.

What is known, and what is new?

- The prognosis of patients with HR-positive BCLM remains poor. Thus, personalized models urgently need to be established to guide the clinical management of such patients.
- To our knowledge, this was the first study to develop comprehensive nomograms for predicting the prognosis of HR-positive BCLM patients. Our nomograms had an area under the curve greater than 0.7, indicating their predictive ability.

What is the implication, and what should change now?

- In the future, real-world data needs to be collected to further refine and adjust the prediction model, which will enable it to provide additional assistance in clinical practice.

Methods

Study population

Using the SEER*Stat program version 8.4.0.1, we obtained HR-positive BCLM data from the SEER database, which comprises one of the largest publicly available cancer data sets. The population included in this analysis was between 2010 and 2015, as the SEER database only started gathering data on the molecular subtypes and locations of distant metastases in 2010.

To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) be an adult female; (II) have been diagnosed by immunohistochemistry; (III) have liver metastasis; and (IV) be HR-positive. Patients

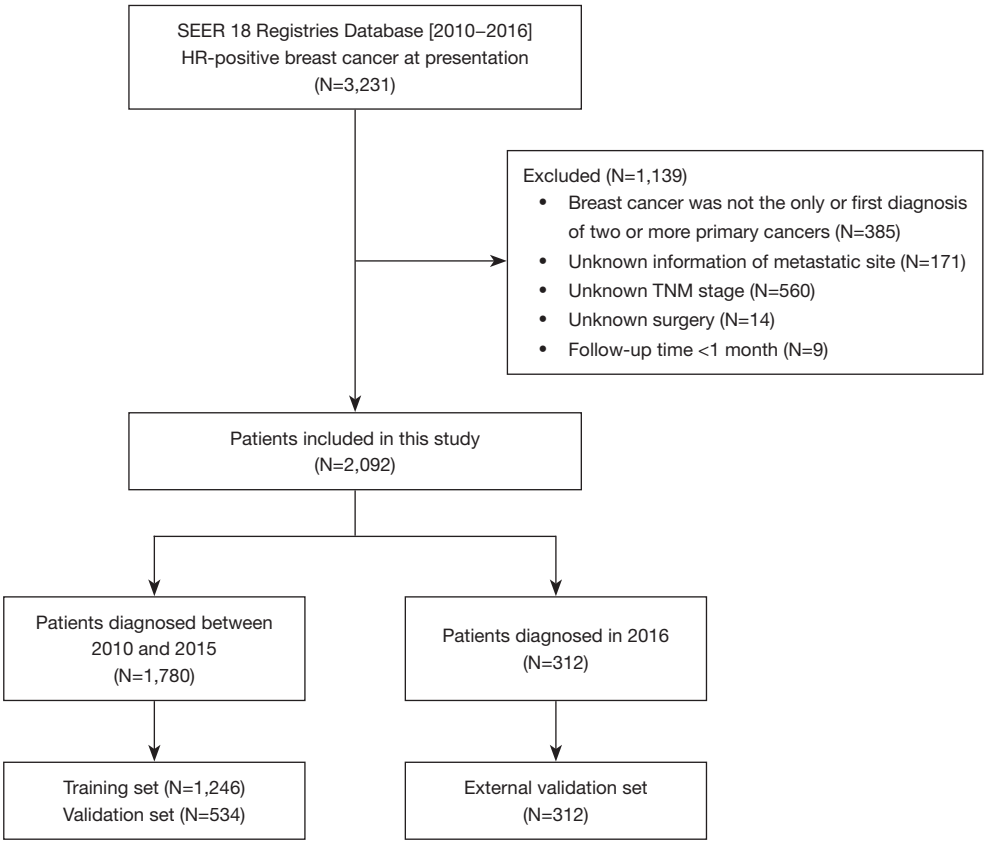

Figure 1 Flowchart of the study. SEER, Surveillance, Epidemiology and End Results; HR, hormone receptor; TNM, tumor-node-metastasis.

were excluded from the study if they met any of the following exclusion criteria: (I) BC was not the only or was not the first diagnosis of two or more primary cancers; (II) essential details, including TNM stage, surgery, information on metastatic sites, HER2 status or survival months, were unavailable; and/or (III) the follow-up duration was <1 month.

Ultimately, a total of 1,780 eligible patients passed the screening process in the study and were randomly categorized into the following two groups using R software: (I) the training group, which comprised 1,246 (70%) patients and was used to develop a nomogram; and (II) the validation group, which comprised 534 (30%) patients and was used to verify it. Moreover, to establish and additional validation cohort for our research, using a similar method, we identified 312 patients in the SEER database who met the criteria in 2016 (see *Figure 1*).

Data from the SEER research database was used in this study. The National Cancer Institute granted us access to the SEER program's data files (reference number: 17868-Nov2021). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The local ethics committee waived the requirement of ethical approval for this study, as the patient data extracted from the database were non-identifiable and available for public use for research purposes.

Variable selection

The variables in the analysis included age at diagnosis, race, marital status, T stage, N stage, grade, histopathological type, HER2 status, location, surgery, radiotherapy, chemotherapy, bone metastasis, lung metastasis, and brain metastasis. In addition, several variables were grouped into a specific category based on the SEER database classification. Age was classified into three categories (i.e., <50, 50–69,

and ≥70 years). Race was stratified as Black, White or other. The patients were allocated to three subgroups based on their marital status (i.e., married, unmarried, or other). The histological categories included duct carcinoma, lobular carcinoma, or other. The locations were classified as inner, outer, or other. The grades were classified into three categories (grades I–II, grades III–IV, and unknown). Finally, the N stage was categorized into two subcategories (N0–N1 and N2–N3).

Statistical analyses

The key results of the analysis were OS and BCSS. BCSS was defined as the period from presentation to death due to BC. OS was defined as the time from diagnosis to death from any cause or the end of follow-up. All the data analyses were performed using R software (version 4.2.1; https://www.r-project.org/).

The features at the baseline were compared using the chi-square test. A univariate Cox regression analysis was used to investigate the prognostic variables associated with both OS and BCSS in patients with HR-positive BCLM. Variables with P values less than 0.05 were considered statistically significant. In addition, a multivariate Cox regression analysis was used to identify independent risk factors.

Based on the separate prognostic indicators identified in the above analyses, nomograms were developed for OS and BCSS at 1, 3, and 5 years. Further, a unique diagnostic nomogram based on independent risk variables was established using the "rms" package. Receiver operating characteristic (ROC) curves of the nomogram and all the independent variables were created to evaluate discrimination. The associated areas under the curve (AUCs) were also determined. As a general rule, AUC values typically run from 0.5 to 1.0, with 0.5 representing random chance and 1.0 representing perfect discriminative power. A calibration plot was also used to evaluate whether the expected outcomes matched the actual findings. Subsequently, the clinical utility of the nomogram was assessed by contrasting the quantitative net benefits under varying probabilities, which were established by the difference between the expected benefit and expected loss in connection with each proceeding project strategy and therapeutic intervention tactic. This was performed using a decision curve analysis (DCA) (16).

Based on the risk ratings calculated from their nomograms, patients from the training and validation data sets were classified into low- and high-risk groups. The efficacy of the nomogram was further investigated using the Kaplan-Meier (K-M) survival curves and log-rank tests to validate whether there was a statistical difference in the survival times between the two data sets. Finally, we used the data of patients from 2016 in the SEER database for the external validation to further predict the model's reliability.

Results

Baseline characteristics

A total of 1,780 patients with BCLM who met the selection criteria were included in the study. Of these patients, 1,109 patients died during the follow-up period, of whom, 767 were in the training group and 342 were in the validation group. The R software used a 7:3 ratio to categorize all patients into the training (n=1,246) and validation cohorts (n=534). Patients aged 50–69 years (n=920, 51.7%) accounted for approximately half of all patients, followed by those aged <50 years (n=517, 29.0%) and ≥70 years (n=343, 19.3%). The most common T and N stages were T3–T4 (n=959, 53.9%) and N0–N1 (n=1,298, 72.9%), respectively. In relation to treatment, most patients opted for chemotherapy (n=1,205, 67.7%) rather than surgery (n=477, 26.8%), and 502 (28.2%) patients were selected for radiotherapy. During the diagnosis, 63.6% of patients with BCLM had bone metastasis, while only 7.9% [140] of the patients had brain metastasis. *Table 1* summarizes the clinical characteristics and demographics of the training and validation groups.

Cox proportional hazards regression analysis

We conducted a univariate analysis using the data of the 1,780 patients with HR-positive BCLM to exclude the associated key factors. P values, hazard ratios, and 95% confidence intervals (CIs) were calculated for each independent parameter. The results of the univariate and multivariate analyses for OS and BCSS are shown in *Tables 2,3*. Ultimately, nine factors, including age, marital status, grade, HER2 status, chemotherapy, surgery, bone metastasis, lung metastasis, and brain metastasis were found to be significantly associated with OS. Conversely, 10 variables, including age, marital status, T stage, grade, HER2 status, chemotherapy, surgery, bone metastasis,

Table 1 Demographic, clinical and laboratory features of patients diagnosed with HR-positive BC

Variables	Overall (n=1,780)	Training (n=1,246)	Validation (n=534)	P
Age				0.950
<50 years	517 (29.0)	364 (29.2)	153 (28.7)	
50–69 years	920 (51.7)	644 (51.7)	276 (51.7)	
≥70 years	343 (19.3)	238 (19.1)	105 (19.7)	
Race				0.908
Black	315 (17.7)	219 (17.6)	96 (18.0)	
White	1,304 (73.3)	912 (73.2)	392 (73.4)	
Other	161 (9.0)	115 (9.2)	46 (8.6)	
Marital status				0.437
Married	802 (45.1)	557 (44.7)	245 (45.9)	
Unmarried	438 (24.6)	300 (24.1)	138 (25.8)	
Other	540 (30.3)	389 (31.2)	151 (28.3)	
Location				0.116
Inner	184 (10.3)	120 (9.6)	64 (12.0)	
Outer	1,065 (59.8)	739 (59.3)	326 (61.0)	
Other	531 (29.8)	387 (31.1)	144 (27.0)	
Histopathology				0.774
Duct carcinoma	1,378 (77.4)	961 (77.1)	417 (78.1)	
Lobular carcinoma	132 (7.4)	96 (7.7)	36 (6.7)	
Other	270 (15.2)	189 (15.2)	81 (15.2)	
Grade				0.065
I–II	735 (41.3)	528 (42.4)	207 (38.8)	
III–IV	801 (45.0)	562 (45.1)	239 (44.8)	
Unknown	244 (13.7)	156 (12.5)	88 (16.5)	
HER2				0.340
Negative	1,122 (63.0)	776 (62.3)	346 (64.8)	
Positive	658 (37.0)	470 (37.7)	188 (35.2)	
T				0.114
T1–T2	821 (46.1)	559 (44.9)	262 (49.1)	
T3–T4	959 (53.9)	687 (55.1)	272 (50.9)	
N				0.898
N0–N1	1,298 (72.9)	907 (72.8)	391 (73.2)	
N2–N3	482 (27.1)	339 (27.2)	143 (26.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Overall (n=1,780)	Training (n=1,246)	Validation (n=534)	P
Bone metastasis				0.739
No	648 (36.4)	450 (36.1)	198 (37.1)	
Yes	1,132 (63.6)	796 (63.9)	336 (62.9)	
Lung metastasis				0.586
No	1,165 (65.4)	810 (65.0)	355 (66.5)	
Yes	615 (34.6)	436 (35.0)	179 (33.5)	
Brain metastasis				0.387
No	1,153 (92.5)	1,153 (92.5)	487 (91.2)	
Yes	140 (7.9)	93 (7.5)	47 (8.8)	
Surgery				0.944
No	1,303 (73.2)	911 (73.1)	392 (73.4)	
Yes	477 (26.8)	335 (26.9)	142 (26.6)	
Chemotherapy				1.000
No/unknown	575 (32.3)	402 (32.3)	173 (32.4)	
Yes	1,205 (67.7)	844 (67.7)	361 (67.6)	
Radiation therapy				0.110
No/unknown	1,278 (71.8)	909 (73.0)	369 (69.1)	
Yes	502 (28.2)	337 (27.0)	165 (30.9)	

In relation to marital status, 'other' comprises patients who are divorced, separated or widowed or whose marital status is unknown. In relation to race, 'other' comprises American Indian, Alaska Native, Asian, and Pacific Islander patients. In relation to location, other includes other types of carcinomas. HR, hormone receptor; BC, breast cancer; HER2, human epidermal growth factor receptor 2.

Table 2 Univariate and multivariate Cox regression analyses of OS in the training group

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age				
<50 years	Reference		Reference	
50–69 years	1.47 (1.26, 1.70)	<0.001	1.25 (1.10, 1.42)	0.003
≥70 years	2.44 (2.03, 2.93)	<0.001	1.65 (1.39, 1.96)	<0.001
Race				
Black	Reference			
White	0.86 (0.73, 1.01)	0.078		
Other	0.85 (0.65, 1.10)	0.219		

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Marital status				
Married	Reference		Reference	
Unmarried	1.12 (0.95, 1.32)	0.147	1.08 (0.94, 1.24)	0.343
Other	1.43 (1.24, 1.65)	<0.001	1.23 (1.08, 1.39)	0.006
Location				
Inner	Reference			
Outer	0.98 (0.77, 1.24)	0.890		
Other	1.18 (0.94, 1.46)	0.137		
Histopathology				
Duct carcinoma	Reference		Reference	
Lobular carcinoma	1.17 (0.93, 1.48)	0.166	1.13 (0.93, 1.39)	0.291
Other	1.21 (1.02, 1.44)	0.025	1.12 (0.96, 1.30)	0.208
Grade				
I–II	Reference		Reference	
III–IV	1.09 (0.95, 1.25)	0.182	1.43 (1.27, 1.61)	<0.001
Unknown	1.40 (1.15, 1.70)	<0.001	1.21 (1.02, 1.44)	0.061
HER2				
Negative	Reference		Reference	
Positive	0.64 (0.56, 0.73)	<0.001	0.70 (0.62, 0.79)	<0.001
T				
T1–T2	Reference		Reference	
T3–T4	1.28 (1.13, 1.45)	<0.001	1.12 (1.00, 1.25)	0.074
N				
N0–N1	Reference		Reference	
N2–N3	0.86 (0.74, 0.99)	0.038	0.89 (0.78, 1.00)	0.128
Bone metastasis				
No	Reference		Reference	
Yes	1.57 (1.40, 1.76)	<0.001	1.41 (1.25, 1.58)	<0.001
Lung metastasis				
No	Reference		Reference	
Yes	1.54 (1.39, 1.72)	<0.001	1.28 (1.14, 1.44)	<0.001
Brain metastasis				
No	Reference		Reference	
Yes	1.62 (1.35, 1.95)	<0.001	1.48 (1.22, 1.81)	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Surgery				
No	Reference		Reference	
Yes	0.55 (0.48, 0.64)	<0.001	0.69 (0.60, 0.79)	<0.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.51 (0.45, 0.58)	<0.001	0.61 (0.54, 0.69)	<0.001
Radiation therapy				
No/unknown	Reference			
Yes	0.96 (0.83, 1.10)	0.591		

In relation to marital status, 'other' comprises patients who are divorced, separated or widowed or whose marital status is unknown. In relation to race, 'other' comprises American Indian, Alaska Native, Asian, and Pacific Islander patients. In relation to location, other includes other types of carcinomas. OS, overall survival; CI, confidence interval; HER2, human epidermal growth factor receptor 2.

Table 3 Univariate and multivariate Cox regression analyses of BCSS in the training group

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age				
<50 years	Reference		Reference	
50–69 years	1.45 (1.25, 1.69)	<0.001	1.24 (1.09, 1.41)	0.005
≥70 years	2.12 (1.75, 2.56)	<0.001	1.46 (1.23, 1.75)	<0.001
Race				
Black	Reference			
White	0.81 (0.68, 0.95)	0.012		
Other	0.82 (0.63, 1.07)	0.159		
Marital status				
Married	Reference		Reference	
Unmarried	1.16 (0.98, 1.36)	0.073	1.14 (0.99, 1.31)	0.120
Other	1.43 (1.23, 1.66)	<0.001	1.22 (1.07, 1.39)	0.011
Location				
Inner	Reference			
Outer	1.08 (0.85, 1.38)	0.509		
Other	1.20 (0.96, 1.51)	0.098		
Histopathology				
Duct carcinoma	Reference			
Lobular carcinoma	1.22 (0.96, 1.54)	0.094		
Other	1.06 (0.88, 1.28)	0.482		

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Grade				
I–II	Reference		Reference	
III–IV	1.10 (0.96, 1.27)	0.141	1.40 (1.24, 1.58)	<0.001
Unknown	1.35 (1.11, 1.64)	0.002	1.15 (0.98, 1.36)	0.144
HER2				
Negative	Reference		Reference	
Positive	0.60 (0.52, 0.69)	<0.001	0.65 (0.57, 0.74)	<0.001
T				
T1–T2	Reference		Reference	
T3–T4	1.34 (1.18, 1.53)	<0.001	1.20 (1.07, 1.34)	0.007
N				
N0–N1	Reference			
N2–N3	0.90 (0.78, 1.04)	0.186		
Bone metastasis				
No	Reference		Reference	
Yes	1.51 (1.32, 1.74)	<0.001	1.33 (1.18, 1.51)	<0.001
Lung metastasis				
No	Reference		Reference	
Yes	1.52 (1.33, 1.74)	<0.001	1.26 (1.12, 1.41)	<0.001
Brain metastasis				
No	Reference		Reference	
Yes	1.70 (1.36, 2.12)	<0.001	1.48 (1.22, 1.79)	<0.001
Surgery				
No	Reference		Reference	
Yes	0.56 (0.48, 0.66)	<0.001	0.70 (0.61, 0.81)	<0.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.50 (0.44, 0.57)	<0.001	0.62 (0.55, 0.71)	<0.001
Radiation therapy				
No/unknown	Reference			
Yes	0.98 (0.85, 1.13)	0.801		

In relation to marital status, 'other' comprises patients who are divorced, separated or widowed or whose marital status is unknown. In relation to race, 'other' comprises American Indian, Alaska Native, Asian, and Pacific Islander patients. In relation to location, other includes other types of carcinomas. BCSS, breast cancer-specific survival; CI, confidence interval; HER2, human epidermal growth factor receptor 2.

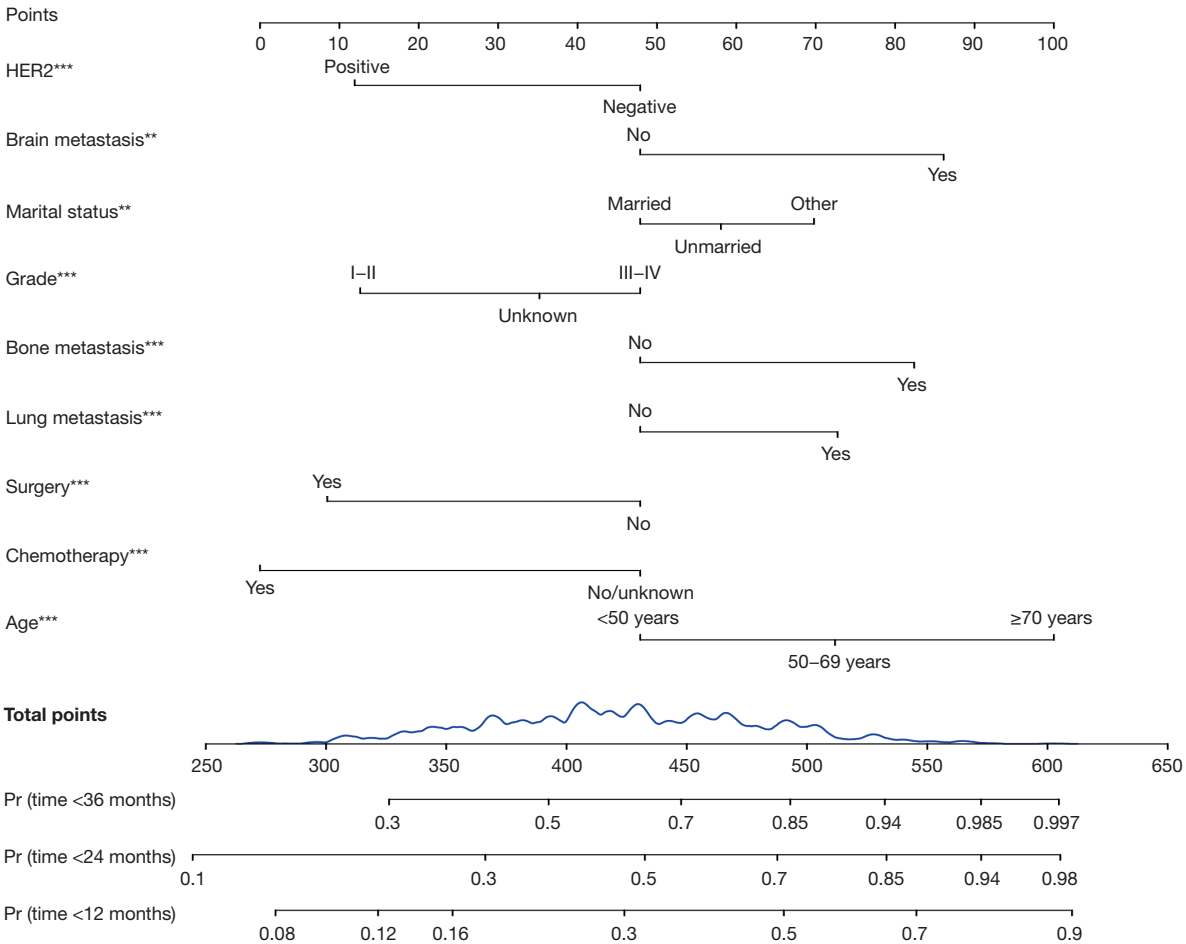

Figure 2 The nomogram to predict 1-, 2-, and 3-year OS of HR-positive BC patients with liver metastasis. **, P<0.01; ***, P<0.001. HER2, human epidermal growth factor receptor 2; OS, overall survival; HR, hormone receptor; BC, breast cancer.

lung metastasis, and brain metastasis, were found to be independent risk factors for BCSS.

Prognostic nomogram development and validation

A nomogram is a user-friendly prediction tool that enables physicians and patients to calculate the ratings of variables to evaluate the likelihood of survival (17). A nomogram for OS and BCSS was established by incorporating the independent prognostic variables (see *Figures 2*,*3*). The ROC curve analysis showed that the AUCs of the nomogram for 1-, 2-, and 3-year OS were 0.724, 0.730, and 0.738 in the training group, 0.731, 0.715, and 0.716 in the validation group and 0.809, 0.785, and 0.758 in the external validation cohort, respectively (see *Figure 4*). For the BCSS model, the AUCs at 1-, 2-, and 3-year were 0.709, 0.719, and 0.724 in the training cohort, 0.775, 0.777, and 0.781 in the validation cohort and 0.807, 0.794, and 0.763 in the external cohort, respectively (see *Figure 5*). These results demonstrate that the OS and BCSS nomograms had a good discriminatory ability. Additionally, the calibration curves for OS and BCSS in the training, validation, and external groups at 1, 2, and 3 years were almost parallel to the standard curve, demonstrating a strong connection between the predictions of the model and the actual observational findings (see *Figures 6*,*7*), respectively. The results of the DCA showed that the nomograms exhibited a greater net benefit in all groups at 1, 2, and 3 years (see *Figures 8*,*9*). Further, according to our models, we calculated the prognostic risk score of each patient with HR-positive BCLM. The patients were the categorized into low- and high-risk groups based on their scores. The K-M survival

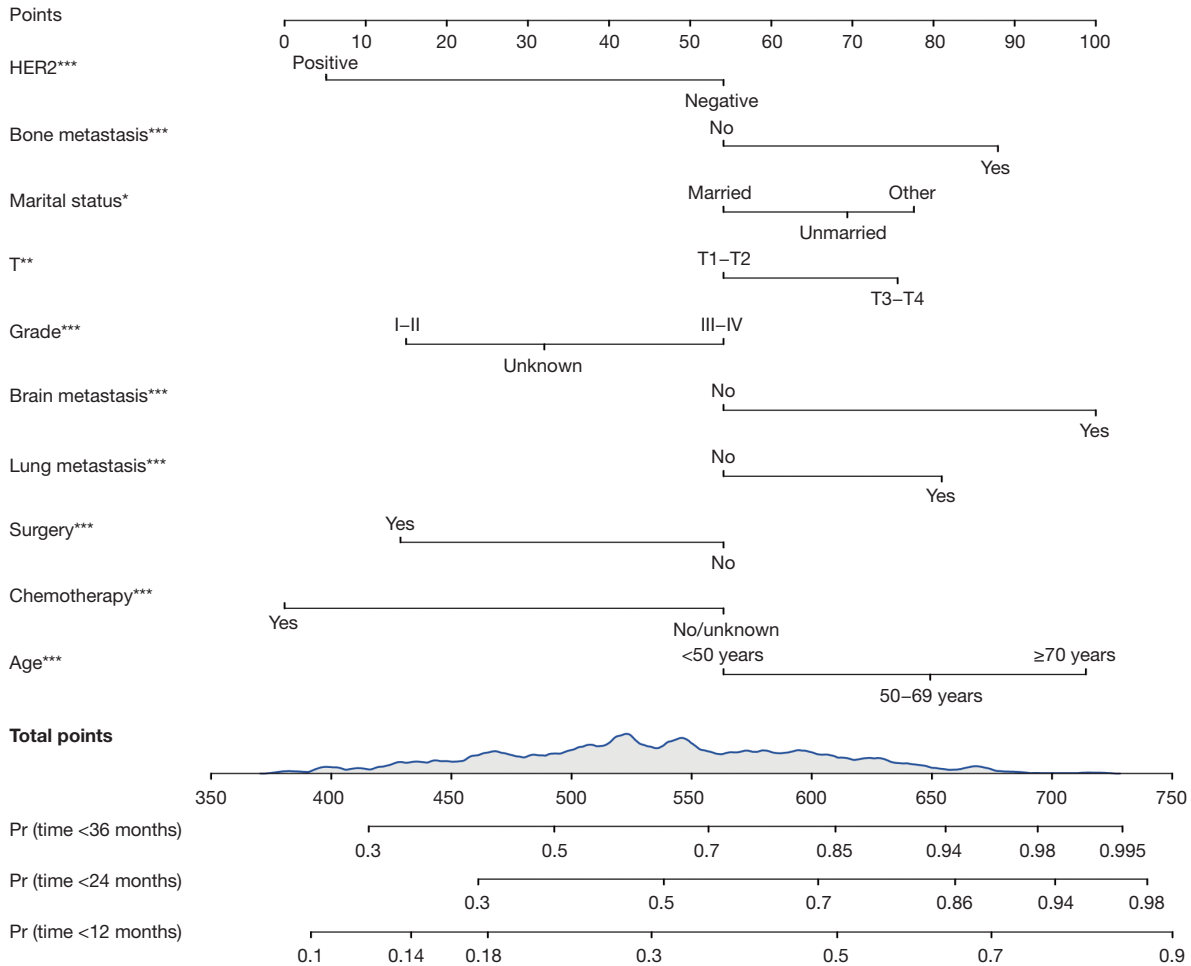

Figure 3 The nomogram to predict 1-, 2-, and 3-year BCSS of HR-positive BC patients with liver metastasis. *, P<0.05; **, P<0.01; ***, P<0.001. HER2, human epidermal growth factor receptor 2; BCSS, breast cancer-specific survival; HR, hormone receptor; BC, breast cancer.

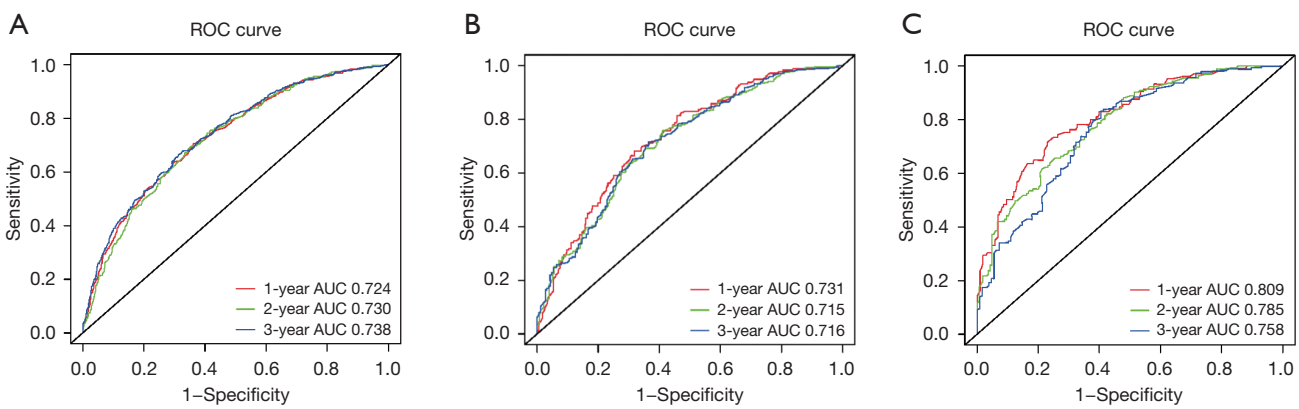

Figure 4 The ROC curves for the OS model for the training (A), internal validation (B), and external (C) cohorts. ROC, receiver operating characteristic; AUC, area under the curve; OS, overall survival.

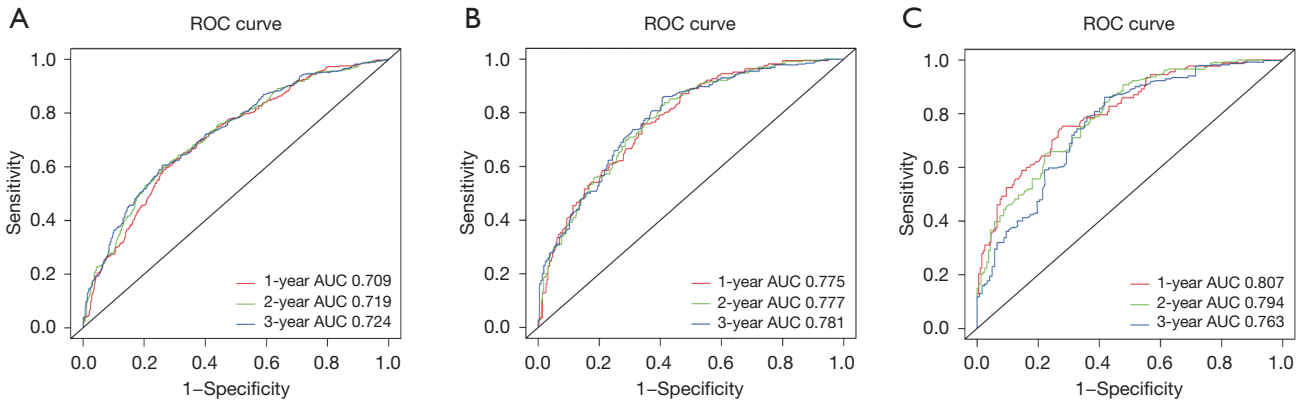

Figure 5 The ROC curves for the BCSS model for the training (A), internal validation (B) and external (C) cohorts. ROC, receiver operating characteristic; AUC, area under the curve; BCSS, breast cancer-specific survival.

analysis of the training, validation, and external groups showed significant survival differences in both cohorts (see *Figures 10*,*11*).

Discussion

BCLM is a heterogeneous illness with various histopathological and molecular characteristics that are linked to various clinical consequences. HR-positive BC, which is dependent on estrogen for growth and survival, accounts for 70–80% of all BCs (18,19). In addition to traditional treatments, such as surgery and chemotherapy, endocrine therapy has emerged as a targeted treatment method for this population subset due to its specific gene expression (20). However, despite dramatic advances in systemic therapy, the prognosis of patients with BCLM remains poor (14). Thus, to advance the research further, we retrospectively analyzed the OS and BCSS of selected patients with liver metastasis from the SEER database, completed the first detailed retrospective analysis using a multicenter cohort and established two nomograms to assist in making treatment decisions for these patients.

Similar to the findings of previous studies (21,22), we found that age was a major independent prognostic indicator, with younger women surviving longer than older women. Some scholars have emphasized that the risk of death associated with BC increases with age, and this is even more pronounced in later years (i.e., among patients aged >70 years) (23). Advanced disease, which is linked to the delayed time to diagnosis, could be an essential contributor to these age-related prognostic disparities (24). In addition, older women present with larger tumors and have higher rates of lymph node metastasis, which may explain their relatively high mortality rates (25-27).

We also found that marriage was an independent protective factor for OS and BCSS in our adult patients with BCLM, which is consistent with the results of a previous meta-analysis by Yuan *et al.* (28). When symptoms first appear, intimate partners may notice them and advise their spouses to seek immediate medical attention (7,28). Additionally, single patients have been shown to experience more distress, depression, and anxiety than married patients (7,28). The results of previous studies also support this hypothesis. Notably, Shrout *et al.* reported that at 6 and 18 months after therapy, married women experienced reductions in their depressive symptoms, tension, and exhaustion, regardless of whether they were content or dissatisfied with their marriages. Conversely, depressive symptoms, stress, exhaustion, and pain did not diminish with time in unmarried (i.e., single, divorced/separated, or widowed) women and remained elevated at 6 and 18 months after the conclusion of therapy (29).

As metastatic BC is incurable in almost all afflicted individuals, surgical therapy is typically only employed for alleviation in metastatic illnesses (30). Thus, performing surgery on such patients remains controversial. In our study, patients who underwent surgery at the main cancer location had a relatively long median OS or BCSS. Rashaan *et al.* theorized that the resection of the malignant tumor results in the restoration of the immune system and the elimination of cancer stem cells, which are believed to oversee the start of tumor development, growth, metastatic properties,

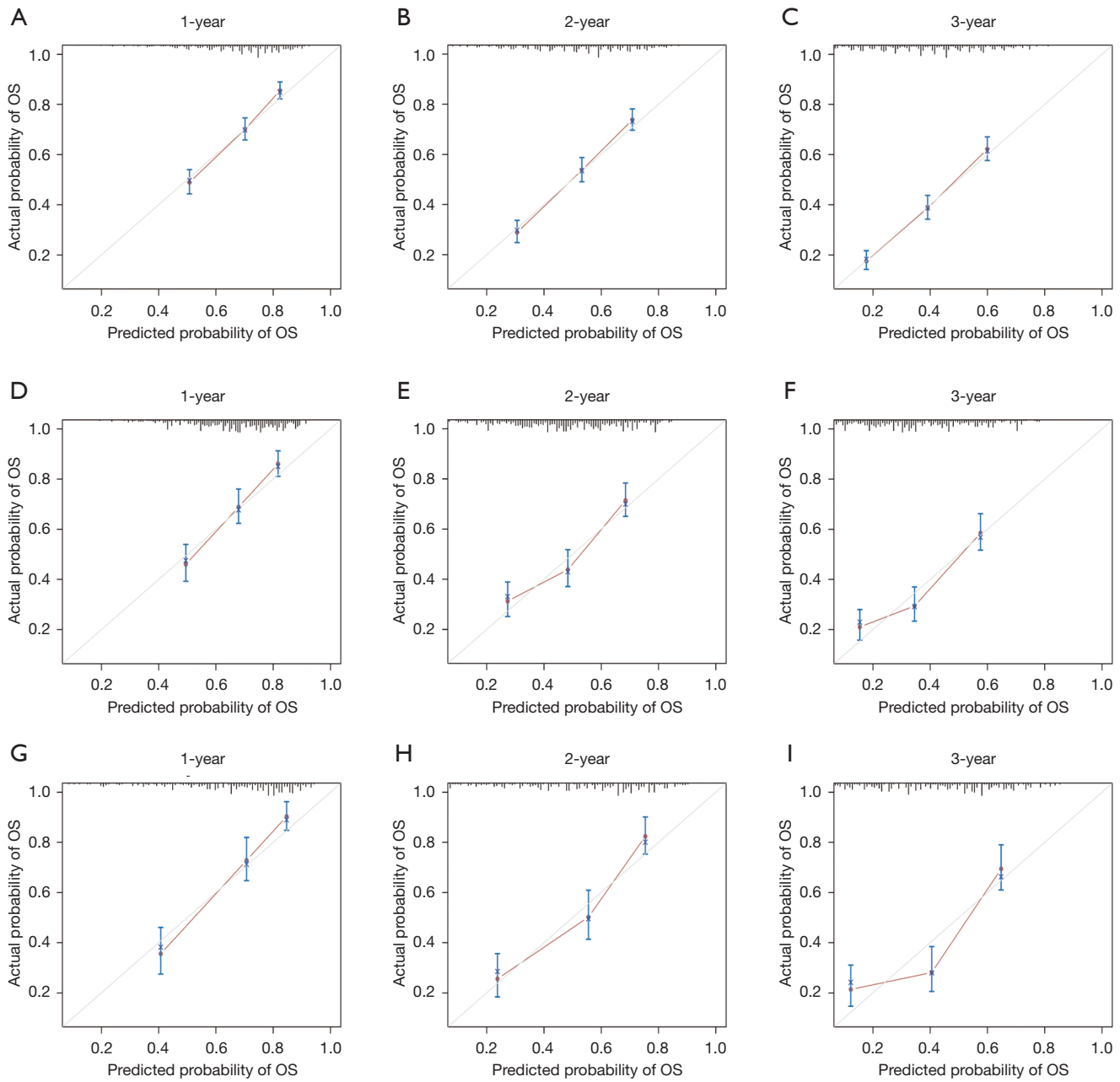

Figure 6 Calibration curves for predicting patients' OS at 1-, 2-, and 3-year for the training (A-C), validation (D-F), and external (G-I) cohorts. OS, overall survival.

and tumor recurrence (31). Another study by Xiong *et al.* found that the surgical excision of the initial malignancy enhanced the survival of individuals with *de novo* stage IV BC (32), which is consistent with the results of our study. According to our study, chemotherapy is another crucial predictor and appears to exert a similar effect by decreasing cancer-related complications by eradicating or suppressing cancer cells, postponing relapse, and lengthening survival time. Unfortunately, because our data lacked specific information on treatment strategies, we were unable to examine how various chemotherapy regimens affected survival rates. Radiotherapy did not affect patient prognosis

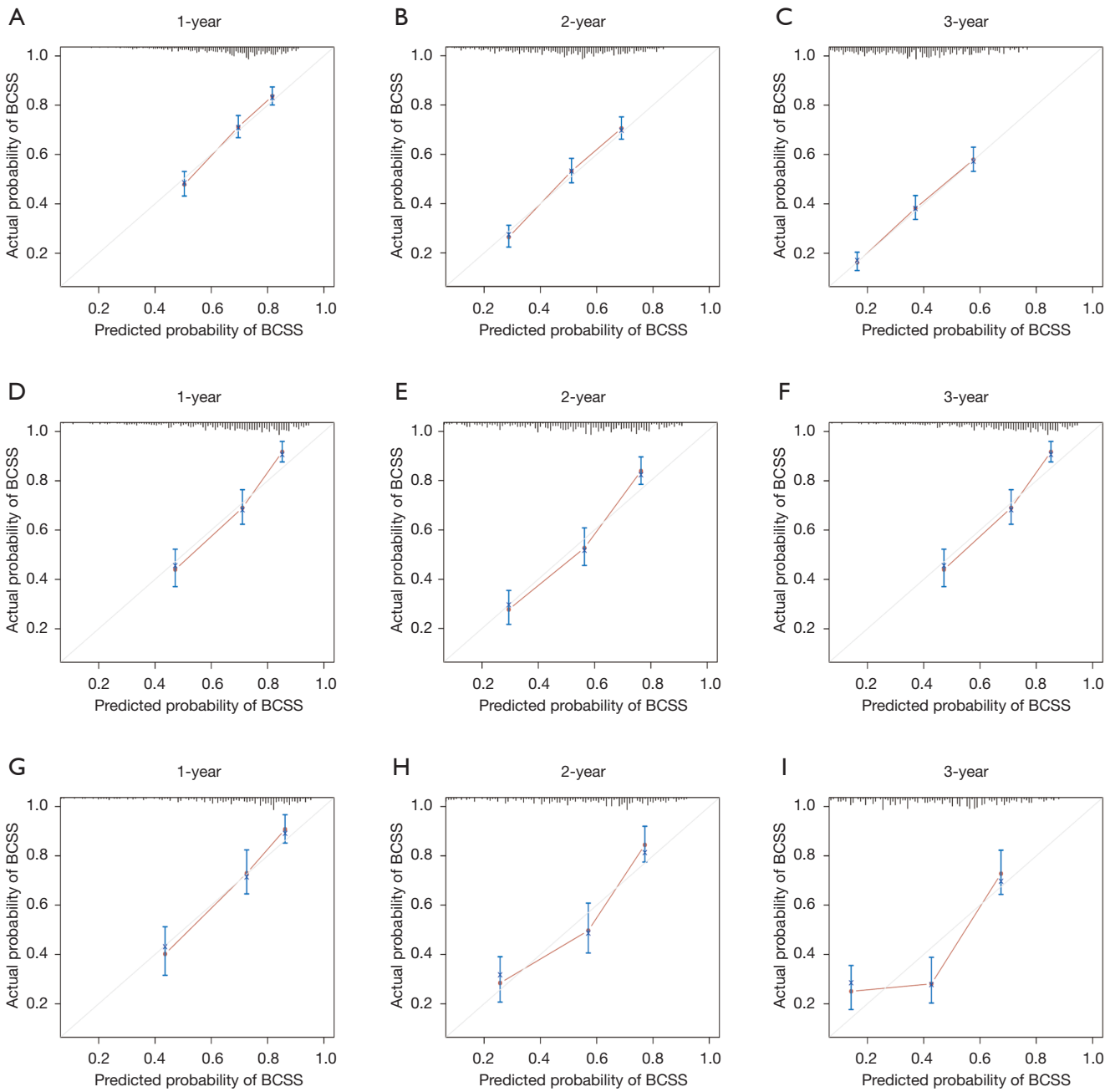

Figure 7 Calibration curves for predicting patients' BCSS at 1-, 2-, and 3-year for the training (A-C), validation (D-F), and external (G-I) cohorts. BCSS, breast cancer-specific survival.

as expected. Indeed, according to a previous study by the Early Breast Cancer Trialists' Collaborative Group, patients with early-stage invasive BC who receive radiotherapy live longer (33). In addition, while there is some evidence that breast radiotherapy and the quantity of the dosage are independently correlated with survival in patients with metastatic cancer, the incurable nature of metastatic disease appears to outweigh any marginal survival benefit provided by breast radiotherapy (34-36).

Despite previous studies linking HER2 overexpression to a negative prognosis (37), our study showed that HER2 positivity was strongly associated with a favorable outcome.

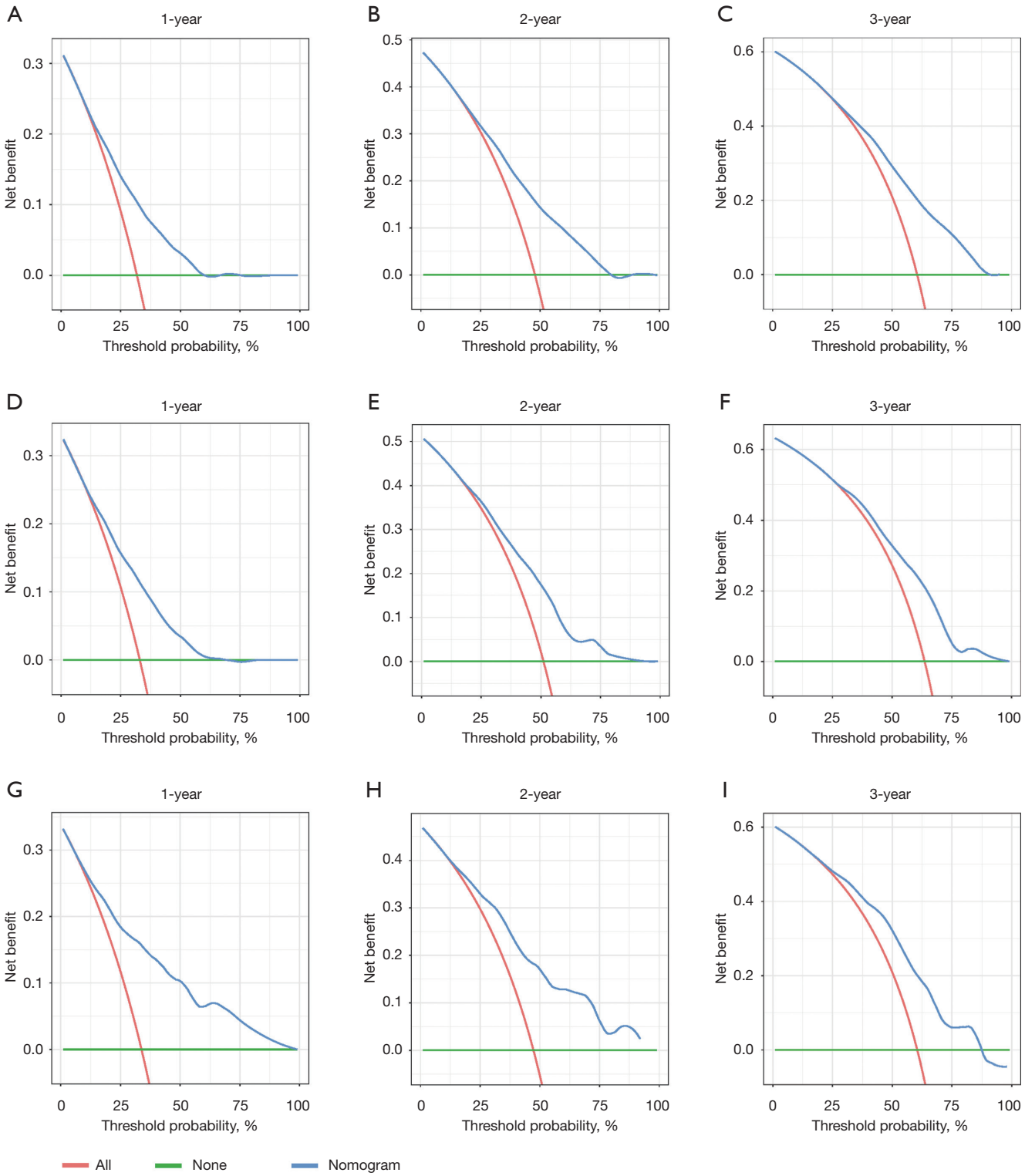

Figure 8 The DCA of the nomogram for predicting 1-, 2-, and 3-year OS for the training (A-C), validation (D-F), and external (G-I) cohorts. DCA, decision curve analysis; OS, overall survival.

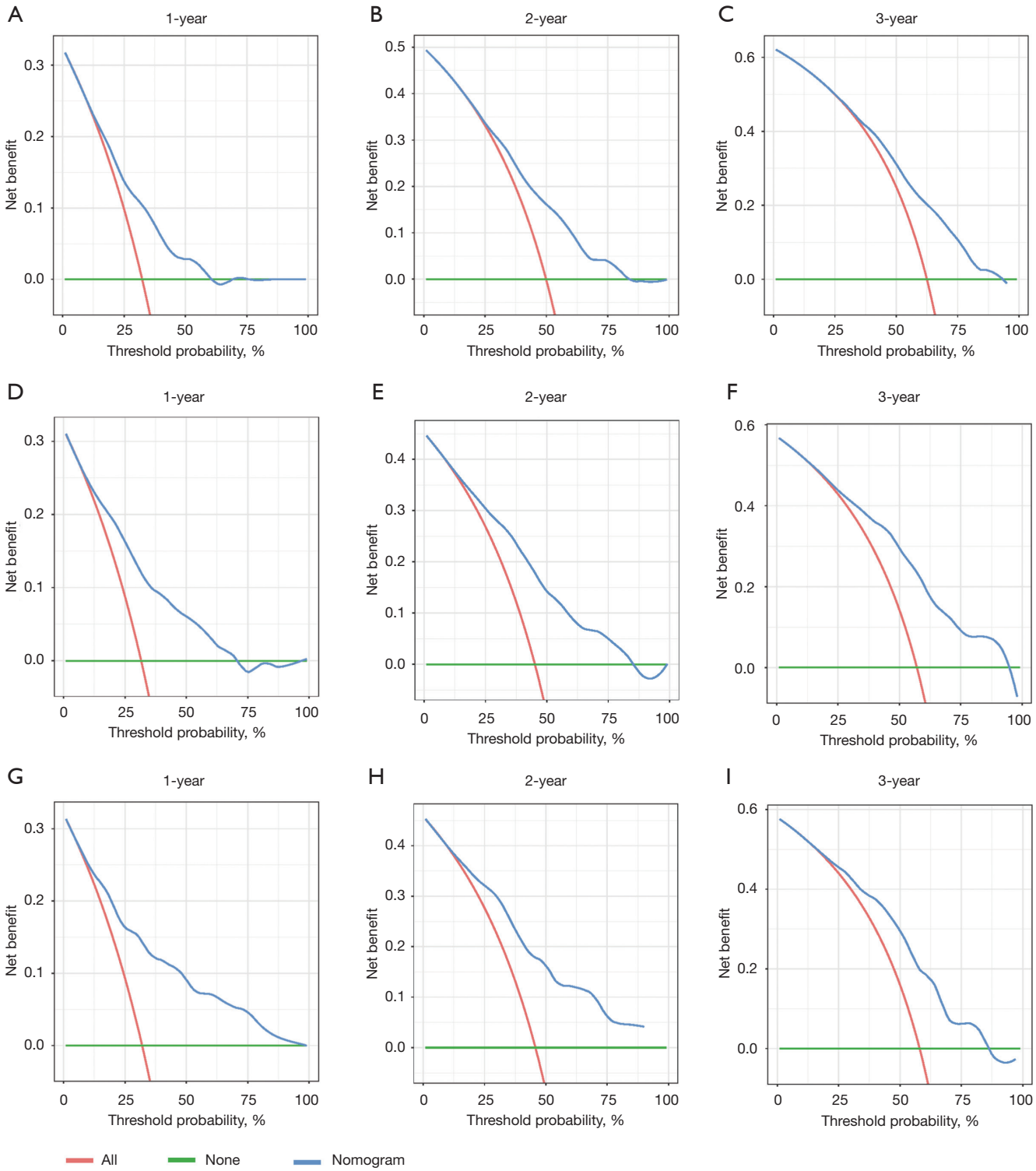

Figure 9 The DCA of the nomogram for predicting 1-, 2-, and 3-year BCSS for the training (A-C), validation (D-F), and external (G-I) cohorts. DCA, decision curve analysis; BCSS, breast cancer-specific survival.

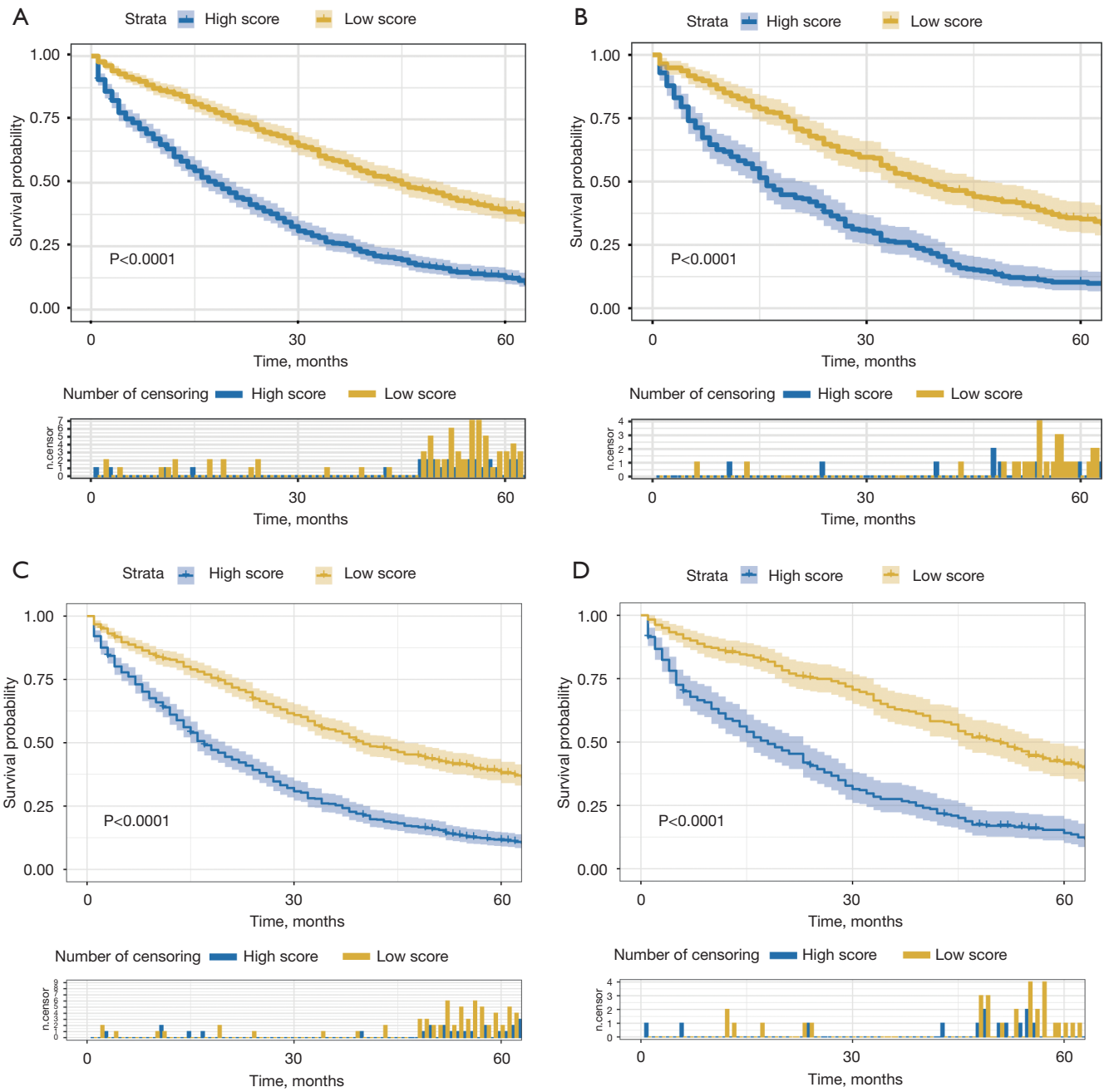

Figure 10 The K-M survival curves of the risk group stratification for OS in the training (A) and validation (B) cohorts and for BCSS in the cohort (C) and validation (D) cohort. K-M, Kaplan-Meier; OS, overall survival; BCSS, breast cancer-specific survival.

This is due to the long-term benefits of trastuzumab with paclitaxel or docetaxel. In addition to the above-mentioned points, T stage, grade, and metastases (other than liver metastasis) were also identified as significant prognostic factors. In our analysis, T stage was a separate predictive factor for BCSS but not for OS. However, this result may be related to the small amount of available data.

To the best of our knowledge, this was the first study to develop nomograms to predict the prognosis of HR-positive BCLM patients. We developed nomograms based

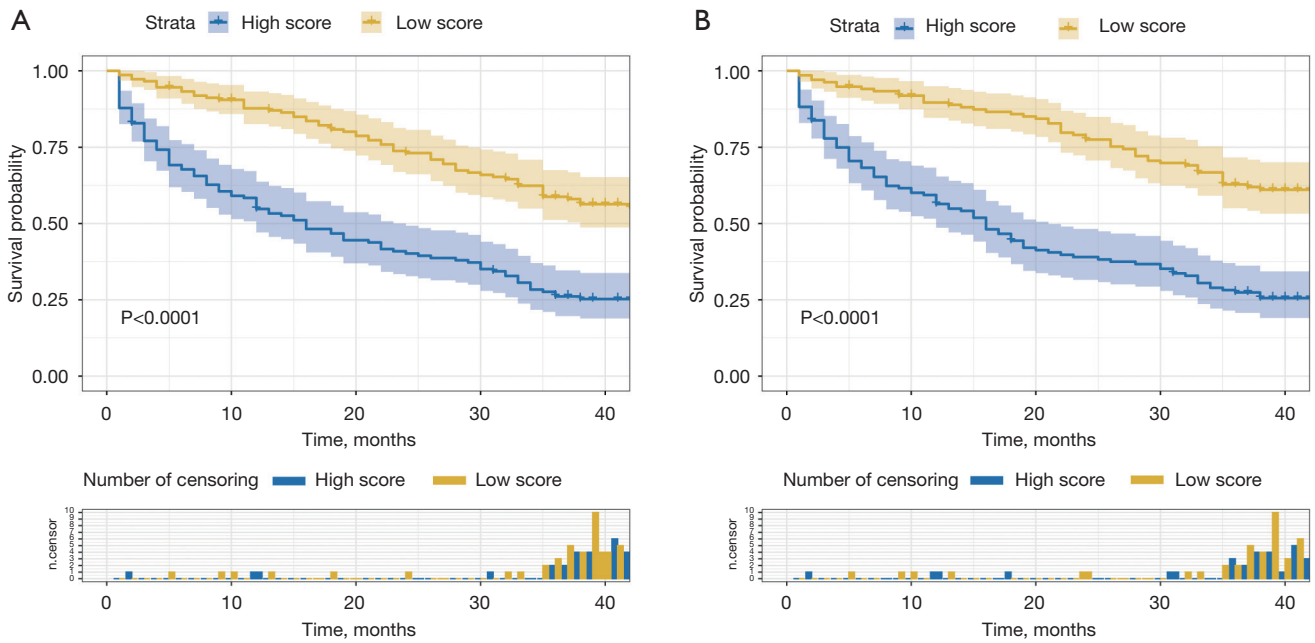

Figure 11 The K-M survival curves of the risk group stratification for OS (A) and BCSS (B) in the external cohort. K-M, Kaplan-Meier; OS, overall survival; BCSS, breast cancer-specific survival.

on the Cox proportional hazards model to predict survival. The calibration plots in our study indicated the standard contractual in the nomograms predicting OS and BCSS to ensure the accuracy of the developed nomograms. Further, ROC curves were constructed and the resulting time-dependent AUCs were used to demonstrate the specific ability of the model. The AUC for each of the study's nomograms was greater than 0.7, indicating that the models could predict patient prognosis. Our study used other appropriate verification techniques and revisited the SEER database to reassess the performance of the nomograms in the absence of external data. Overall, these nomograms were able to predict the likelihood of survival for patients receiving various types of therapies with a high degree of confidence. Thus, these nomograms could help physicians make better clinical decisions.

It should be noted that distinct histopathological classifications of BC are frequently associated with varying prognoses in clinical practice. For example, patients diagnosed with pure mucinous carcinoma often exhibit more favorable prognostic outcomes, and consequently distinctive treatment approaches have been established to treat this particular subtype (38). However, it should be noted that due primarily to constraints stemming from sample size, the categorization of patients in this study was limited to invasive lobular carcinoma, invasive ductal carcinoma and other unspecified categories. Further, in this study, histopathology did not emerge as an independent risk factor for patients. In addition, our models enabled the personalized prediction of patients with HR-positive BCLM. Conversely, the conventional American Joint Committee on Cancer-TNM staging system adds scores for each variable to screen high- and low-risk patients for various readily available treatments. This is consistent with the growing emphasis on the individualized treatment of patients with cancer. For example, more aggressive care and therapy may be appropriate for high-risk patients. Simultaneously, avoiding unnecessary therapy can lessen the physical and financial strain placed on low-risk patients.

This study had certain limitations. First, due to its retrospective design, this study was inevitably flawed by bias. Second, the SEER database lacks detailed data on therapeutic approaches, including operations, chemotherapy regimens, and endocrine and targeted medicines, which might have affected our findings. Third, since the SEER database only contains data regarding a patient's condition at the first diagnosis, we were unable to obtain any data on individuals who subsequently developed liver metastasis.

Fourth, most of our patients were White (73.3%) or Black (17.7%), but race did not affect the prognosis of patients with BCLM in this study. However, it is currently unclear whether our model applies to other racial groups. Further, it is important to acknowledge that the absence of comprehensive data regarding patient comorbidities and health status in this study represents a significant limitation that could potentially influence our approach to practical treatment strategies. However, it is crucial to note that efforts will be made in subsequent research endeavors to address and rectify this limitation, ensuring a more thorough and informed analysis of these factors that are integral to patient care and decision-making processes.

Conclusions

This study created nomograms to obtain individualized survival estimates for patients with HR-positive BCLM. Additionally, a thorough analysis of the prognosis of these patients was performed using the SEER population-level information. Our nomograms will aid in clinical decision making and can be used to reliably and successfully forecast patient survival data.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-874/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-874/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-874/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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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