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ORIGINAL ARTICLE

Nomograms predicting overall survival and cancer-specific survival in metaplastic breast cancer patients

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Summary

Purpose: *To establish and validate nomograms to predict the overall survival (OS) and cancer-specific survival (CSS) of metaplastic breast cancer(MBC) patients.*

Methods: *We retrospectively enrolled 948 patients with MBC from the Surveillance, Epidemiology and End Results (SEER) database between 2010 and 2016.Univariate and multivariate Cox analyses were used to determine independent prognostic factors to be included in nomograms for predicting the probabilities of OS and CSS at 1, 2, and 3 years. The concordance index (C-index), receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis were used to check the effectiveness and clinical application of the models.*

Results: *In total, 948 patients were enrolled and randomly assigned to the training (n=664) and validation (n=284) cohorts. Age, tumor size, ethnicity, AJCC stage, radiotherapy, and surgery were identified as independent prognostic factors for OS, while age, tumor size, and AJCC stage were identified as independent prognostic factors for CSS (all p <0.05) and further incorporated into the nomograms. The C-indices for OS and CSS predictions were 0.790 and 0.792 for internal validation and 0.772 and 0.768 for external validation. Both the internal and external validation calibration plots showed excellent agreement between the nomogram predictions and actual survival. ROC curves demonstrated good discriminative ability of the nomograms.*

Conclusions: *Nomograms were developed to predict OS and CSS in patients with MBC. These nomograms can help clinicians make more accurate survival assessments and identify patients at high risk of death.*

Key words: *cancer-specific survival, MBC, nomogram, overall survival, SEER database*

Introduction

Breast cancer (BC) is the most common cancer in women worldwide [1,2]. The disease is highly heterogeneous, with wide variations in prognosis [3].Metaplastic breast cancer (MBC) is a rare histological variant of BC that is thought to be more aggressive than typical invasive ductal carcinoma [4,5]. MBC is associated with high tumor grades, large tumor sizes, less advanced nodal involvement, and high rates of metastasis [6,7].MBC accounts for 0.2-5% of all breast cancers, yet the lack of an accepted definition may contribute to the varying prevalence rates [5].Most MBCs have a triple-negative phenotype, with no estrogen receptor (ER) or progesterone receptor (PR) expression and no overexpression of ERBB2 [8,9]. The clinical presentation of MBC is characterized by a rapidly growing tumor mass at diagnosis, with a higher incidence of stage III and IV disease and a higher risk of local recurrence than invasive ductal carcinomas [10,11]. MBC is typically chemoresistant.

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Neoadjuvant chemotherapy and metastatic treatment are of limited efficacy for reducing tumor burden and preventing disease progression [12]. Survival is lower in MBC patients than in non-MBC patients [13,14]. Therefore, accurate estimates of MBC patient prognoses based on clinical characteristics would help clinicians provide appropriate individual treatment.

The Surveillance, Epidemiology, and End Results (SEER) program covers approximately 30% of the population in the United States [15,16]. It provides complete patient data, including demographic, clinical and follow-up data updated annually by the National Center for Health Statistics. MBC is a rare disease, so we utilized the population-based SEER database to identify patients with primary MBC for analysis. Nomograms are useful scoring and visual prediction tools that estimate the survival rate of individual patients with greater accuracy than the widely used American Joint Committee on Cancer (AJCC) TNM staging system. Nomograms have been widely used in a variety of cancers [17,18] and are based on a series of factors.

The aim of this study was to establish nomograms for predicting long-term overall survival (OS) and cancer-specific survival (CSS) based on a variety of clinical characteristics to improve treatment and follow-up strategies for patients with MBC.

Methods

Ethics statement

This study was approved by the Ethics Committee of Yinchuan Maternal and Child Health Hospital Cancer Center. Data published from the SEER database do not require informed consent from patients because cancer is a reportable disease in every state in the United States.

Data source

The SEER database was used to identify patients diagnosed with MBC from 2010 to 2016. Patients with a diagnosis of BC and a histological type identified as MBC (8575/3) according to the International Classification of Cancer Diseases (ICD-O-3) were included. This was a retrospective cohort study using data from the SEER database. SEER collects cancer incidence data from population-based cancer registries covering approximately 34.6% of the US population [19]. The information in the SEER database is accrued from 18 regional cancer registries, including information on patients' demographics, cancer diagnosis, and treatment, as well as the cause of death [19].

Patient qualification and study variables

The SEER database was accessed using SEER * Stat software (version 8.3.6, National Cancer Institute, Washington DC, USA), and a data use agreement was signed for this study. Patients were included in the study according to the following inclusion and exclusion criteria:

Table 1. The demographic and clinicopathological variables of the training set and validation set of SEER

Variables	*n (%)*
Entire	948 (100)
Age, years	
≤50	212 (22.3)
51-70	443 (46.7)
>70	293 (31)
Race	
White	722 (76.2)
Not-white	226 (23.8)
Sex	
Female	945 (99.6)
Male	3 (0.4)
Laterality	
Left	477 (50.3)
Right	471 (49.7)
Grade	
I	23 (2.4)
II	124 (13.1)
III	778 (82.1)
IV	23 (2.4)
AJCC stage*	
I	210 (22.2)
II	564 (59)
III	131 (13.8)
IV	43 (5)
T	
T1	232 (24.5)
T2	477 (50.3)
T3	157 (16.6)
T4	82 (8.6)
N	
N0	722 (76.2)
N1	154 (16.2)
N2	48 (5.1)
N3	24 (2.5)
M	
M0	905 (95.5)
M1	43 (4.5)
Breast subtype	
1HR+/HER2- (Luminal A)	235 (24.8
2HR+/HER2+ (Luminal B)	21 (2.2)
3HR-/HER2+ (HER2 enriched)	37 (4)
4HR-/HER2- (Triple Negative)	655 (69)
Surgery	
No	32 (3.4)
Yes	916 (96.6)
Radiotherapy	
No	470 (49.6)
Yes	478 (50.4
Chemotherapy	
No	298 (31.4)
Yes	650 (68.6)
Marital status	
No	425 (44.8)
Yes	523 (55.2)

*AJCC: American Joint Committee on Cancer TNM staging system

the inclusion criteria were as follows: (1) the patient was diagnosed with MBC; (2) BC was the first primary malignant tumor; and (3) the follow-up time was greater than 1 month. The exclusion criteria were as follows: (1) unknown tumor grade; (2) missing follow-up data; and (3) unknown information on molecular subtypes. A total of 27 variables were selected in this study, including patient ID, follow-up (OS,CSS), race, age, laterality, tumor size, grade, AJCC stage 7th edition (2010+) I-IV, TNM stage, metastasis status (bone, brain, lung, liver), BC molecular subtype, hormone receptor status (ER,PR), human epidermal growth factor receptor 2 (HER2) status, surgery, radiotherapy, chemotherapy, marital status, insurance, etc.

Statistics

Based on univariate and multivariate Cox regression analyses, prognostic nomograms for 1-, 2-, and 3-year OS and CSS were constructed. Internal and external validation were performed for the prognostic nomograms. Harrell's concordance index (C-index) was used to evaluate the performance of the prognostic nomograms [20]. C-indices ranged from 0.5 to 1.0, representing poor to great concordance or goodness-of-fit [21]. Calibration curves were constructed to compare the consistency of the predicted survival with the observed survival. Receiver operating characteristic (ROC) curves were used to measure the discriminative ability of the nomogram. Decision curve analysis (DCA) was used to evaluate the clinical application of the nomograms. SPSS 25.0 software (IBM Corp, Armonk, NY, USA) was used to perform the chi-square test and univariate and multivariate Cox analyses. The RMS software package in R software (version 3.6.1) was used to construct and validate the prognostic nomograms. The difference was considered significant at $p < 0.05$ (two-sided).

Results

Patient baseline characteristics

According to the inclusion and exclusion criteria, a total of 948 patients with MBC were identified from the SEER database between 2010 and 2016. The patients were randomly divided into a training set (n=664) and a validation set (n=284). The training set was used for the construction and internal verification of the nomogram. The verification set was used for the external verification of the nomogram.

Table 1 summarizes the characteristics of the patients. In this study, there were 945 (99.6%) female patients and 3 (0.4%) male patients. Among the 948 patients, 235 had luminal A BC (24.8%), 21 had luminal B BC (2.2%), 37 had HER2-positive BC (4%), and the main molecular type was triple-negative BC with 655 cases (69%). Among these patients, the majority were over 50 years (77.7%) and white (76.2%). In addition, the degree of differentiation of grade II and III tumors accounted for 59% and 13.8% of all cases, respectively.

Univariate and multivariate Cox proportional hazards regression analyses of the training set

The data of the training cohort, including patient age, sex, major site, tumor size, histology, surgical stage, surgery, chemotherapy and radiation, were used for univariate Cox analysis. The analysis results (Table 2) showed that the OS-related variables included patient age, tumor size, AJCC stage, TNM stage, metastatic site, surgical method, radiotherapy, chemotherapy and the other 10 variables ($p<0.05$), while the remaining variables lost meaning. In addition, 8 variables, including patient age, tumor size, AJCC stage, TNM stage, metastatic site, surgical method, radiotherapy and chemotherapy were associated with CSS ($p<0.05$), and the other variables were not statistically significant (Table 3). Multivariate Cox analysis (Tables 2 and 3) was further performed to constrain confounding variables. From the results of multivariate analysis, age, race, AJCC stage, radiotherapy, surgery and tumor size were identified as independent prognostic factors for OS ($p<0.05$), and the other variables were nonsignificant. Age, tumor size, and AJCC stage were identified as independent prognostic factors for CSS ($p<0.05$), while the other variables were nonsignificant.

Construction and validation of the nomograms for OS and CSS

After identifying significant factors, we used patient age, ethnicity, AJCC staging, radiotherapy, surgery, and tumor size to construct the prognostic nomogram for predicting the OS of patients with MBC at 1 year, 2 years, and 3 years (Figure 1) and used age, AJCC stage, and tumor size to construct a prognostic nomogram for predicting the CSS of patients with MBC at 1 year, 2 years, and 3 years (Figure 2). Internal and external validation was performed for the prognostic nomograms. The true predictive abilities of the final prognostic nomogram models were assessed by the C-index. For the internal validation of the OS and CSS nomograms in the training cohort, the C-indices were 0.790 (95% CI, 0.755 to 0.825) and 0.792 (95% CI, 0.753 to 0.831), respectively. For OS and CSS nomograms, the externally verified C-indices were 0.772 (95% CI, 0.727 to 0.817) and 0.768 (95% CI, 0.705 to 0.831), respectively. The calibration plots showed good agreement between the nomogram predictions and actual survival rates (Figures 3 and 4). These prognostic nomograms can be used by surgeons to estimate the prognosis of patients with MBC with the following data: age, ethnicity, AJCC stage, radiotherapy, surgical method and tumor size.

The 1-year, 3-year, and 5-year time-dependent area under the curve (AUC) values were used to

Table 2. Cox regression analysis for overall survival in the metaplastic breast cancer patients

	Univariate COX analysis			*Multivariate COX analysis*		
	HR	*95.0% CI*	*p*	*HR*	*95.0% CI*	*p*
Size (mm)*						
<44				<0.001		<0.001
44-67	2.555	1.800-3.627	<0.001	1.661	1.136-2.429	0.009
>67	5.990	4.165-8.614	<0.001	3.510	2.271-5.425	<0.001
Age, years						
<56				<0.001		<0.001
56-80	1.765	1.226-2.541	0.002	2.355	1.598-3.470	<0.001
>80	3.273	2.071-5.172	<0.001	4.395	2.675-7.221	<0.001
Race						
Black				0.102		0.019
Other	0.702	0.378-1.302	0.261	0.554	0.290-1.056	0.073
White	0.668	0.461-0.968	0.033	0.564	0.384-0.829	0.004
Sex (male)	0.050	<0.001-96453.199	0.684			
Grade						
1			0.115			
2	1.679	0.499-5.651	0.403			
3	2.231	0.711-6.998	0.169			
4	4.049	1.046-15.673	0.043			
Laterality (R)	0.801	0.596-1.075	0.139			
AJCC stage*						
I			<0.001			<0.001
II	3.721	2.036-6.802	<0.001	2.732	1.468-5.083	0.002
III	9.710	5.152-18.302	<0.001	5.093	2.530-10.251	<0.001
IV	29.012	14.528-57.934	<0.001	14.870	6.969-31.729	<0.001
T						
T1				<0.001		
T2	2.339	1.395-3.923	0.001			
T3	6.493	3.802-11.088	<0.001			
T4	9.170	5.169-16.269	<0.001			
N						
N0				<0.001		
N1	2.552	1.788-3.641	<0.001			
N2	3.079	1.843-5.142	<0.001			
N3	5.564	3.054-10.135	<0.001			
M	7.758	5.083-11.841	<0.001			
Surgery	0.249	0.138-0.448	<0.001	0.330	0.179-0.609	<0.001
Radiation	0.652	0.485-0.876	0.005	0.622	0.453-0.854	0.003
Chemotherapy	0.652	0.483-0.879	0.005			
Metastatic site						
1			<0.001			
2	7.945	4.774-13.223	<0.001			
3	25.540	9.225-70.709	<0.001			
4	13.970	3.432-56.854	<0.001			
Breast cancer subtype						
HR+/HER2-			0.157			
HR+/HER2+	1.333	0.411-4.327	0.632			
HR-/HER2+	0.989	0.417-2.344	0.980			
HR-/HER2-	1.490	1.035-2.146	0.032			
ER	0.733	0.495-1.085	0.121			
PR	0.745	0.481-1.155	0.188			
HER2	0.803	0.411-1.571	0.522			
Insurance	0.828	0.116-5.916	0.851			
Marital status	0.808	0.602-1.083	0.153			

*AJCC: American Joint Committee on Cancer TNM staging system

Table 3. Cox regression analysis for cancer-specific survival in the metaplastic breast cancer patients

	Univariate COX analysis			*Multivariate COX analysis*		
	HR	*95.0% CI*	*p*	*HR*	*95.0% CI*	*p*
Size (mm)						
<40				<0.001		<0.001
40-67	1.999	1.321-3.024	0.001	1.018	0.647-1.601	0.938
>67	8.488	5.399-13.343	<0.001	2.646	1.555-4.502	<0.001
Age,years						
<56				0.025		<0.001
56-73	1.537	1.026-2.301	0.037	1.899	1.247-2.894	0.003
>73	1.816	1.165-2.833	0.008	2.458	1.546-3.908	<0.001
Race						
Black				0.228		
Other	0.942	0.494-1.797	0.856			
White	0.714	0.466-1.092	0.120			
Sex (male)	0.050	<0.001-525447.9	0.716			
Grade						
1				0.325		
2	1.170	0.336-4.071	0.805			
3	1.797	0.571-5.650	0.316			
4	2.247	0.503-10.050	0.289			
Laterality(R)	0.742	0.533-1.033	0.077			
AJCC stage						
I				<0.001		<0.001
II	4.495	2.060-9.807	<0.001	3.973	1.711-9.227	0.001
III	14.914	6.714-33.127	<0.001	10.091	4.136-24.616	<0.001
IV	45.933	19.745-106.854	<0.001	31.507	12.242-81.09	<0.001
T						
T1				<0.001		
T2	3.239	1.653-6.348	0.001			
T3	9.375	4.712-18.654	<0.001			
T4	15.189	7.456-30.939	<0.001			
N						
N0				<0.001		
N1	3.242	2.209-4.757	<0.001			
N2	3.995	2.329-6.852	<0.001			
N3	6.258	3.229-12.128	<0.001			
M	9.448	6.091-14.656	<0.001			
Surgery	0.354	0.165-0.757	0.007			
Radiation	0.738	0.531-1.025	0.070			
Chemotherapy	1.143	0.791-1.651	0.477			
Metastatic site						
1				<0.001		
2	9.390	5.522-15.969	<0.001			
3	32.844	11.773-91.625	<0.001			
4	17.007	4.164-69.460	<0.001			
Breast cancer subtype						
HR+/HER2-				0.399		
HR+/HER2+	1.554	0.475-5.086	0.466			
HR-/HER2+	0.979	0.381-2.518	0.965			
HR-/HER2-	1.381	0.924-2.063	0.115			
ER	0.779	0.506-1.200	0.257			
PR	0.870	0.548-1.383	0.557			
HER2	1.117	0.547¬-2.280	0.761			
Insurance	0.655	0.092-4.687	0.673			
Marital status	1.014	0.730-1.408	0.935			

Metastatic sites. 1: bone metastasis; 2: brain metastasis; 3: liver metastasis; 4: lung metastasis.

measure the discriminative ability of the nomograms (an AUC value equal to 0.5 indicates that the nomogram has no predictive effect, and an AUC value equal to 1 indicates that the nomogram has an excellent predictive effect). Patients with different survival rates can be completely distinguished (the higher the value between 0.5 and 1, the better the discriminative ability of the nomogram), and other prognostic factors can be compared to further verify their superiority and to see which factor had largest contribution to the survival rate in the nomogram. In the main cohort, the discriminative ability shown by the OS nomogram was compared with that of other prognostic factors (1-year AUC: 0.859;

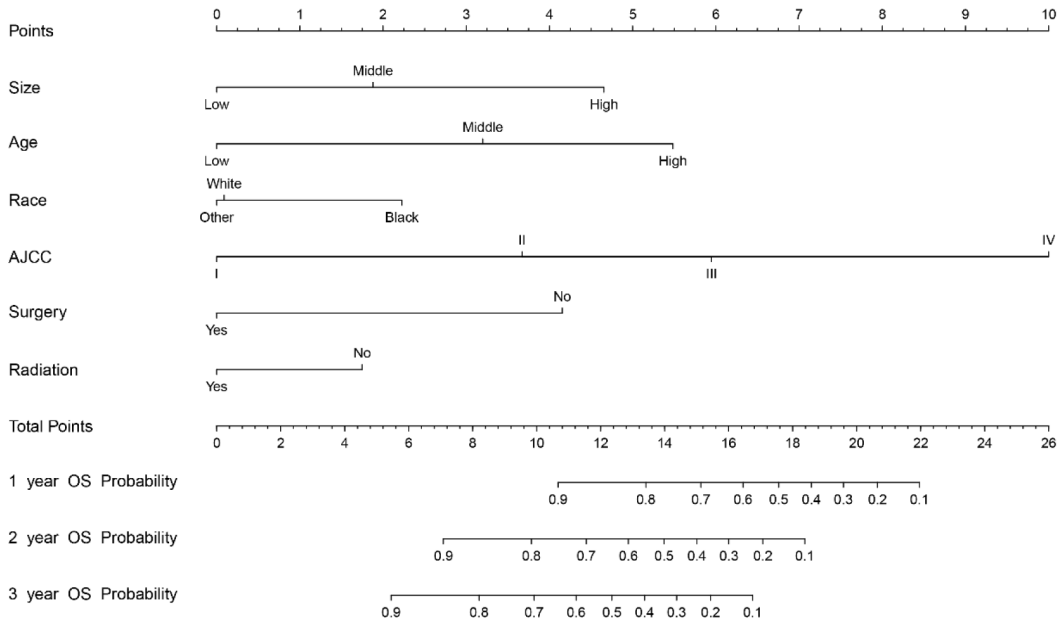

Figure 1. The graphs show the nomograms that predict the 1-, 2- and 3-year overall survival and of metaplastic breast cancer patients. Points for each variable are acquired by drawing a vertical line between each variable and the points scale. After totaling the points of each variable, draw a vertical line between the Total Points scale and overall survival or cancer-specific survival scale to calculate the predicted 1-, 2- and 3-year survival.

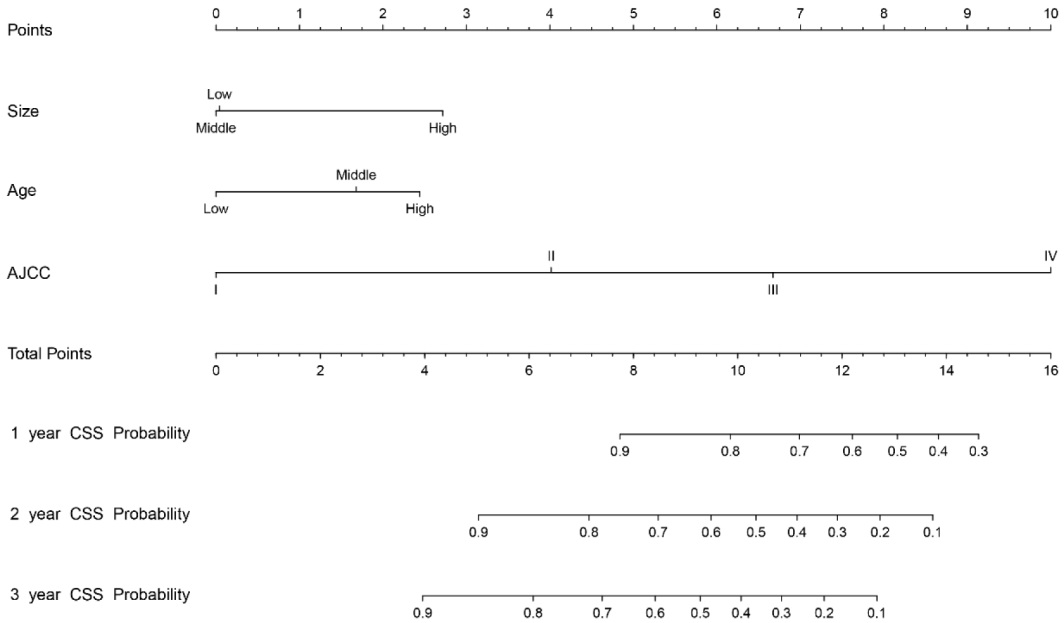

Figure 2. The graphs show the nomograms that predict the 1-, 2- and 3-year cancer-specific survival of metaplastic breast cancer patients. Points for each variable are acquired by drawing a vertical line between each variable and the points scale. After totaling the points of each variable, draw a vertical line between the Total Points scale and overall survival or cancer-specific survival scale to calculate the predicted 1-, 2- and 3-year survival.

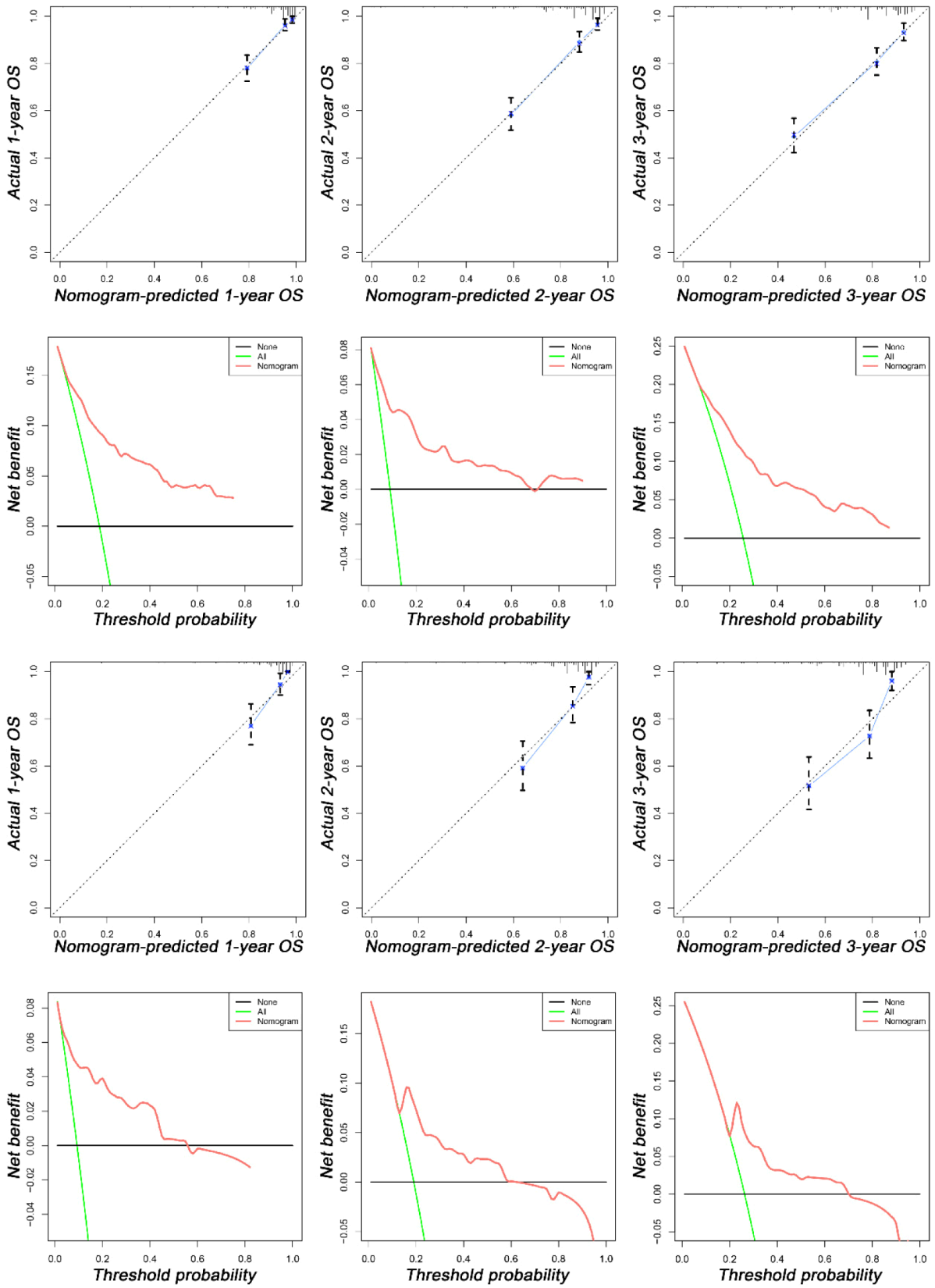

Figure 3. The calibration curves of the nomogram for predicting 1-, 2-, and 3-year OS in the primary cohort. The calibration curves of the nomogram for predicting 1-, 2-, and 3-year OS in the external validation cohort. The nomogram-predicted OS is plotted on the x-axis; the actual OS is plotted on the y-axis. The faint line indicates a perfect calibration model in which the predicted probabilities are identical to the actual survival outcomes. Decision curve analysis of the nomogram for predicting OS at 1-, 2- and 3-year points in the training cohort and at 1-, 2- and 3-year points in the validation cohort. The x-axis represents the percentage of threshold probability, whereas the y-axis represents the net benefit, calculated by adding the true positives and subtracting the false positives.

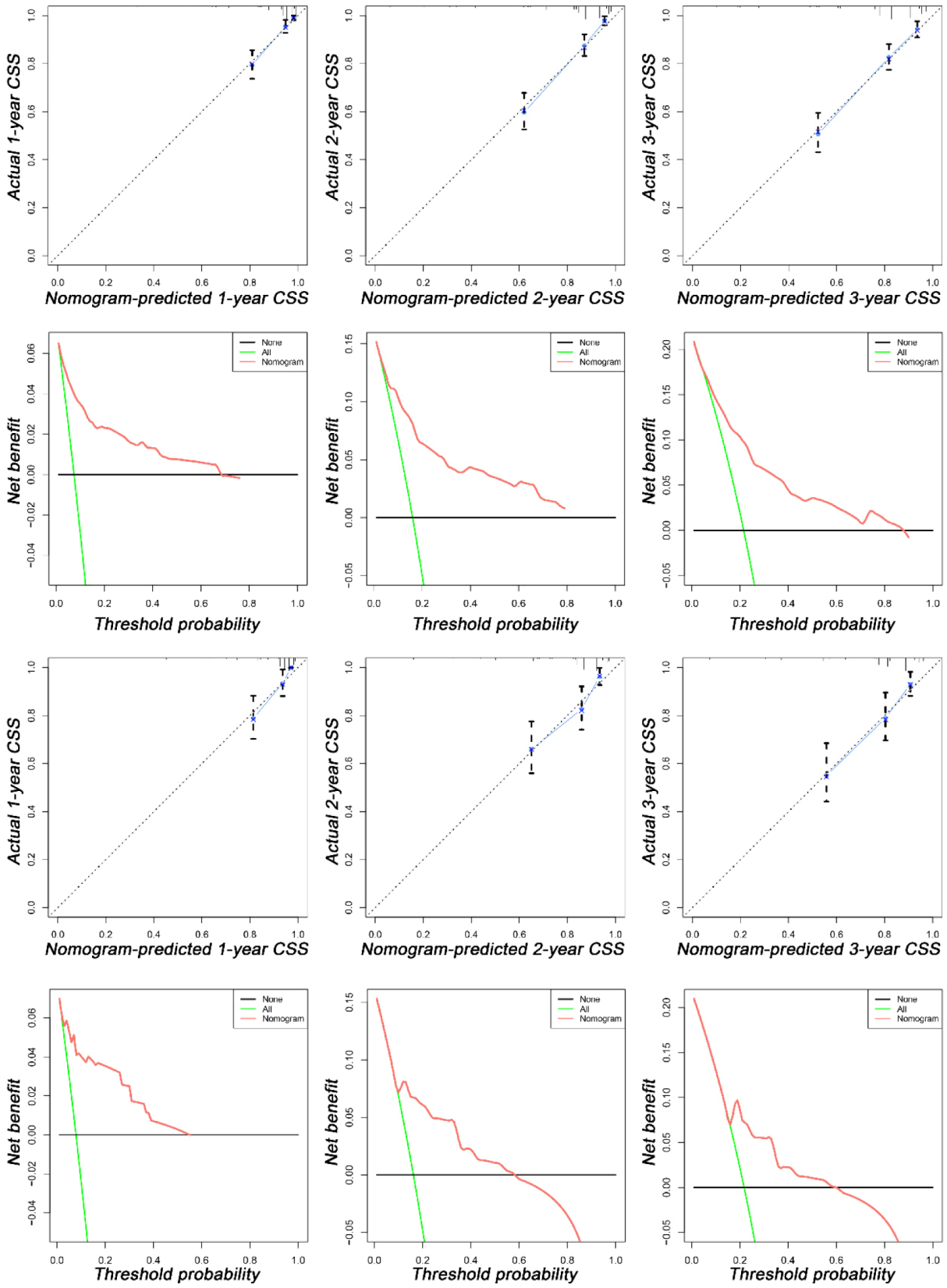

Figure 4. The calibration curves of the nomogram for predicting 1-, 2-, and 3-year CSS in the primary cohort. The calibration curves of the nomogram for predicting 1-, 2-, and 3-year CSS in the external validation cohort. The nomogram-predicted CSS is plotted on the x-axis; the actual CSS is plotted on the y-axis. The faint line indicates a perfect calibration model in which the predicted probabilities are identical to the actual survival outcomes. Decision curve analysis of the nomogram for predicting OS at 1-, 2- and 3-year points in the training cohort and at 1-,2- and 3-year points in the validation cohort. The x-axis represents the percentage of threshold probability, whereas the y-axis represents the net benefit, calculated by adding the true positives and subtracting the false positives.

2-year AUC: 0.838; 3-year AUC: 0.800; Figure 5). In addition, in the external verification cohort, the AUC values for 1-year, 2-year, and 3-year OS were 0.859, 0808, and 0.791, respectively. Compared with other prognostic factors, the CSS nomogram showed advantages in the test set (1-year AUC: 0.856; 2-year AUC: 0.834; 3-year AUC: 0.796; Figure 6). In addition, in the external verification cohort, the AUC values for 1-year, 2-year, and 3-year CSS were 0.890, 0.785, and 0.779, respectively.

Clinical application

As shown in Figures 2 and 3, the nomograms have a substantial positive net benefit across a wide range of death risks in the two cohorts, indicating that they are predictive of 1-, 2- and 3-year OS and CSS and have good clinical application value.

With the help of nomograms (Figure 1), we can predict the survival probability of an individual patient based on personalized information. For example, for a 50-year-old woman who was diagnosed with MBC with a primary breast lesion of 10.0 cm, who received chemotherapy and then underwent surgery to remove the primary lesion, according to the nomogram, this patient has a score of 10.5 on the OS nomogram. Therefore, for this patient, the estimated 1-, 2-, and 3-year OS rates were 90%, 75%, and 65%, respectively. Similarly, we can use CSS nomogram to predict 1-, 2-, and 3-year CSS.

Discussion

MBC is highly heterogeneous. Another notorious feature of MBC is the ineffectiveness of chemotherapy [22]. As the incidence is rare and the prognosis is poor, it is necessary to understand the prognostic factors that affect MBC and guide clinical diagnosis and treatment decisions in order to improvetheprognosisof patients with MBC. This study suggests that age, race, AJCC stage, radiotherapy, surgery and tumor size are independent prognostic factors of OS. A nomogram for OS was created based on these prognostic factors and used to predict OS at 1, 2, and 3 years for patients with MBC. This study also found that age, AJCC stage and tumor size are independent prognostic factors of CSS, and based on these prognostic factors, a prognostic nomogram of CSS was created. The factors integrated into the OS and CSS nomograms performed better than the other prognostic factors.

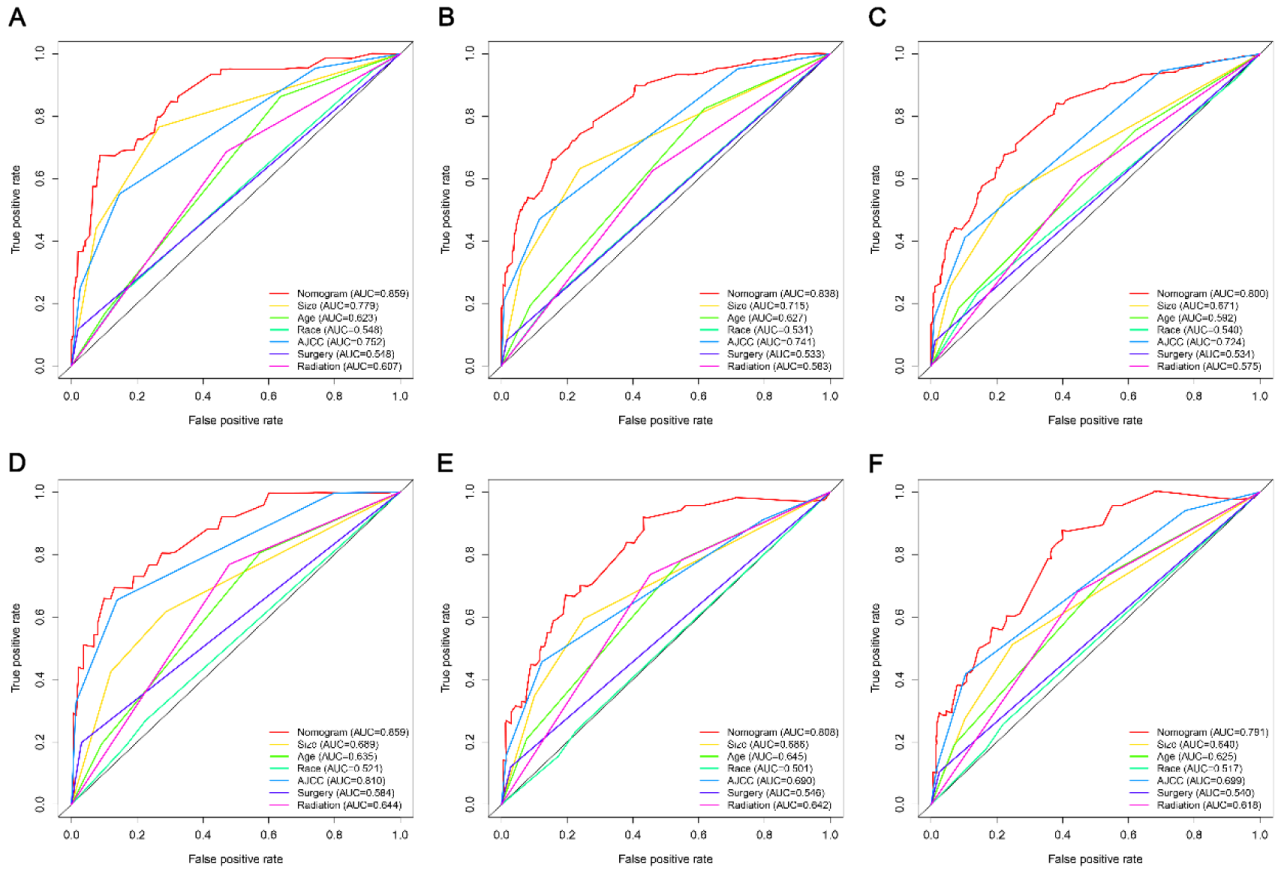

Figure 5. ROC curves of the nomogram and the other prognostic factors for predicting 1- **(A)**, 2- **(B)**, and 3-year **(C)** OS in the training cohort. ROC curves of the nomogram and the other prognostic factors for predicting 1- **(D)**, 2- **(E)**, and 3-year **(F)** OS in the validation cohort.

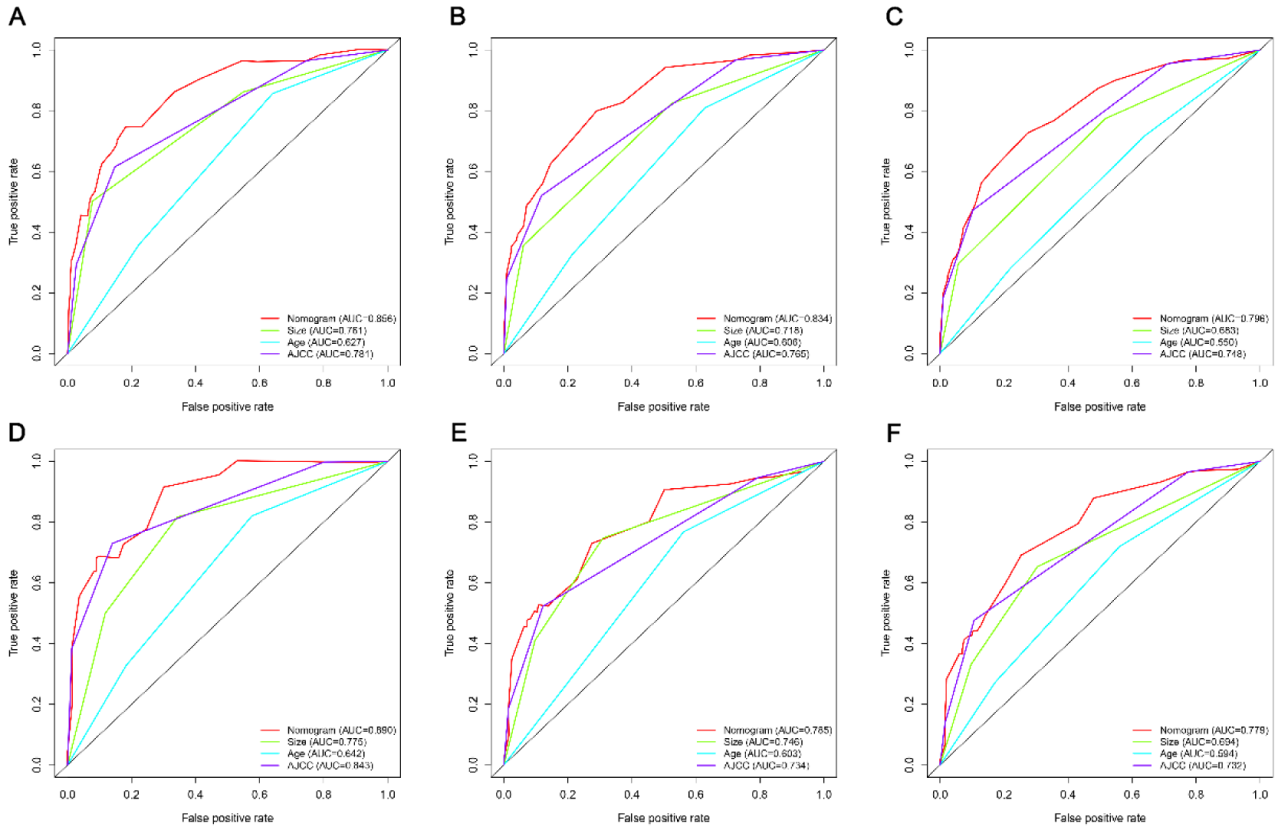

Figure 6. ROC curves of the nomogram and the other prognostic factors for predicting 1-year **(A)**, 2-year **(B)**, and 3-year **(C)** CSS in the training cohort. ROC curves of the nomogram and the other prognostic factors for predicting 1-year **(D)**, 2-year **(E)**, and 3-year **(F)** CSS in the validation cohort.

Previous studies have confirmed that factors such as tumor size, grade, and radiation treatment are independent prognostic factors for MBC [5]. However, due to the low incidence, the study included fewer than 100 cases and did not use these independent prognostic factors as overall prognostic factors to assess the prognosis of MBC. To the best of our knowledge, nomograms have been applied to predict the survival status of various cancers [23,24]. Since nomograms quantify risk by combining and illustrating the relative importance of various prognostic factors, they have been used in clinical oncology assessments. Moreover, nomograms are arguably the most valuable in situations where the potential benefits of added therapy are unclear [25,26]. Such tools are useful for personalizing risk stratification to help physicians make decisions when there may not be strict guidelines for management. Such tailored plans match the rationale behind a nomogram for predicting a patient's prognosis. Nomograms address the complexity of balancing different factors through statistical modeling and risk quantification in a way accessible to both patients and physicians. Their systematic approach also avoids the bias of individual doctors or individual abnormal clinical variables. Based on the independent prognostic factors of OS and CSS in MBC, we established nomograms for OS and CSS. According to the nomograms, the AJCC classification has an important contribution to both OS and CSS in patients with MBC, followed by the age and tumor size, with the calibration curves showing the survival rate between the predicted and actual observations in the training and validation groups. The best consistency of the results were demonstrated by the ROC curves, which also showed that both the OS and CSS nomograms have better diagnostic performance outcomes than the other independent prognostic factors, indicating that the nomograms established in the current study are reliable and sensitive. DCA showed these two nomograms have a substantial positive net benefit across a wide range of death risks, indicating that they are predictive of 1-, 2- and 3-year OS and CSS, and explained the columns we established. The nomograms have good clinical application value.

To the best of our knowledge, there are no clear reports of OS and CSS nomograms in patients with MBC. Viable prognostic nomograms can help surgeons approximate the likelihood of survival at different time intervals anddiscernpatients with a higher risk of early death.

Several potential limitations of this study should still be considered. First, we used only 1-, 2-, and 3-yearsurvival rates as the primary endpoint but did not consider local recurrences, which are not available in the SEER database. Second, the treatments included in this study only involved whether surgery, chemotherapy, and radiotherapy were used but did not involve specific treatment options, which may also bring certain limitations. Again, the information we used to construct and verify the nomograms all came from the same SEER registry which reduces the dependability of the nomograms. It would be useful to corroborate the prognostic nomograms in this study using another data set.

Conclusions

Age, race, AJCC stage, surgery, radiotherapy, and tumor size were all identified as independent prognostic factors of OS for MBC patients, while age, AJCC stage, and tumor size were all identified as independent prognostic factors of CSS. We included these prognostic factors in the construction of prognostic nomograms to predict the OS and CSS of these patients at one, two, and three years. The nomograms constructed in this study can be used convenient and effective assessment tools to help surgeons perform personalized survival assessments and death risk designations in patients with MBC.

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Conflict of interests

The authors declare no conflict of interests.

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