Original Article

Prognosis prediction model for patients with breast cancer with bone metastasis: based on a population database

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Background: Prognosis prediction for breast cancer bone metastasis (BCBM) patients is related to the development of further treatment options, and the judgment of prognosis is often not determined by one factor, which requires a comprehensive assessment of the patient's condition.

Methods: Through the search of the National Cancer Institute database, BCBM patients registered between January 1, 2010 and December 31, 2015 were selected as research goals. All patients were randomly assigned to the model establishment group and validation group at a ratio of 7:3. Log-rank test and multivariate cox regression analysis are used to evaluate each prognostic factor. Selecting the prognostic factor of log-rank test P<0.001 to plot Kaplan-Meier survival curves and use the model establishment group to draw nomgrams. Concordance index (C-index), Receiver Operating Characteristic (ROC) curve and calibration plot are used for internal and external verification.

Results: A total of 13,773 BCBM patients were included in this article, 9,644 BCBM patients were assigned to the model establishment group and 4,129 BCBM patients were assigned to the validation group. Two nomgrams for predicting OS and BCRS are plotted, with C-index of 0.716 and 0.735, respectively. The ROC curve and the calibration plot drawn using the model establishment group and validation group confirm the prediction accuracy of the two nomgrams.

Conclusions: The final nomograms obtained satisfactory results after a series of internal and external verifications, verifying the accuracy of their predictions. Other samples are needed in the future for more comprehensive external validation of the model, but at this stage, this model will help physicians and patients to have a more accurate judgment of the prognosis.

Keywords: Breast cancer bone metastasis (BCBM); Surveillance; Epidemiology, and End Results (SEER); nomogram

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Introduction

In 2018, the global cancer report reported by WHO showed that the incidence of breast cancer is second, and it is also one of the most common types of cancer in women (1). Although there are clear early diagnosis and standard treatment methods for breast cancer, the mortality rate remains high (1). Breast cancer is prone to distant metastasis. The incidence of bone metastases in advanced breast cancer patients is about 70% (2). The first part of the patients with metastases is bone (2,3). Even breast cancer patients who are reasonably treated have a risk of developing bone metastases (3). Breast cancer bone metastasis (BCBM) often has no obvious symptoms in the early stage, so it is easy to be ignored by patients (4). If the symptoms of bone pain occur, the patient has already entered the late stage of breast cancer (5). The most common manifestations of breast cancer patients with bone metastases are severe pain, pathological fractures, spinal cord compression and other bone-related adverse events (4,5). Because breast cancer patients usually have a long survival time, the existence of these adverse events seriously affects the quality of life of BCBM patients.

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Establishing a prognostic prediction model usually requires a suitable statistical method and a relatively large sample size. By summarizing the basic conditions and treatment of a large number of breast cancer patients, and using reasonable statistical methods to analyze the prognosis related factors, and then establish a simple and efficient prognosis prediction model. The Surveillance, Epidemiology, and End Results (SEER) database administered by the National Cancer Institute contains data on cancer patients from a number of medical centers, providing a large and well-established demographic, tumor pathology, and treatment information for breast cancer patients. It is essential for us to use the big data to establish a reasonable prognostic prediction model (6).

The aim of this study was to collect information on the demographics, tumor pathology, and treatment of patients with breast cancer who were diagnosed with bone metastases in the SEER database. Describe the basic condition and median survival time of BCBM patients. In addition, multivariate cox regression was used to evaluate the impact of each independent factor on prognosis. Finally, cox regression results were visualized by plotting nomograms, and internal and external validation of these nomograms was performed to measure the accuracy of these nomograms for prognosis prediction. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tbcr-20-14).

Methods

Data collection

The National Cancer Institute's SEER database covers about 28% of the population of the United States and collects data on cancer patients from 18 tumor registration centers (6). The latest data for the (1973–2016 varying) database released in November 2018 was obtained using SEER stat special software (version 8.3.5), and data acquisition was done in client-server mode (7). During the period from January 1, 2010 to December 31, 2015, a total of 13,773 breast cancer patients were diagnosed with bone metastases. Exclusion criteria include: no/unknown breast cancer patients with bone metastases, unknown survival time and vital status.

Inclusion codes and criteria

The main end points of the study were overall survival (OS) and breast cancer-related survival (BCRS). In this study, we classified patients according to the following factors, such as age (≤45, 46–65, 66–85, ≤86), gender (Famale, Male), race (White, Black, Asian or Pacific Islander, Others) and marital status (Married, Unmarried, Unknown).

For the tumor , the tumors were classified according to grade(I, II, III, IV, Unknown), laterality (Left, Right, Other), tumor size (≤20 mm, 21–50 mm, >50 mm), T stage (0, 1, 2, 3, 4, X), N stage (0, 1, 2, 3, X), histological type (Ductal, Lobular, Adenocarcinoma, Other), subtypes (HR+/HER2– (Luminal A), HR+/HER2+ (Luminal B), HR–/HER2+ (HER2 enriched), HR–/HER2– (Triple Negative), Unknown) and number of extra-bone (brain, liver and lung) metastatic organs (0, 1, 2, 3, Unknown). In addition, this study also collected treatments for primary breast cancer lesions, including surgery (Yes, No), chemotherapy (Yes, No) and radiotherapy (Yes, No).

Patients grouping

In order to establish an effective prognostic prediction model, all patients were divided into a model establishment group and a verification group according to a random assignment method. Among them, the model establishment group included a total of 9,464 patients, and the validation group included 4,129 patients. Both groups of patients will be considered when the final nomograms are drawn.

Statistical analysis

Basic information about BCBM patients using a method of descriptive statistics. The chi-square test was used to analyze the dead/live of categorical variables of prognostic factors in BCBM patients. The survival time of each prognostic factor is expressed as the median and interquartile ranges. Kaplan-Meier survival curves and log-rank test were used to analyze the OS and BCRS for each prognostic factor. Multivariate cox regression analysis was used to analyze all-cause mortality (ACM) and breast cancer-related mortality (BCRM) for each prognostic factor and categorical variable. Moreover, the hazard ratios (HR) and 95% CIs for all strata of each factor are also calculated. The P value <0.05 is considered statistically significant.

Plotting Kaplan-Meier survival curves and construction of nomograms

Selecting the prognostic factor of log-rank test P<0.001

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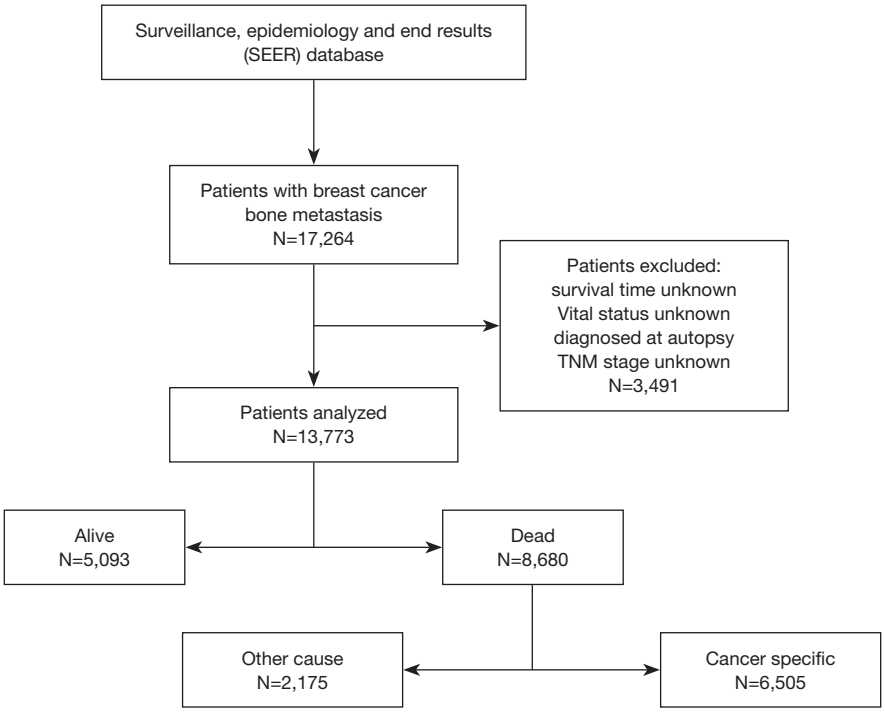

Figure 1 Flowchart of patients identification and selection.

to plot Kaplan-Meier survival curves. Based on the results of multivariate cox regression analysis, the prognostic predictors of P<0.001 in the log-rank test were included in the nomogram. The model was used to model establishment group data for internal verification of the nomograms, and the validation group data was used for external verification of the nomograms. The Concordance index (C-index), Receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the predictive power of the model (8). The C-index is between 0.5 and 1, 0.5 is completely inconsistent, indicating that the model has no predictive effect, and 1 is completely consistent, indicating that the model's prediction results are completely consistent with the actual. In general, the C-index is less accurate at 0.50–0.70: moderate accuracy between 0.71 and 0.90; and high accuracy above 0.90. The area under the ROC curve (AUC) refers to the area around the ROC curve and the x-axis, (1,0)–(1,1). Similar to the C-index, the AUC is less accurate at 0.50–0.70: moderate accuracy between 0.71 and 0.90; and high accuracy above 0.90 (9,10). The predicted probability of the nomograms of the OS and BCRS for 1, 3 and 5 years are compared with the observed survival probability to obtain calibration plots. All statistical analysis, model establishment group and validation group generation and construction of nomograms were performed by R project (Version 3.6.0).

Results

Demographic and tumor pathological features of BCBM patients

The specific screening process is shown in *Figure 1*. Between Jan 1, 2010 and Dec 31, 2015, 13,773 BCBM patients were included in this article, 9,644 BCBM patients were assigned to the model establishment group and 4,129 BCBM patients were assigned to the validation group. From 2010 to 2015, the number of BCBM patients was basically stable. The demographic and tumor pathology information of BCBM was shown in *Table 1*, and the median survival was shown in *Table 2*.

The mean age and median age of 13,773 patients were 62.05 and 62 years, respectively. In entire group, the majority of the categorical variables in this study were 46–65 years old (60.3%), female (98.7%), white (77.0%), unmarried (51.9%), grade II (34.7%), left (48.3%), tumor size 21–50 mm (35.5%), T4 (26.7%), N1 (41.0%), ductal (61.6%), number of extra-bone metastatic organs was

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Table 1 Demographic information and tumor pathology information of BCBM

Characteristics	Entire Group		Model Establishment Group		Validation Group	
	No	%	No	%	No	%
Total	13,773	100.00	9,644	1.000	4,129	100.00
Age at diagnosis						
≤45	1,688	12.30	1,164	0.121	524	12.70
46–65	6,643	48.20	4,696	0.487	1,947	47.20
66–85	4,773	34.70	3,321	0.344	1,452	35.20
≥86	669	4.90	463	0.048	206	5.00
Gender						
Female	13,600	98.70	9,519	0.987	4,081	98.80
Male	173	1.30	125	0.013	48	1.20
Race						
White	10,612	77.00	7,425	0.770	3,187	77.20
Black	2,126	15.40	1,477	0.153	649	15.70
Asian or Pacific Islander	911	6.60	654	0.068	257	6.20
Other	124	0.90	88	0.009	36	0.90
Marital status						
Married	5,876	42.70	4,107	0.426	1,769	42.80
Unmarried	7,146	51.90	5,022	0.521	2,124	51.40
Unknown	751	5.50	515	0.053	236	5.70
Year of diagnosis						
2010	2,062	15.00	1,469	0.152	593	14.40
2011	2,214	16.10	1,541	0.160	673	16.30
2012	2,229	16.20	1,560	0.162	669	16.20
2013	2,450	17.80	1,702	0.176	748	18.10
2014	2,418	17.60	1,678	0.174	740	17.90
2015	2,400	17.40	1,694	0.176	706	17.10
Grade						
I	994	7.20	699	0.072	295	7.10
II	4,773	34.70	3,334	0.346	1,439	34.90
III	4,256	30.90	2,956	0.307	1,300	31.50
IV	64	0.50	51	0.005	13	0.30
Unknown	3,686	26.80	2,604	0.270	1,082	26.20
Laterality						
Left	6,652	48.30	4,649	0.482	2,003	48.50
Right	6,347	46.10	4,464	0.463	1,883	45.60
Other	774	5.60	531	0.055	243	5.90

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Entire Group		Model Establishment Group		Validation Group	
	No	%	No	%	No	%
Tumor size						
≤20 mm	2,249	16.30	1,588	0.165	661	16.00
21-50 mm	4,892	35.50	3,401	0.353	1,491	36.10
>50 mm	3,933	28.60	2,772	0.287	1,161	28.10
Unknown	2,699	19.60	1,883	0.195	816	19.80
stage_T						
T0	305	2.20	212	0.022	93	2.30
T1	1,594	11.60	1,131	0.117	463	11.20
T2	3,627	26.30	2,520	0.261	1,107	26.80
T3	1,874	13.60	1,301	0.135	573	13.90
T4	3,683	26.70	2,738	0.284	945	22.90
TX	2,510	18.20	1,742	0.181	768	18.60
stage_N						
N0	3,455	25.10	2,442	0.253	1,013	24.50
N1	5,650	41.00	3,960	0.411	1,690	40.90
N2	1,321	9.60	910	0.094	411	10.00
N3	1,615	11.70	1,115	0.116	500	12.10
NX	1,732	12.60	1,217	0.126	515	12.50
Histological type						
Ductal	8,480	61.60	5,978	0.620	2,502	60.60
Lobular	1,727	12.50	1,179	0.122	548	13.30
Adenocarcinoma	872	6.30	604	0.063	268	6.50
Other	2,694	19.60	1,883	0.195	811	19.60
Other metastases*						
0	7,445	54.10	5,216	0.541	2,229	54.00
1	3,838	27.90	2,687	0.279	1,151	27.90
2	1,368	9.90	954	0.099	414	10.00
3	239	1.70	169	0.018	70	1.70
Unknown	883	6.40	618	0.064	265	6.40
Subtypes						
HR+/HER2– (Luminal A)	7,945	57.70	5,538	0.574	2,407	58.30
HR+/HER2+ (Luminal B)	1,844	13.40	1,315	0.136	529	12.80
HR–/HER2+ (HER2 enriched)	715	5.20	488	0.051	227	5.50
HR–/HER2– (Triple negative)	1,081	7.80	747	0.077	334	8.10
Unknown	2,188	15.90	1,556	0.161	632	15.30

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Entire Group		Model Establishment Group		Validation Group	
	No	%	No	%	No	%
Surgery						
Yes	3,461	25.10	2,420	0.251	1,041	25.20
No	10,312	74.90	7,224	0.749	3,088	74.80
Chemotherapy						
Yes	6,549	47.50	4,601	0.477	1,948	47.20
No	7,224	52.50	5,043	0.523	2,181	52.80
Radiotherapy						
Yes	4,688	34.00	3,320	0.344	1,368	33.10
No	9,085	66.00	6,324	0.656	2,761	66.90

*, number of extra-bone (brain, liver and lung) metastatic organs. BCBM, breast cancer bone metastasis.

0 (54.1%), luminal A (57.7%), no surgery (74.9%), no chemotherapy (52.5%), and no radiotherapy (66.0%).

In model establishment group, the majority of the categorical variables in this study were 46–65 years old (48.7%), female (98.7%), white (77.0%), unmarried (52.1%), grade II (34.6%), left (48.2%), tumor size 21–50 mm (35.3%), T4 (28.4%), N1 (41.1%), ductal (62.0%), number of extra-bone metastatic organs was 0 (54.1%), luminal A (57.4%), no surgery (74.9%), no chemotherapy (52.3%), and no radiotherapy (65.6%).

In validation group, the majority of the categorical variables in this study were 46–65 years old (47.2%), female (98.8%), white (77.2%), unmarried (51.4%), grade II (34.9%), left (48.5%), tumor size 21–50 mm (36.1%), T2 (26.8%), N1 (40.9%), ductal (60.6%), number of extra-bone metastatic organs was 0(54.0%), luminal A (58.3%), no surgery (74.8%), no chemotherapy (52.8%), and no radiotherapy (66.9%).

The impact of different variables on ACM and BCRM

Among all 13,773 BCBM patients, 8,680 (63.0%) patients with ACM, while 5,093 (43.9%) died of breast cancer (*Figure 1*, *Table 3*). Observing the demographic data, whether due to ACM or BCRM, with the age at diagnosis increases, the mortality rate also increases significantly (P<0.001 and P<0.001), however, gender has no significant effect on mortality in patients with breast cancer with bone metastasis (P=0.638 and P=0.876). Blacks have the highest ACM (69.8%) and BCRM (63.6%). Unmarried patients have the highest ACM (68.1%) and BCRM (61.2%). The diagnosis year was from 2010 to 2015, and the patient's ACM and BCRM decreased gradually.

Observing tumor pathology data, ACM and BCRM are basically the same between the left and right primary tumors. As the size of the primary tumor increases, ACM and BCRM also show an upward trend. Primary tumor of stage T4 has the highest ACM (68.1%) and BCRM (61.2%). Primary tumor of stage NX has the highest ACM (74.8%) and BCRM (68.4%), however, ACM and BCRM in N0 to N4 are basically the same. Among the histological types, ACM and BCRM of ductal and lobular carcinoma are basically the same, and both are lower than adenocarcinoma. Patients with extra-bone metastases in the brain, lung and liver have the highest ACM (86.2%) and BCRM (83.7%). In addition, the increase in the number of extra-bone metastatic organs, ACM and BCRM have also increased. Among the subtypes, triple negative breast cancer patients have the highest ACM and BCRM.

Observing treatment data, ACM (66.7% *vs.* 52.2%, P<0.001) and BCRM (60.1% *vs.* 44.6%, P<0.001) in those patients with primary tumors who were not undergoing surgery were significantly higher than those undergoing surgery. ACM (69.2% *vs.* 56.2%, P<0.001) and BCRM (62.0% *vs.* 50.1%, P<0.001) were significantly higher in those who did not receive chemotherapy than those receiving chemotherapy. Similarly, patients who did not receive radiotherapy had significantly higher ACM (64.3% *vs.* 60.5%, P<0.001) and BCRM (56.9% *vs.* 54.6%, P=0.016) than those receiving radiotherapy.

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Table 2 Median survival and survival months of BCBM patients

Characteristics	Patients, No	Median survival months
Total	13,773	20.0 [7–36]
Age at diagnosis		
≤45	1,688	27.0 [14–43]
46-65	6,643	22.0 [10–38]
66-85	4,773	17.0 [4–32]
≥86	669	8.0 [1–22]
Gender		
Female	13,600	20.0 [7–36]
Male	173	18.0 [7–33]
Race		
White	10,612	20.0 [7–37]
Black	2,126	17.0 [6–31]
Asian or Pacific Islander	911	21.0 [8–36]
Other	124	18.0 [8–35]
Marital status		
Married	5,876	23.0 [11–39]
Unmarried	7,146	18.0 [5–33]
Unknown	751	20.0 [8–34]
Grade		
I	994	26.0 [14–42]
II	4,773	24.0 [12–40]
III	4,256	18.0 [7–33]
IV	64	13.5 [5–29]
Unknown	3,686	16.0 [3–32]
Laterality		
Left	6,652	20.0 [7–36]
Right	6,347	21.0 [7–37]
Other	774	16.0 [3–30]
Tumor size		
≤20 mm	2,249	23.0 [10–39]
21–50 mm	4,892	22.0 [9–38]
>50 mm	3,933	19.0 [7–35]
Unknown	2,699	15.0 [3–31]
stage_T		
T0	305	19.0 [7–35]
T1	1,594	24.0 [11–40]
T2	3,627	23.0 [12–40]
T3	1,874	21.0 [11–38]
T4	3,683	18.0 [6–33]
TX	2,510	15.0 [2–31]
stage_N		
N0	3,455	20.0 [6–36]
N1	5,650	20.0 [9–36]
N2	1,321	23.0 [12–39]
N3	1,615	21.0 [11–38]
NX	1,732	13.5 [2–31]
Histological type		
Ductal	8,480	21.0 [9–38]
Lobular	1,727	23.0 [11–38]
Adenocarcinoma	872	15.0 [3–31]
Other	2,694	16.0 [3–31]
Other metastases*		
0	7,445	24.0 [13–40]
1	3,838	17.0 [5–33]
2	1,368	10.0 [2–25]
3	239	4.0 [1–16]
Unknown	883	15.0 [3–31]
Subtypes		
HR+/HER2– (Luminal A)	7,945	23.0 [12–38]
HR+/HER2+ (Luminal B)	1,844	24.0 [12–41]
HR–/HER2+ (HER2 enriched)	715	18.0 [6–35]
HR–/HER2– (Triple negative)	1,081	9.0 [3–17]
Unknown	2,188	10.0 [1–28]
Surgery		
Yes	3,461	29.0 [16–47]
No	10,312	17.0 [5–32]
Chemotherapy		
Yes	6,549	22.0 [12–39]
No	7,224	17.0 [3–33]
Radiotherapy		
Yes	4,688	23.0 [11–40]
No	9,085	18.0 [5–34]

*, number of extra-bone (brain, liver and lung) metastatic organs.

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Table 3 Univariate survival analyses of BCBM patients according to various clinicopathological variables Chi-square test)

Characteristics	All cause						Breast cancer-related					
	Total	Dead		Alive		P	Total	Dead		Alive		P
		No	%	No	%			No	%	No	%	
N	13,773	8,680	0.63	5,093	0.37		11,598	6,505	56.10	5,093	43.90	
Age at diagnosis						<0.001						<0.001
≤45	1,688	867	0.514	821	0.486		1,542	721	46.80	821	53.20	
46–65	6,643	3,946	0.594	2,697	0.406		5,814	3,117	53.60	2,697	46.40	
66–85	4,773	3,307	0.693	1,466	0.307		3,770	2,304	61.10	1,466	38.90	
≥86	669	560	0.837	109	0.163		472	363	76.90	109	23.10	
Gender						0.638						0.876
Female	13,600	8,568	0.63	5,032	0.37		11,457	6,425	56.10	5,032	43.90	
Male	173	112	0.647	61	0.353		141	80	56.70	61	43.30	
Race						<0.001						<0.001
White	10,612	6,611	0.623	4,001	0.377		8,930	4,929	55.20	4,001	44.80	
Black	2,126	1,485	0.698	641	0.302		1,762	1,121	63.60	641	36.40	
Asian or Pacific Islander	911	524	0.575	387	0.425		801	414	51.70	387	48.30	
Other	124	60	0.484	64	0.516		105	41	39.00	64	61.00	
Marital status						<0.001						<0.001
Married	5,876	3,344	0.569	2,532	0.431		5,084	2,552	50.20	2,532	49.80	
Unmarried	7,146	4,865	0.681	2,281	0.319		5,883	3,602	61.20	2,281	38.80	
Unknown	751	471	0.627	280	0.373		631	351	55.60	280	44.40	
Year of diagnosis						<0.001						<0.001
2010	2,062	1,684	0.817	378	0.183		1,629	1,251	76.80	378	23.20	
2011	2,214	1,749	0.79	465	0.21		1,802	1,337	74.20	465	25.80	
2012	2,229	1,585	0.711	644	0.289		1,839	1,195	65.00	644	35.00	
2013	2,450	1,554	0.634	896	0.366		2,076	1,180	56.80	896	43.20	
2014	2,418	1,255	0.519	1,163	0.481		2,059	896	43.50	1,163	56.50	
2015	2,400	853	0.355	1,547	0.645		2,193	646	29.50	1,547	70.50	
Grade						<0.001						<0.001
I	994	492	0.495	502	0.505		835	333	39.90	502	60.10	
II	4,773	2,682	0.562	2,091	0.438		4,061	1,970	48.50	2,091	51.50	
III	4,256	2,861	0.672	1,395	0.328		3,643	2,248	61.70	1,395	38.30	
IV	64	58	0.906	6	0.094		50	44	88.00	6	12.00	
Unknown	3,686	2,587	0.702	1,099	0.298		3,009	1,910	63.50	1,099	36.50	
Laterality						<0.001						<0.001
Left	6,652	4,152	0.624	2,500	0.376		5,634	3,134	55.60	2,500	44.40	

Table 3 (*continued*)

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Table 3 (*continued*)

Characteristics	All cause						Breast cancer-related					
	Total	Dead		Alive		P	Total	Dead		Alive		P
		No	%	No	%			No	%	No	%	
Right	6,347	3,981	0.627	2,366	0.373		5,339	2,973	55.70	2,366	44.30	
Other	774	547	0.707	227	0.293		625	398	63.70	227	36.30	
Tumor size						<0.001						<0.001
≤20 mm	2,249	1,289	0.573	960	0.427		1,795	835	46.50	960	53.50	
21–50 mm	4,892	2,858	0.584	2,034	0.416		4,155	2,121	51.00	2,034	49.00	
>50 mm	3,933	2,589	0.658	1,344	0.342		3,448	2,104	61.00	1,344	39.00	
Unknown	2,699	1,944	0.72	755	0.28		2,200	1,445	65.70	755	34.30	
stage_T						<0.001						<0.001
T0	305	197	0.646	108	0.354		238	130	54.60	108	45.40	
T1	1,594	859	0.539	735	0.461		1,271	536	42.20	735	57.80	
T2	3,627	2,030	0.56	1,597	0.44		3,091	1,494	48.30	1,597	51.70	
T3	1,874	1,140	0.608	734	0.392		1,642	908	27.20	734	44.70	
T4	3,863	2,654	0.687	1,209	0.313		3,341	2,132	63.80	1,209	36.20	
TX	2,510	1,800	0.717	710	0.283		2,015	1,305	64.80	710	35.20	
stage_N						<0.001						<0.001
N0	3,455	2,132	0.617	1,323	0.383		2,767	1,444	52.20	1,323	47.80	
N1	5,650	3,433	0.608	2,217	0.392		4,912	2,695	54.90	2,217	45.10	
N2	1,321	797	0.603	524	0.397		1,152	628	54.50	524	45.50	
N3	1,615	1,023	0.633	592	0.367		1,382	790	57.20	592	42.80	
NX	1,732	1,295	0.748	437	0.252		1,385	948	68.40	437	31.60	
Histological type						<0.001						<0.001
Ductal	8,480	5,129	0.605	3,351	0.395		7,241	3,890	53.70	3,351	46.30	
Lobular	1,727	1,067	0.618	660	0.382		1,425	765	53.70	660	46.30	
Adenocarcinoma	872	603	0.692	269	0.308		723	454	62.80	269	37.20	
Other	2,694	1,881	0.698	813	0.302		2,209	1,396	63.20	813	36.80	
Other metastases*						<0.001						<0.001
0	7,445	4,058	0.545	3,387	0.455		6,311	2,924	46.30	3,387	53.70	
1	3,838	2,661	0.693	1,177	0.307		3,222	2,045	63.50	1,177	36.50	
2	1,368	1,088	0.795	280	0.205		1,149	869	75.60	280	24.40	
3	239	206	0.862	33	0.138		202	169	83.70	33	16.30	
Unknown	883	667	0.755	216	0.245		714	498	69.70	216	30.30	
Subtypes						<0.001						<0.001
HR+/HER2– (Luminal A)	7,945	4,708	0.593	3,237	0.407		6,714	3,477	51.80	3,237	48.20	

Table 3 (*continued*)

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Table 3 (*continued*)

Characteristics	All cause						Breast cancer-related					
	Total	Dead		Alive		P	Total	Dead		Alive		P
		No	%	No	%			No	%	No	%	
HR+/HER2+ (Luminal B)	1,844	928	0.503	916	0.497		1,668	752	45.10	916	54.90	
HR–/HER2+ (HER2 enriched)	715	426	0.596	289	0.404		632	343	54.30	289	45.70	
HR–/HER2– (Triple negative)	1,081	937	0.867	144	0.133		856	712	83.20	144	16.80	
Unknown	2,188	1,681	0.768	507	0.232		1,728	1,221	70.70	507	29.30	
Surgery						<0.001						<0.001
Yes	3,461	1,807	0.522	1,654	0.478		2,986	1,332	44.60	1,654	55.40	
No	10,312	6,873	0.667	3,439	0.333		8,612	5,173	60.10	3,439	39.90	
Chemotherapy						<0.001						<0.001
Yes	6,549	3,678	0.562	2,871	0.438		5,754	2,883	50.10	2,871	49.90	
No	7,224	5,002	0.692	2,222	0.308		5,844	3,622	62.00	2,222	38.00	
Radiotherapy						<0.001						0.016
Yes	4,688	2,835	0.605	1,853	0.395		4,080	2,227	54.60	1,853	45.40	
No	9,085	5,845	0.643	3,240	0.357		7,518	4,278	56.90	3,240	43.10	

*, number of extra-bone (brain, liver and lung) metastatic organs.

We plotted Kaplan-Meier survival curves for age, grade, subtype, histological type, number of extra-bone metastatic organs, surgery, radiotherapy, and chemotherapy, based on OS and BCRS for BCBM patients (*Figure 2*). In addition, log-rank test for all variables is shown in *Table 4*. It is observed from the figure that the increase in age is significantly related to the worsening prognosis (*Figure 2A*, *Figure 2B*). The primary tumor has a low degree of differentiation, and the high degree of malignancy is significantly associated with poor prognosis (*Figure 2C*, *Figure 2D*). Observing the relationship between tumor subtype and prognosis, triple-negative breast cancer is significantly associated with poor prognosis (*Figure 2E*, *Figure 2F*). Observing the relationship between histological type and prognosis, the prognosis of ductal carcinoma and lobular carcinoma is significantly better than adenocarcinoma and other types (*Figure 2G*, *Figure 2H*). The increase in the number of extra-bone metastatic organs is significantly associated with poor prognosis (*Figure 2I*, *Figure 2J*). Observing the relationship between treatment and prognosis, no surgery at the primary site is significantly associated with poor prognosis (*Figure 2K*, *Figure 2L*). Patients who did not receive radiotherapy or chemotherapy were significantly associated with poor prognosis (radiotherapy: *Figure 2M*, *Figure 2N*; chemotherapy: *Figure 2O*, *Figure 2P*).

Multivariate Cox regression of prognostic factors in BCBM patients and the construction of nomogram

Multivariate Cox regression analysis of all variables, and hazard ratios (HR) and 95% CIs are shown in *Table 4*. In the final established OS and BCRS prognostic prediction models, variables such as age, grade, subtypes, histological type, number of extra-bone metastatic organs, surgery, radiotherapy, and chemotherapy were included. After that, the nomograms were constructed using the prognosis to predict the risk results (*Figures 3*,*4*).

Interior and external verification of nomogram

The multivariate cox regression model was used to generate 1, 3, and 5 years of nomograms for OS and BCRS. In the model establishment group, the C-index of nomgrams of OS and BCRS is 0.716 and 0.726, respectively. In the

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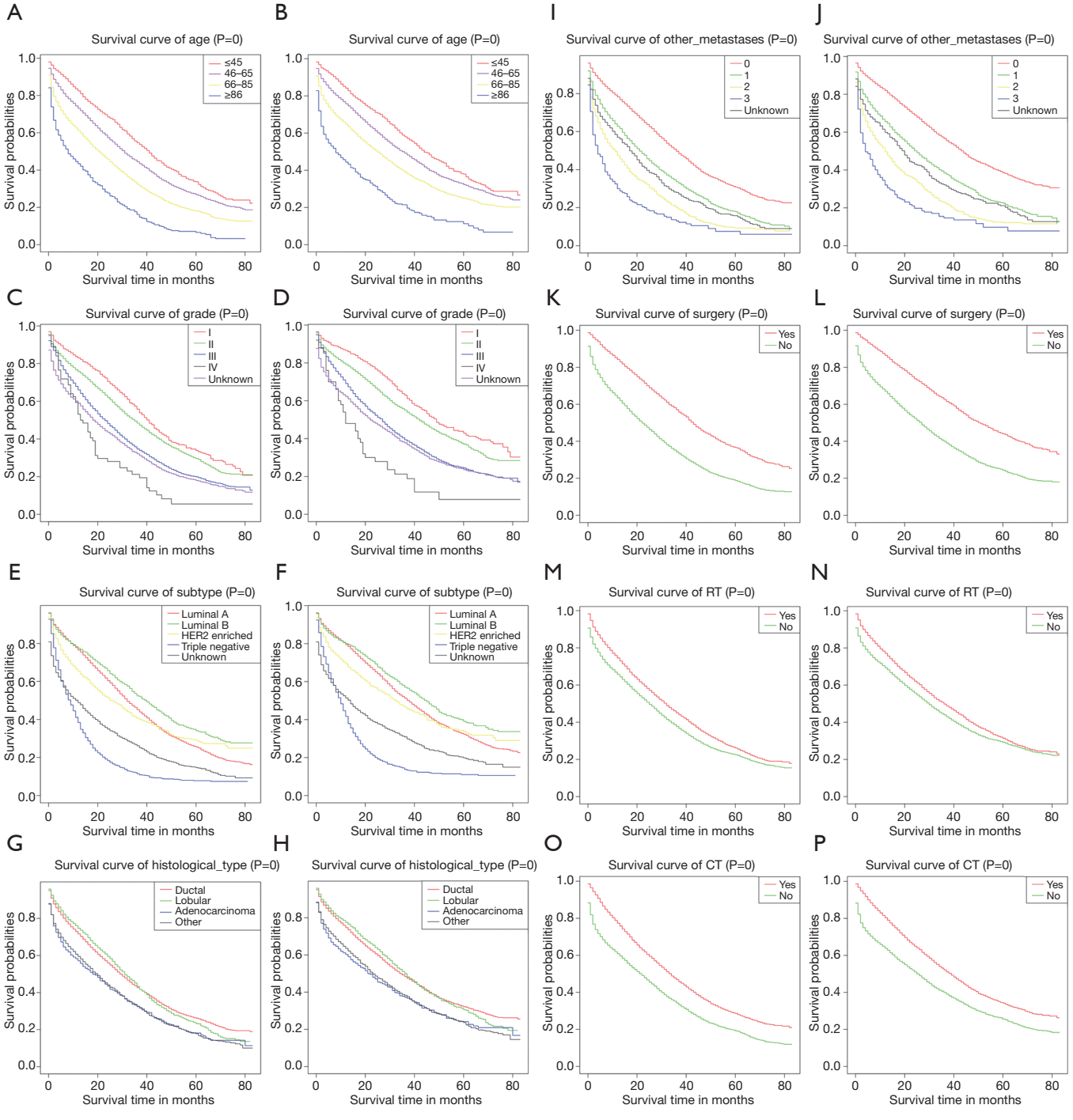

Figure 2 Survival curves in BCBM patients according to different factors. Kaplan-Meier curves among patients stratified by age at diagnosis for OS (A) and BCRS (B); Kaplan-Meier curves among patients stratified by grade for OS (C) and BCRS (D); Kaplan-Meier curves among patients stratified by subtype for OS (E) and BCRS (F). Kaplan-Meier curves among patients stratified by histological type for OS (G) and BCRS (H); Kaplan-Meier curves among patients stratified by other metastases for OS (I) and BCRS (J); Kaplan-Meier curves among patients stratified by surgery/No surgery for OS (K) and BCRS (L); Kaplan-Meier curves among patients stratified by RT/No RT for OS (M) and BCRS (N); Kaplan-Meier curves among patients stratified by CT/No CT for OS (O) and BCRS (P). BCBM, breast cancer bone metastasis; OS, overall survival; BCRS, breast cancer-related survival; CT, chemotherapy; RT, radiotherapy.

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Table 4 Multivariate Cox regression analysis for ACM and BCRM in BCBM patients

Characteristics	ACM				BCRM			
	HR	95% CI	P value	Log-rank (P value)	HR	95% CI	P value	Log-rank (P value)
Age at diagnosis				<0.001				<0.001
≤45	1.000 [reference]				1.000 [reference]			
46-65	1.207	1.121–1.300	<0.001		1.181	1.088–1.282	<0.001	
66-85	1.558	1.441–1.684	<0.001		1.454	1.332–1.587	<0.001	
≥86	2.324	2.076–2.600	<0.001		2.265	1.983–2.588	<0.001	
Gender				0.318				0.457
Female	1.000 [reference]				1.000 [reference]			
Male	1.099	0.911–1.326	0.324		1.028	0.823–1.286	0.809	
Race				0.003				0.002
White	1.000 [reference]				1.000 [reference]			
Black	1.208	1.140–1.281	<0.001		1.220	1.141–1.304	<0.001	
Asian or Pacific Islander	0.979	0.895–1.071	0.648		0.965	0.872–1.068	0.489	
Other	0.793	0.615–1.023	0.075		0.685	0.504–0.933	0.016	
Marital status				0.019				0.013
Married	1.000 [reference]				1.000 [reference]			
Unmarried	1.224	1.169–1.281	<0.001		1.213	1.150–1.278	<0.001	
Unknown	1.056	0.958–1.164	0.274		1.051	0.939–1.176	0.39	
Grade				<0.001				<0.001
I	1.000 [reference]				1.000 [reference]			
II	1.195	1.085–1.317	<0.001		1.258	1.119–1.415	<0.001	
III	1.663	1.504–1.839	<0.001		1.838	1.629–2.074	<0.001	
IV	2.083	1.581–2.745	<0.001		2.480	1.802–3.412	<0.001	
Unknown	1.408	1.271–1.560	<0.001		1.509	1.334–1.706	<0.001	
Laterality				0.008				0.004
Left	1.000 [reference]				1.000 [reference]			
Right	0.967	0.926–1.010	0.129		0.970	0.922–1.020	0.231	
Other	0.819	0.735–0.912	<0.001		0.866	0.764–0.982	0.025	
Tumor size				0.002				<0.001
<20 mm	1.000 [reference]				1.000 [reference]			
20-50 mm	0.992	0.867–1.136	0.910		1.014	0.866–1.188	0.86	
>50 mm	1.144	1.008–1.300	0.038		1.225	1.056–1.420	0.007	
Unknown	1.061	0.932–1.208	0.372		1.136	0.975–1.323	0.101	
stage_T				0.005				0.002
T0	1.000 [reference]				1.000 [reference]			
T1	0.98	0.825–1.163	0.813		0.977	0.791–1.206	0.826	

Table 4 (*continued*)

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Table 4 (*continued*)

Characteristics	ACM				BCRM			
	HR	95% CI	P value	Log-rank (P value)	HR	95% CI	P value	Log-rank (P value)
T2	1.074	0.868–1.329	0.513		1.156	0.896–1.492	0.264	
T3	1.043	0.844–1.288	0.697		1.118	0.869–1.438	0.384	
T4	1.197	0.979–1.463	0.08		1.305	1.026–1.661	0.03	
TX	1.204	0.986–1.469	0.068		1.249	0.982–1.588	0.07	
stage_N				0.016				0.007
N0	1.000 [reference]				1.000 [reference]			
N1	0.956	0.904–1.011	0.116		1.008	0.944–1.077	0.809	
N2	1.018	0.934–1.108	0.691		1.079	0.978–1.190	0.13	
N3	1.052	0.972–1.138	0.208		1.085	0.991–1.189	0.079	
NX	1.068	0.991–1.150	0.083		1.13	1.035–1.234	0.006	
Histological type				<0.001				<0.001
Ductal	1.000 [reference]				1.000 [reference]			
Lobular	1.095	1.021–1.174	0.011		1.121	1.033–1.218	0.007	
Adenocarcinoma	1.025	0.933–1.127	0.603		1.040	0.932–1.160	0.481	
Other	1.194	1.126–1.265	<0.001		1.206	1.128–1.291	<0.001	
Other metastases*				<0.001				<0.001
0	1.000 [reference]				1.000 [reference]			
1	1.573	1.495–1.655	<0.001		1.658	1.564–1.758	<0.001	
2	2.414	2.251–2.589	<0.001		2.599	2.401–2.815	<0.001	
3	3.521	3.050–4.064	<0.001		3.783	3.226–4.437	<0.001	
Unknown	1.500	1.379–1.632	<0.001		1.610	1.461–1.775	<0.001	
Subtypes				<0.001				<0.001
HR+/HER2– (Luminal A)	1.000 [reference]				1.000 [reference]			
HR+/HER2+ (Luminal B)	0.856	0.795–0.922	<0.001		0.856	0.788–0.930	<0.001	
HR–/HER2+ (HER2 enriched)	1.144	1.031–1.270	0.011		1.109	0.987–1.247	0.083	
HR–/HER2– (Triple negative)	2.745	2.542–2.963	<0.001		2.858	2.616–3.121	<0.001	
Unknown	1.519	1.428–1.615	<0.001		1.568	1.459–1.685	<0.001	
Surgery				<0.001				<0.001
Yes	1.000 [reference]				1.000 [reference]			
No	1.529	1.444–1.620	<0.001		1.571	1.469–1.679	<0.001	
Chemotherapy				<0.001				<0.001
Yes	1.000 [reference]				1.000 [reference]			
No	1.540	1.465–1.618	<0.001		1.601	1.513–1.695	<0.001	
Radiotherapy				<0.001				<0.001
Yes	1.000 [reference]				1.000 [reference]			
No	1.095	1.045–1.146	<0.001		1.057	1.003–1.114	0.039	

*, number of extra-bone (brain, liver and lung) metastatic organs. ACM, analyze all-cause mortality; BCRM, breast cancer-related mortality.

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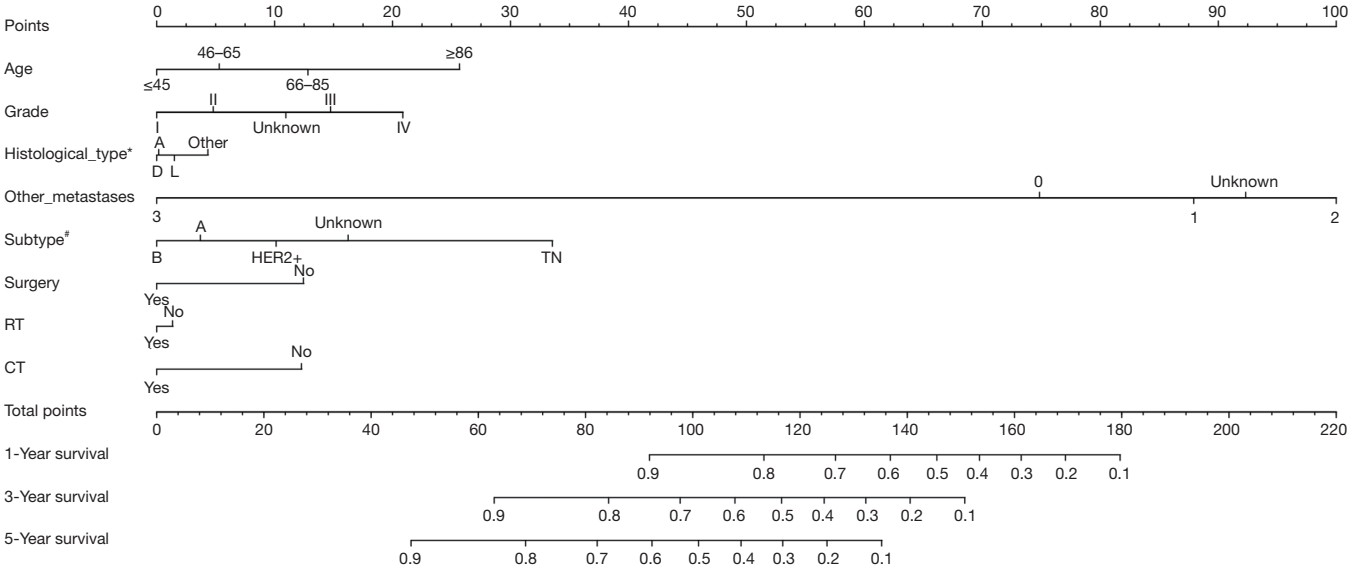

Figure 3 Nomogram of overall survival at 1, 3, and 5 years in patients with breast cancer bone metastasis prediction. *, A, adenocarcinoma; D, ductal carcinoma; L, lobular carcinoma; #, A, luminal A; B, luminal B; HER2+, HER2 enriched; TN, triple negative.

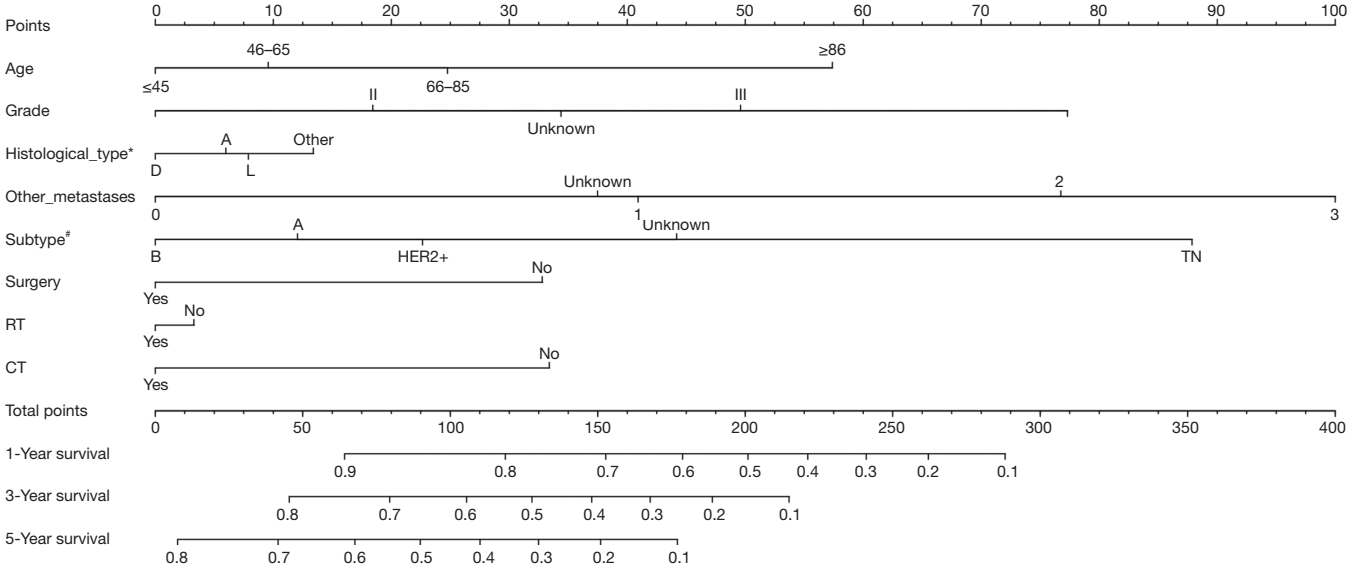

Figure 4 Nomogram of breast cancer-related survival at 1, 3, and 5 years in patients with breast cancer bone metastasis prediction. *, A, adenocarcinoma; D, ductal carcinoma; L, lobular carcinoma; #, A, luminal A; B, luminal B; HER2+, HER2 enriched; TN, triple negative.

validation group, the C-index of nomogram of OS and BCRS is 0.716 and 0.735, respectively. The ROC curve results of the model establishment group and the validation group are shown in *Figures 5* and *Figure 6*, respectively. The calibration plots of the model establishment group and the validation group show a good consistency between the predicted nomograms of OS and BCRS (*Figures 7,8*).

Discussion

The incidence of bone metastasis in breast cancer is high (11). Individualized comprehensive treatment plans should be developed according to the specific conditions to reduce or avoid bone-related events, prolong the survival of patients and improve the quality of life (12-14). The

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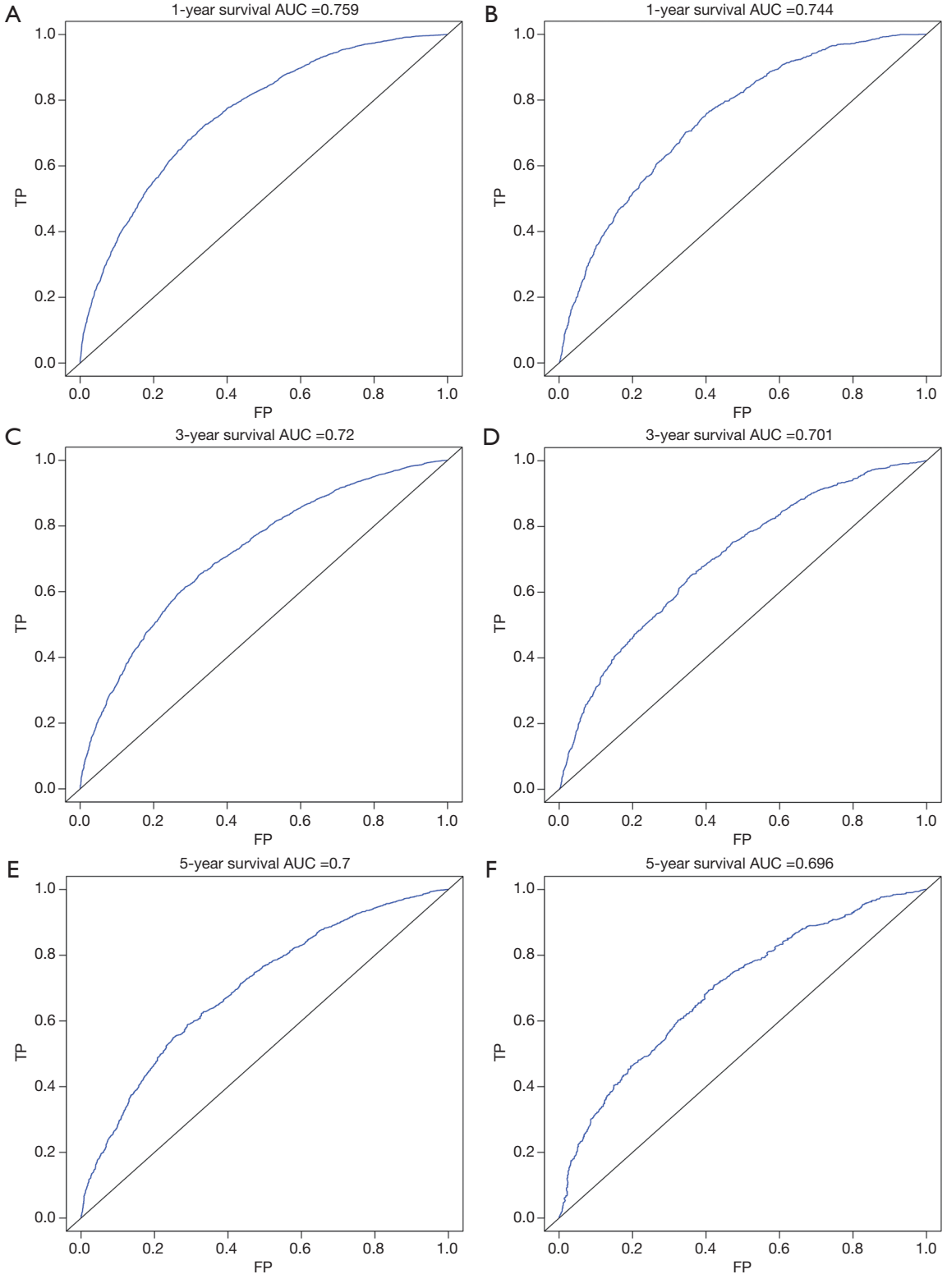

Figure 5 ROC curve of overall survival (OS). ROC curves for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group; ROC curves for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group. AUC, area under the ROC curve.

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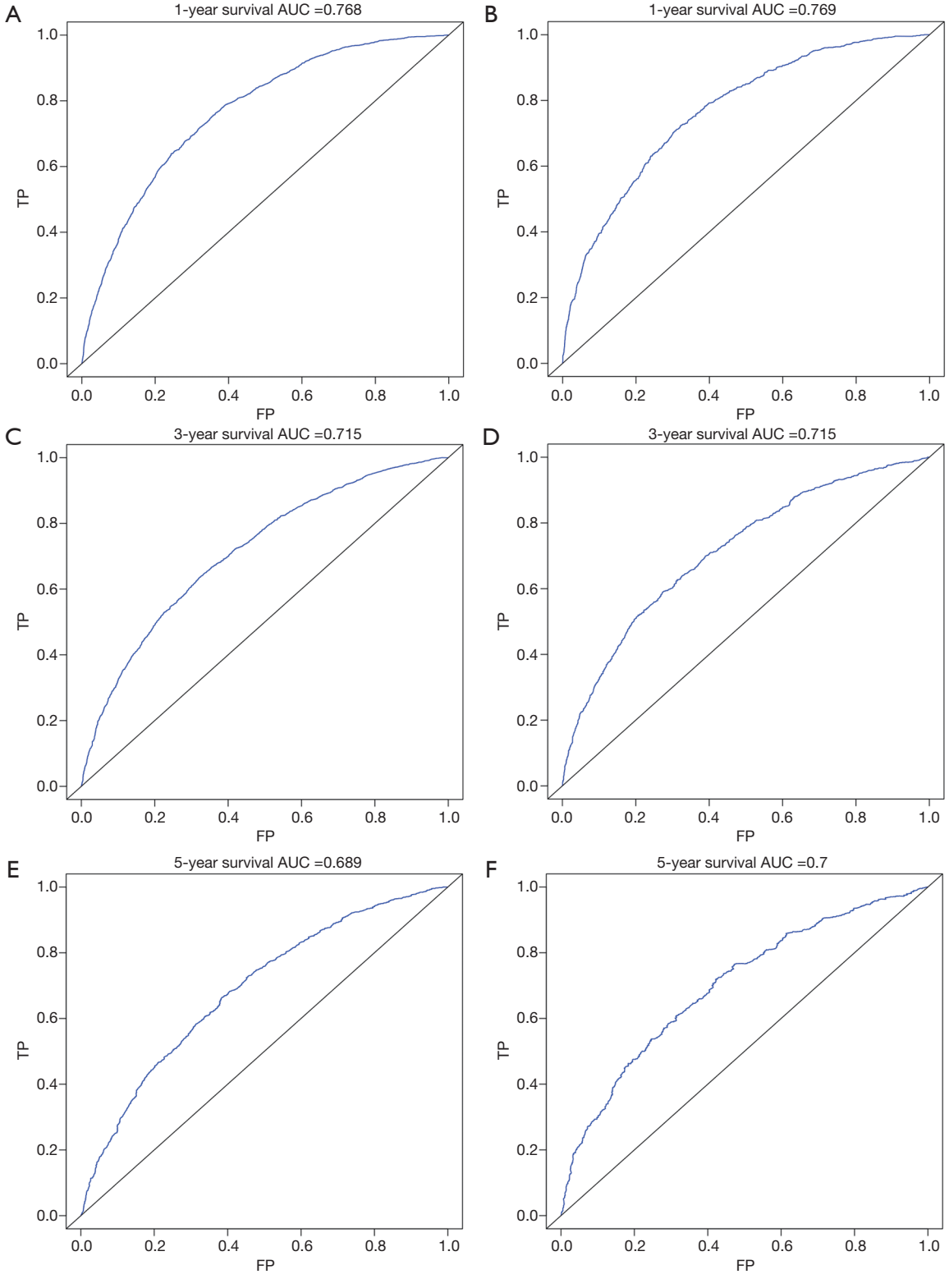

Figure 6 ROC curve of breast cancer-related survival (BCRS). ROC curves for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group; ROC curves for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group. AUC, area under the ROC curve.

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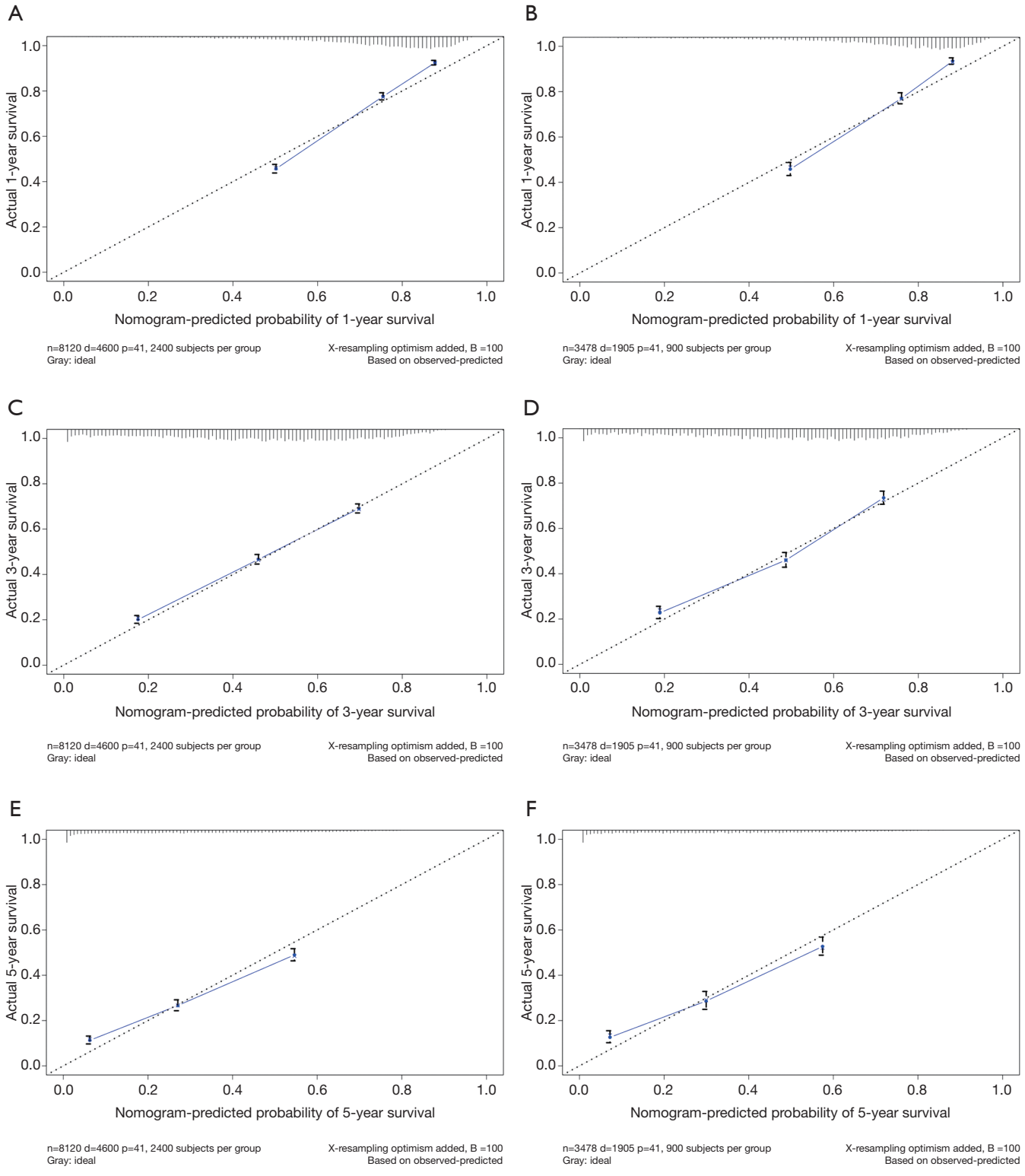

Figure 7 Calibration plots of overall survival (OS). Calibration plots for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group. Calibration plots for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group.

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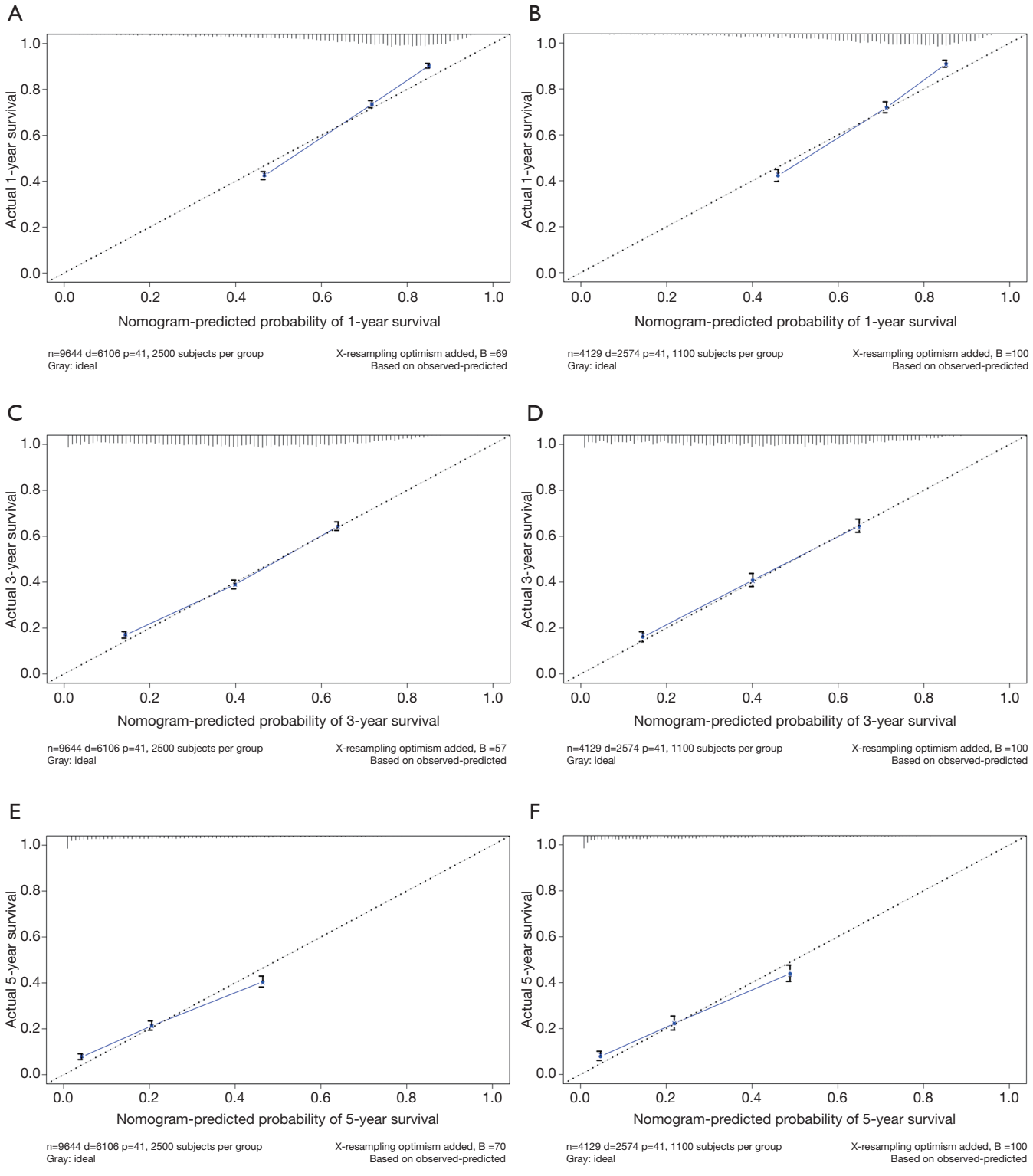

Figure 8 Calibration plots of breast cancer-related survival (BCRS). Calibration plots for 1 year (A), 3 years (C), and 5 years (E), respectively, validated by the model establishment group. Calibration plots for 1 year (B), 3 years (D), and 5 years (F), respectively, validated by the validation group.

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key to developing an individualized treatment plan is to fully evaluate the prognosis of the patient. The SEER database provides a wealth of complete information on demographics, oncology, and treatment of breast cancer patients, providing appropriate sample data for establishing clinical predictive models.

Demographic information for BCBM patients

Median survival time is the most intuitive indicator of the prognosis of BCBM patients. Sciubba *et al.* (15) reviewed 327 patients with bone metastases, and the median survival of the overall cohort was 21.7 months. In our study, 13,773 patients with confirmed breast cancer with bone metastases were included, with a median survival of 20.0 months, similar to previous reports. Our research is more convincing due to the expansion of the sample size. In entire group, the main age of patients was 46–65 years old (48.2%) and 66–85 years old (34.7%), which was consistent with the double-peak pattern of breast cancer in women, the age of onset of early peak was 52 years old, and the age of onset of late peak was 71 years old (16,17). In addition, the increase in age is accompanied by a gradual increase in mortality, so age is considered to be one of the important factors predicting prognosis. In terms of gender, the literature reports that male breast cancer is a relatively rare disease, accounting for about 1% of breast cancer patients (18). In our study, 173 (1.3%) male breast cancer patients with bone metastases were included, although the proportion was not high. However, it is still higher than the documented incidence rate. On the one hand, it shows that the incidence of breast cancer in men is low. On the other hand, it is indicated that male breast cancer is generally not easy to attract attention, so it is mostly advanced at the time of diagnosis. However, gender differences did not result in significant differences in BCRM between male and female (56.7% *vs.* 56.1%, P=0.876). In terms of ethnicity, 10,612 (77.0%) white BCBM patients were included in the study, which constitute the main ethnic group in our study. According to the literature, although the incidence of white breast cancer is higher, the mortality rate of black breast cancer patients is higher, which is consistent with the results of our study (19). The breast cancer-related mortality rates of black and white in our study are 63.6% and 55.2%, respectively. Marital status is considered to be an important factor in the development of breast cancer, and unmarried status is a high-risk factor for breast cancer (20). In our study, the proportion of patients who were unmarried in the study was higher than the married status (51.9% *vs.* 42.7%). In addition, unmarried patients also had higher BCRM than married patients (61.2% *vs.* 50.2%).

Tumor pathology and treatment information for BCBM patients

In entire group, grade II (34.7%) and grade III (30.9%) were dominant. As with other tumors, the degree of differentiation was low, and the mortality rate of patients with high altitude was higher. Among the histological types, ductal carcinoma patients (61.6%) had the most, but the BCRM of adenocarcinoma was higher than that of ductal carcinoma and lobular carcinoma (62.8% *vs.* 53.7% *vs.* 53.7%). In recent years, DNA microarray technology and multi-gene RT-PCR quantitative detection methods for molecular classification of breast cancer to predict the risk of breast cancer recurrence and metastasis and its response to treatment, the molecular sub-technical technology combined with immunohistochemistry, breast cancer can be classified into four categories: HR+/HER2– (Luminal A), HR+/HER2+ (Luminal B), HR–/HER2+ (HER2 enriched), and HR–/HER2– (Triple Negative) (19,20). The clinical response and survival of different molecular subtypes of breast cancer are different, and more and more attention has been paid to it. Among the four subtypes, luminal A is the most common, and studies have shown that the percentage of breast cancer in each subtype is 50%, 14.1%, 12.7%, and 23.2%, respectively. In our study, luminal A still accounted for the vast majority, with the percentages of each subtype being 57.7%, 13.4%, 5.2%, and 7.8%, respectively. In terms of treatment, it can be clearly observed in *Table 3* that patients who did not receive surgery, radiotherapy or chemotherapy had significantly higher BCRM than patients who received the corresponding treatment. This also suggests that aggressive treatment can help improve the prognosis of BCBM patients.

Evaluation of predictive models

Prognostic factors with P<0.001 were selected by log-rank test, and nomograms of OS and BCRS were constructed according to multivariate cox regression analysis. Internal and external verification of nomograms using C-index, ROC curves and calibration plots. The C- index represents the predictive accuracy of nomograms, and the C-index of both nomograms is greater than 0.7, achieving moderate prediction accuracy. The AUC of the ROC curve represents

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the prediction accuracy of nomograms. For the OS nomogram, only the validation group had an AUC of less than 0.7 in the 5-year survival prediction, demonstrating that the 1- and 3-year survival prediction models of OS achieved moderate accuracy. For the BCRS nomogram, only the model establishment group had an AUC of less than 0.7 in the 5-year survival prediction, demonstrating that the 1- and 3-year survival prediction models of BCRS achieved moderate accuracy. The calibration chart can assess the consistency of the predicted and observed conditions. The 1-, 3- and 5-year calibration plots of OS and BCRS show an excellent consistency, which proves that the two nomograms have good predictive ability. The predictive model of this study has been tested for predictive ability by three methods and has achieved satisfactory results. In addition, the model is based on a large sample of the SEER database and is more convincing.

Limitations

This study is based on a retrospective study conducted by the SEER database. Due to the limitations of the data included in the database itself, more detailed patient information is not available. We are unable to obtain the patient's physical condition before diagnosis, whether it is accompanied by other diseases, surgical methods, chemotherapy drugs, dose of radiotherapy, and the specific follow-up time for each patient, which limits our further evaluation. In addition, we are unable to obtain short-term or long-term complications after treatment, which severely limits our effective judgment of prognosis. Finally, this study uses only a set of data to split the internal and external verification of the prediction model, which itself has a great bias. However, because the objectivity and authenticity of the SEER database can be guaranteed, we still have reason to believe the nomograms obtained in this study, and then we can further select other samples to verify the model.

Conclusions

In this study, the SEER database was collected to analyze the factors affecting the prognosis of patients with BCBM, and to select a number of factors that have significant effects on prognosis to establish a predictive model. The final nomograms obtained satisfactory results after a series of internal and external verifications, verifying the accuracy of their predictions. Other samples are needed in the future for more comprehensive external validation of the model, but at this stage, this model will help physicians and patients to have a more accurate judgment of the prognosis.

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Footnote

Reporting Checklist: The author has completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tbcr-20-14

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tbcr-20-14). The author has no conflicts of interest to declare.

Ethical Statement: The author is 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. Ethical Approval and Informed Consent are not applicable. The data comes from the public SEER database. The database has completed Ethical Approval/Informed Consent when acquiring relevant data.

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