Original Article

Novel prognostic nomograms for female patients with breast cancer and bone metastasis at presentation

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Background: There is a paucity of literature about prognostic evaluation for patients with breast cancer (BC) and bone metastasis at presentation. To date, little is known about how to accurately predict the prognosis of BC patients with bone metastasis at presentation. Thus, an accurate prediction tool of prognosis in this population is urgently needed. Our goal is to construct novel and prognostic nomograms for BC patients with bone metastasis at presentation.

Methods: We searched Surveillance, Epidemiology, and End Results (SEER) database for BC patients with bone metastasis at presentation between 2010 and 2016. Multivariate analysis was performed to obtain significantly independent variables. Then, novel prognostic nomograms were constructed based on those independent predictors.

Results: Tumor grade, histological type, primary tumor size, tumor subtype, surgery, chemotherapy and number of metastatic organs except bone were recognized as significantly independent variables of both overall survival (OS) and cancer-specific survival (CSS). Then those significant variables were integrated to construct nomograms for 3- and 5-year survival. Calibration plots for the 3- and 5-year survival in training and validation sets showed that the prediction curve was close to a 45 degree slash. The C-indices of OS in training and validation cohorts were 0.705 and 0.678, respectively. Similar results were observed for CSS in training and validation cohorts.

Conclusions: Our proposed nomograms can effectively and accurately predict the prognosis of BC patients with bone metastasis at presentation, which provide a basis for individual treatments for metastatic lesions.

Keywords: Breast cancer (BC); bone metastasis; nomogram; predictor; prognosis

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Introduction

Breast cancer (BC) is the most frequently diagnosed female malignance, which ranks the second leading cause of cancer death (1,2). BC cells most frequently metastasize to the bone, with up to 75% of stage IV BC patients developing bone metastasis (3). Multiple systemic organ metastases from BC are common, and 17–37% patients have diseases limited to the skeleton (4-6). Patients with bone-only first metastasis tend to experience a better prognosis than those with other-only first metastasis (7). Patients with disease that remains confined to the bone have longer survival than patients with subsequent visceral involvement (8). Bone metastasis can result in poor survival, considerable morbidity, intractable pain and decreased quality of life (9-11).

The 3- and 5-year survival rates of BC patients with bone metastasis were 25% and 13%, respectively (12). Pogoda *et al.* (13) reported that the median overall survival (OS) was only 5.5 months after the detection of bone metastasis among triple-negative BC patients. However, with the development of hormone or bone-targeted drug therapies, BC patients including metastatic BC patients experienced a better prognosis (14,15). Additionally, surgery or radiotherapy for patients with bone metastasis can provide effective local control and improve quality of life (16-20), especially for patients with pathologic fractures (9).

To our knowledge, the risk factors and their effects on prognosis of patients with BC and bone metastasis are rarely explored. Ahn *et al.* (21) reported that bisphosphonate treatment was the most significant positive predictor of OS among BC patients with bone-only metastasis. Amanda Parkes *et al.* (22) found that multiple bone metastasis and both axial and appendicular skeleton involvement were independent predictors of decreased OS. Among BC patients with spine metastases, Zhao *et al.* (23) found that no visceral metastasis, solitary spine metastasis and postoperative chemotherapy performed were independent prognostic factors of increased OS. Other significant independent predictors for survival among patients with BC and bone metastasis were race, age, tumor grade, tumor subtype, surgery for primary tumor (24).

Standard treatments for patients with BC and bone metastasis are lacking. In order to provide personalized and reasonable treatment strategies, we need to make an accurate prediction of outcome in patients with BC and bone metastasis. Recently, the nomogram is widely used in various cancers to conveniently and accurately predict the outcomes (25-27). It can be recognized as a helpful tool in terms of multidisciplinary decision-making and optimizing treatment options especially for metastatic lesions. However, no systematic attempts have ever been made to develop prognostic nomograms for BC patients with bone metastasis. Therefore, we aim to develop and validate nomograms for those patients and assist clinicians to accurately predict survival.

Methods

Patients selection and data acquisition

From 2010 to 2016, patients with a diagnosis of BC and bone metastasis at presentation were identified using the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/). Patient data extraction were performed using the case-listing session procedure from the SEER program (28).

Variables selected from SEER database were as follows: race, age, gender, laterality, pathological pattern, tumor grade, T, N stage (AJCC stage group 7th edition, 2010), tumor size, tumor subtype, surgery, radiotherapy, chemotherapy, cause of death, vital status and survival time. Patients were included according to the following criteria: (I) female patients; (II) diagnosis confirmed by histology; (III) age at diagnosis 20–80 years. Patients were excluded for the following reasons: (I) cases with a diagnosis according to clinical or imaging findings or autopsy; (II) cases with unknown variables; (III) cases with unknown survival time or survival time less than one month (*Figure 1*).

A total of 5,860 patients with BC and bone metastasis at presentation were identified from 18 SEER registries. We randomly selected patients from nine registries (Detroit, Alaska Natives, Atlanta, Kentucky, Greater Hawaii, Iowa, Georgia, Connecticut, and California) as the training cohort (n=3,311), and patients from the other nine registries were regarded as the validation cohort (n=2,549). Radiotherapy or surgical treatment in this research was performed to treat the primary lesion.

Statistical analysis

We first performed univariate and multivariate Cox regression analysis to evaluate and reveal significant risk factors of OS or cancer-specific survival (CSS). CSS was calculated from initial diagnosis to death specific to the cancer-related diagnosis (28). Meanwhile, we obtained the hazard ratios (HRs) with 95% confidence intervals (CIs) of

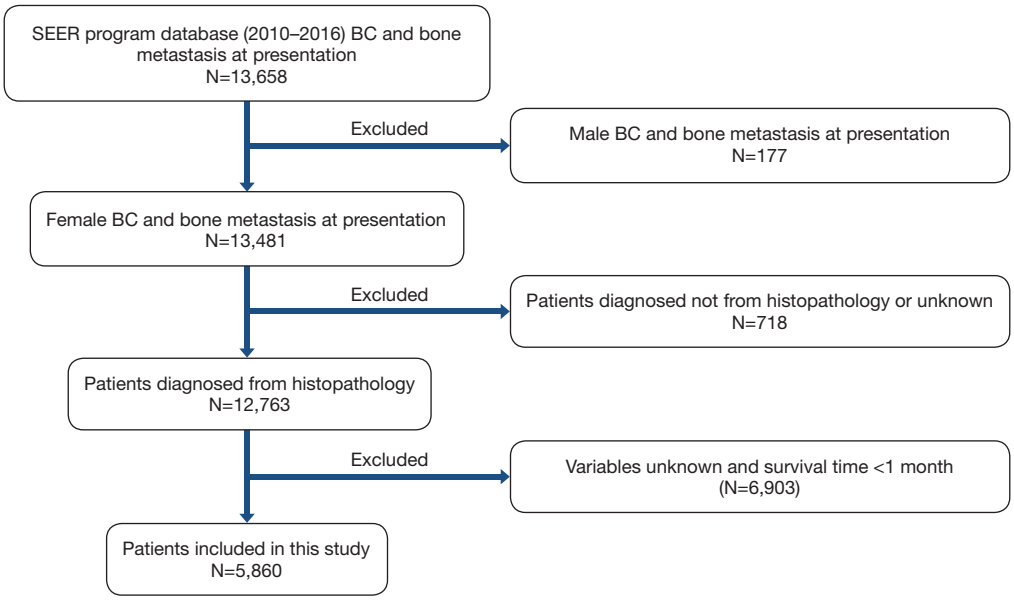

Figure 1 The flow chart for selection of study population.

various predictors. IBM SPSS Statistics v220.0 was used for the above statistical analyses.

Nomograms were constructed and validated based on a set of significant variables of multivariate analysis from the training set. The performance of prognostic models was evaluated based on concordance index (C-index) and calibration plots in training and validation cohorts (29). We performed bootstraps with 1,000 resamples to validate the nomograms in training and validation cohorts (30). R version 3.6.0 software (https://www.r-project.org/) was applied for the above statistical analyses.

Results

Baseline characteristics

Detailed clinical characteristics of all cases were shown in *Table 1*. All BC patients had bone metastasis at initial diagnosis. Mean and median ages of the entire cohort were 57 and 58 years (range, 21–80 years), respectively. More than three out of four patients (n=4,455, 76.0%) were white race. About half (n=3,021, 51.6%) of the patients were left—origin of primary BC. Majority of patients were diagnosed with tumor grade II or III/IV BC (46.7% and 44.1%, respectively), and only 535 patients (9.1%) were with tumor grade I. The most common histological type was ductal cancer (78.5%). The mean and median tumor sizes were 5.1 and 4.1 cm, respectively. The proportions of patients diagnosed with luminal A, luminal B, HER2$^+$ and triple-negative were 65.5%, 18.2%, 6.7% and 9.6%, respectively. Almost half of all patients received radiotherapy (n=2,483, 42.4%). About one third of patients had surgical treatment (n=2,131, 36.4%). Approximately two-thirds of patients received chemotherapy (n=3,650, 62.3%). In terms of metastatic types, 3,520 patients (60.1%) had bone-only metastatic pattern, 1,684 patients (28.7%) had bone and one visceral metastatic pattern, 656 patients (11.2%) had bone and ≥2 visceral metastatic pattern. The survival outcome was poor with 5-year OS and CSS rate of 31.4% and 33.8%, respectively.

Independent predictors in the study population

The detailed results of the univariate analysis from the training set were shown in *Table 2*. Tumor grade, T stage, histological type, tumor size, tumor subtype, surgery, chemotherapy and number of metastatic organs except bone were shown to be significantly associated with both OS and CSS. Then those significant variables were included for further multivariate Cox proportional-hazard regression analysis. We used the backwards selection procedure to perform the variable selection, which is helpful for determine the independent predictors that effectively contribute to patients' survival. Ultimately, tumor grade,

Table 1 Clinical characteristics of 5,860 patients with breast cancer with identified bone metastases at diagnosis

Variable	Value
Age (years)	
Mean	57
Median	58
20–40	614 (10.5)
41–60	2,755 (47.0)
61–80	2,491 (42.5)
Race	
White	4,455 (76.0)
Black	926 (15.8)
Others	479 (8.2)
Laterality	
Left	3,021 (51.6)
Right	2,839 (48.4)
Tumor grade	
I	535 (9.1)
II	2,739 (46.7)
III/IV	2,586 (44.1)
T stage	
T1	752 (12.8)
T2	2,182 (37.2)
T3	1,188 (20.3)
T4	1,738 (29.7)
N stage	
N0	1,253 (21.4)
N1	2,840 (48.5)
N2	803 (13.7)
N3	964 (16.5)
Histological type	
Ductal	4,603 (78.5)
Lobular	657 (11.2)
Mixed ductal and lobular	328 (5.6)
Others	272 (4.6)
Tumor size (cm)	
Mean	5.1
Median	4.1
<5	3,417 (58.3)
5–10	2,062 (35.2)
>10	381 (6.5)
Tumor subtype	
Luminal A	3,839 (65.5)
Luminal B	1,065 (18.2)
HER2+	391 (6.7)
Triple-negative	565 (9.6)
Surgery	
Yes	2,131 (36.4)
No	3,729 (63.6)
Radiotherapy	
Yes	2,483 (42.4)
No	3,377 (57.6)
Chemotherapy	
Yes	3,650 (62.3)
No	2,210 (37.7)
Brain metastasis	
Yes	360 (6.1)
No	5,500 (93.9)
Liver metastasis	
Yes	1,331 (22.7)
No	4,529 (77.3)
Lung metastasis	
Yes	1,396 (23.8)
No	4,464 (76.2)
Number of metastatic organs except bone	
0	3,520 (60.1)
1	1,684 (28.7)
≥2	656 (11.2)
Status	
Alive	3,086 (52.7)
Dead	2,774 (47.3)
3-year OS rate	51.7%
3-year CSS rate	53.6%
5-year OS rate	31.4%
5-year CSS rate	33.8%

Grade I: well differentiated; Grade II: moderately differentiated; Grade III: poorly differentiated; Grade IV: undifferentiated anaplastic. OS, overall survival; CSS, cancer-specific survival.

Table 2 Univariate Cox regression analysis of OS and CSS in the training cohort

Variable	OS			CSS		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
20–40	1			1		
41–60	0.922	0.779–1.092	0.347	0.945	0.790–1.130	0.534
61–80	0.854	0.719–1.014	0.071	0.868	0.724–1.042	0.128
Race						
White	1			1		
Black	1.076	0.941–1.231	0.282	1.061	0.921–1.222	0.413
Others	1.114	0.934–1.329	0.229	1.075	0.891–1.298	0.447
Laterality						
Left	1			1		
Right	1.043	0.946–1.150	0.397	1.04	0.939–1.152	0.454
Tumor grade						
I	1			1		
II	1.299	1.065–1.585	0.01	1.404	1.130–1.745	0.002
III/IV	1.952	1.605–2.375	<0.001	2.155	1.739–2.670	<0.001
T stage						
T1	1			1		
T2	1.002	0.847–1.187	0.978	0.97	0.813–1.157	0.733
T3	1.205	1.005–1.445	0.044	1.2	0.993–1.451	0.06
T4	1.394	1.176–1.651	<0.001	1.397	1.170–1.667	<0.001
N stage						
N0	1			1		
N1	0.99	0.872–1.124	0.878	0.998	0.872–1.141	0.972
N2	0.902	0.762–1.069	0.234	0.899	0.751–1.077	0.248
N3	1.003	0.858–1.173	0.967	1.042	0.884–1.227	0.627
Histological type						
Ductal	1			1		
Lobular	0.959	0.817–1.125	0.606	0.964	0.815–1.140	0.67
Mixed ductal and lobular	0.857	0.684–1.074	0.181	0.859	0.678–1.088	0.208
Others	1.642	1.349–1.999	<0.001	1.705	1.392–2.088	<0.001
Tumor size (cm)						
<5	1			1		
5–10	1.235	1.114–1.369	<0.001	1.263	1.134–1.408	<0.001
>10	1.836	1.521–2.215	<0.001	1.954	1.613–2.368	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Variable	OS			CSS		
	HR	95% CI	P	HR	95% CI	P
Tumor subtype						
Luminal A	1			1		
Luminal B	0.883	0.767–1.017	0.085	0.865	0.746–1.004	0.056
HER2+	1.175	0.959–1.439	0.119	1.168	0.944–1.444	0.153
Triple-negative	3.366	2.931–3.866	<0.001	3.482	3.013–4.023	<0.001
Surgery						
Yes	1			1		
No	1.842	1.658–2.047	<0.001	1.814	1.624–2.026	<0.001
Radiotherapy						
Yes	1			1		
No	0.996	0.903–1.098	0.928	0.959	0.865–1.063	0.424
Chemotherapy						
Yes	1			1		
No	1.269	1.150–1.401	<0.001	1.238	1.116–1.374	<0.001
Number of metastatic organs except bone						
0	1			1		
1	1.678	1.504–1.873	<0.001	1.735	1.547–1.947	<0.001
≥2	3.078	2.676–3.541	<0.001	3.24	2.798–3.751	<0.001

Grade I: well differentiated; Grade II: moderately differentiated; Grade III: poorly differentiated; Grade IV: undifferentiated anaplastic. OS, overall survival; CSS, cancer-specific survival.

histological type, tumor size, tumor subtype, surgery, chemotherapy and number of metastatic organs except bone were included to develop the nomogram. Multivariate analysis of the training set also revealed that these final seven variables were significant predictors of OS and CSS (*Table 3*).

Prognostic nomogram building and validation

For the development of nomogram for BC patients with bone metastasis, final seven independent risk factors of survival from the training set were incorporated. The nomograms (*Figures 2,3*) revealed that tumor subtype and number of metastatic organs except bone contributed most to both OS and CSS. Nomogram as a predictive tool is quite user-friendly. Clinicians or patients can sum the scores of each covariate and draw a vertical line straight downwards to determine the probabilities of survival of each patient. The scores assigned to each variable can be viewed in detail in *Table 4*.

For instance, a BC woman patient presented bone metastasis at diagnosis. The primary tumor was identified as grade II and ductal type with size 6.0 cm. The tumor subtype proved to be luminal B. She then received surgery for primary tumor and chemotherapy. No other visceral metastasis was found. We add the scores of all the variables together to get the total scores of 8.2 points for OS and 8.8 points for CSS. Thus, this patient's corresponding 3-year OS and cancer specific survival rates were about 70% and 72%, respectively.

Performance of models was validated and revealed internally and externally. As shown in *Figures 4* and *5*, the prediction curves in both training and validation sets were close to a 45 degree slash, which indicated that

Table 3 Multivariate Cox regression analysis of OS and CSS in the training cohort

Variable	OS			CSS		
	HR	95% CI	P	HR	95% CI	P
Tumor grade						
I	1			1		
II	1.373	1.122–1.680	0.002	1.497	1.201–1.867	<0.001
III/IV	1.956	1.587–2.410	<0.001	2.197	1.749–2.760	<0.001
T stage						
T1	1			1		
T2	0.95	0.801–1.126	0.553	0.906	0.757–1.083	0.277
T3	0.88	0.698–1.109	0.279	0.832	0.653–1.061	0.138
T4	0.951	0.779–1.161	0.622	0.9	0.730–1.109	0.323
Histological type						
Ductal	1			1		
Lobular	1.275	1.077–1.509	0.005	1.327	1.111–1.586	0.002
Mixed ductal and lobular	1.115	0.887–1.401	0.351	1.139	0.896–1.447	0.288
Others	1.415	1.160–1.726	0.001	1.438	1.171–1.765	0.001
Tumor size (cm)						
<5	1			1		
5–10	1.242	1.070–1.442	0.004	1.274	1.089–1.490	0.002
>10	1.581	1.269–1.970	<0.001	2.674	1.334–2.100	<0.001
Tumor subtype						
Luminal A	1			1		
Luminal B	0.831	0.714–0.968	0.017	0.783	0.667–0.919	0.003
HER2+	0.987	0.795–1.226	0.907	0.94	0.750–1.179	0.592
Triple-negative	3.217	2.755–3.757	<0.001	3.196	2.720–3.756	<0.001
Surgery						
Yes	1			1		
No	1.664	1.490–1.858	<0.001	1.65	1.470–1.852	<0.001
Chemotherapy						
Yes	1			1		
No	1.595	1.426–1.783	<0.001	1.557	1.385–1.751	<0.001
Number of metastatic organs except bone						
0	1			1		
1	1.585	1.414–1.777	<0.001	1.655	1.468–1.867	<0.001
≥2	2.664	2.294–3.093	<0.001	2.843	2.430–3.326	<0.001

Grade I: well differentiated; Grade II: moderately differentiated; Grade III: poorly differentiated; Grade IV: undifferentiated anaplastic. OS, overall survival; CSS, cancer-specific survival.

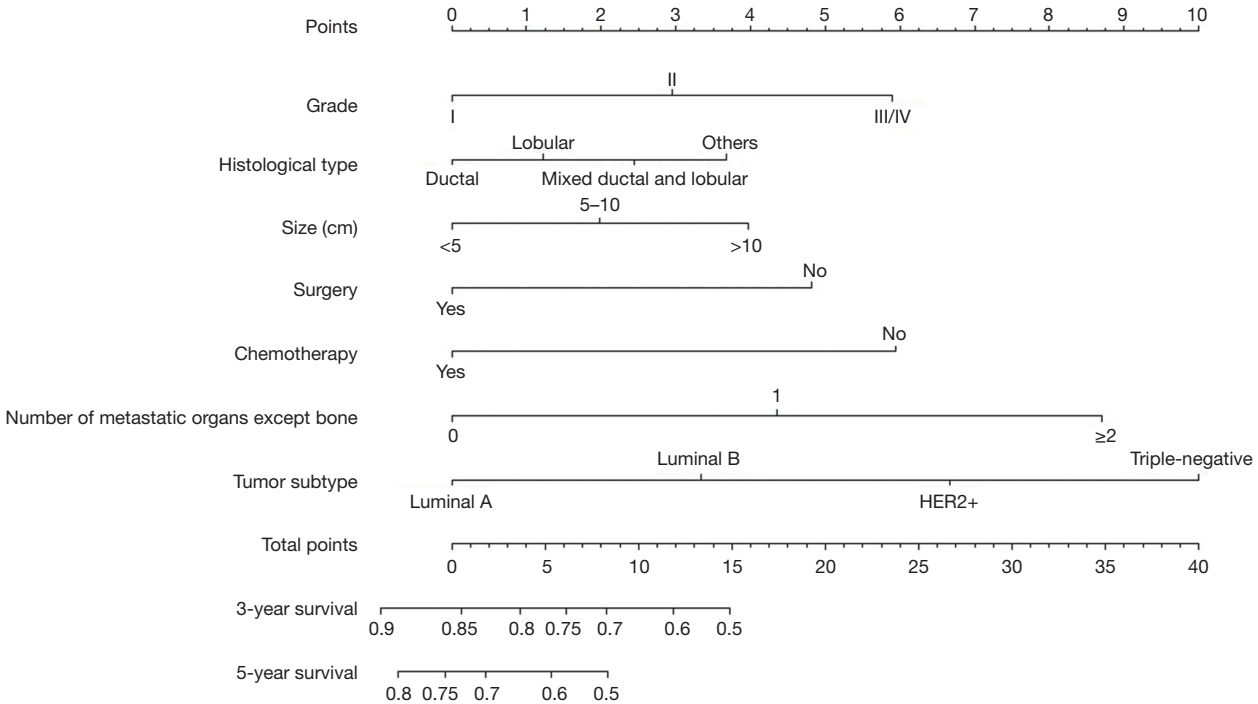

Figure 2 Nomogram for predicting 3- and 5-year overall survival of patients with breast cancer and bone metastasis at presentation.

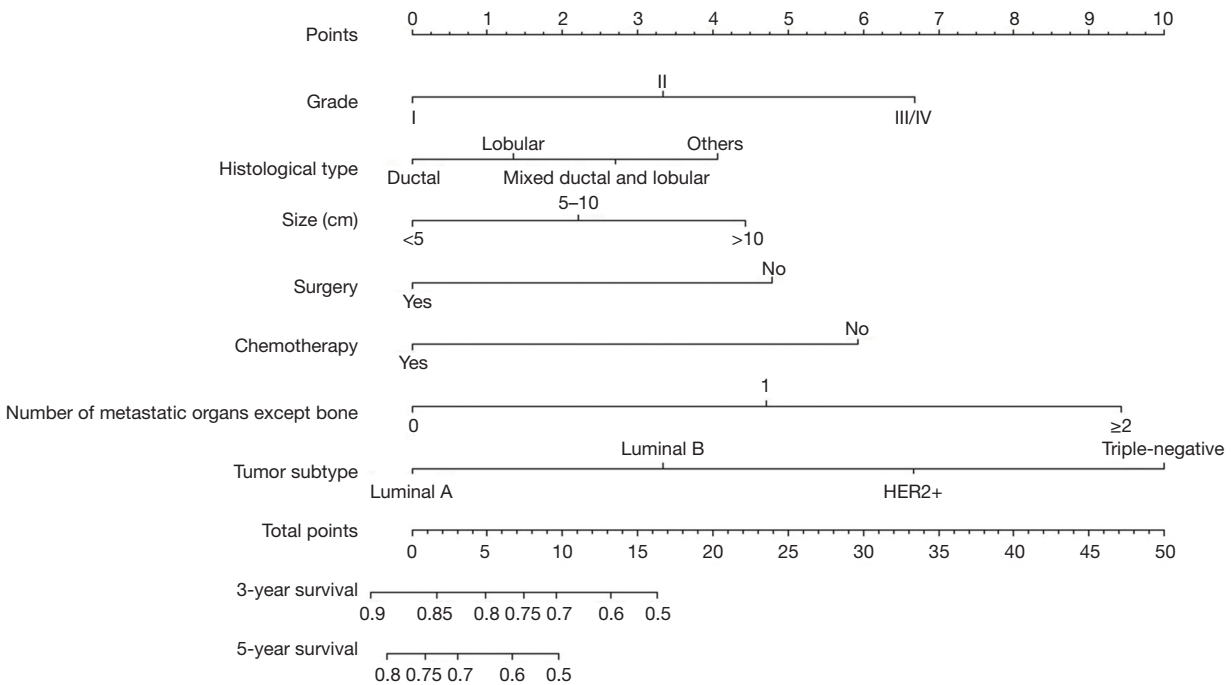

Figure 3 Nomogram predicting 3- and 5-year cancer-specific survival of patients with breast cancer and bone metastasis at presentation.

Table 4 Point assignment for specific categories of the variables included in the nomograms

Variable	OS nomogram	CSS nomogram
Tumor grade		
I	0	0
II	2.9	3.3
III/IV	5.9	6.7
Histological types		
Ductal	0	0
Lobular	1.2	1.4
Mixed ductal and lobular	2.4	2.7
Others	3.7	4.1
Tumor size (cm)		
<5	0	0
5–10	2	2.2
>10	4	4.4
Tumor subtype		
Luminal A	0	0
Luminal B	3.3	3.3
HER2+	6.7	6.7
Triple-negative	10	10
Surgery		
Yes	0	0
No	4.8	4.8
Chemotherapy		
Yes	0	0
No	5.9	5.9
Number of metastatic organs except bone		
0	0	0
1	4.4	4.7
≥2	8.7	9.4

Grade I: well differentiated; Grade II: moderately differentiated; Grade III: poorly differentiated; Grade IV: undifferentiated anaplastic. OS, overall survival; CSS, cancer-specific survival.

nomogram prediction has an obvious correlation with actual observation. The C-indices of OS in training and validation cohorts were 0.705 (95% CI, 0.691–0.719) and 0.678 (95% CI, 0.661–0.695), respectively. The C-indices of CSS in training and validation cohorts were 0.710 (95% CI, 0.696–0.724) and 0.684 (95% CI, 0.666–0.702), respectively.

Discussion

BC patients with bone metastasis were more likely to experience poor prognosis and quality of life (9,10). Moreover, little is known about how to accurately predict the prognosis of this population. In order to provide some useful insights into the prognosis and treatment strategies for this challenging disease, we retrospectively analyzed BC patients with bone metastasis at presentation (n=5,860) from the SEER database.

In this study, we identified seven independent prognostic predictors of BC patients with bone metastasis. Tumor grade was a significant variable of OS and CSS, which was in accordance with the previous studies (31,32). Histological type was found to be an independent predictor of survival among BC patients with bone metastasis. Patients in ductal group had better survival compared with lobular group. Tumor size is usually recognized as an important risk factor of survival among BC patients (33,34). Our multivariate analysis also revealed that tumor size less than 5 cm was significantly associated with increased survival. Kim *et al.* (35) reported that molecular subtype can predict the prognosis for BC patients with brain metastasis. The TNBC subtype as an aggressive form, showed the worst prognosis in BC patients with brain metastasis, consistent with our results. Moreover, patients with bone-only metastasis had better survival than that of patients with additional visceral metastasis. Other studies also reached the same conclusion (6,31,36). One possible reason for this may be that bone is not a vital organ (31).

Surgical treatment for primary lesion is generally performed as a palliative surgery for metastatic BC patients. Recently, some studies reported that local surgery may achieve improvement in survival of metastatic BC (37-40). Moreover, Xiong *et al.* (40) reported that surgical treatment for primary lesion prolonged survival among selected stage IV BC patients, such as those with bone- or soft tissue-only metastasis. Similarly, our multivariate analysis showed that local surgery significantly improved the survival. For metastatic BC, chemotherapy is recommended as it can prolong survival, decrease cancer-related complications, and improve quality of life (41). Our research also revealed that BC patients with bone metastasis who received

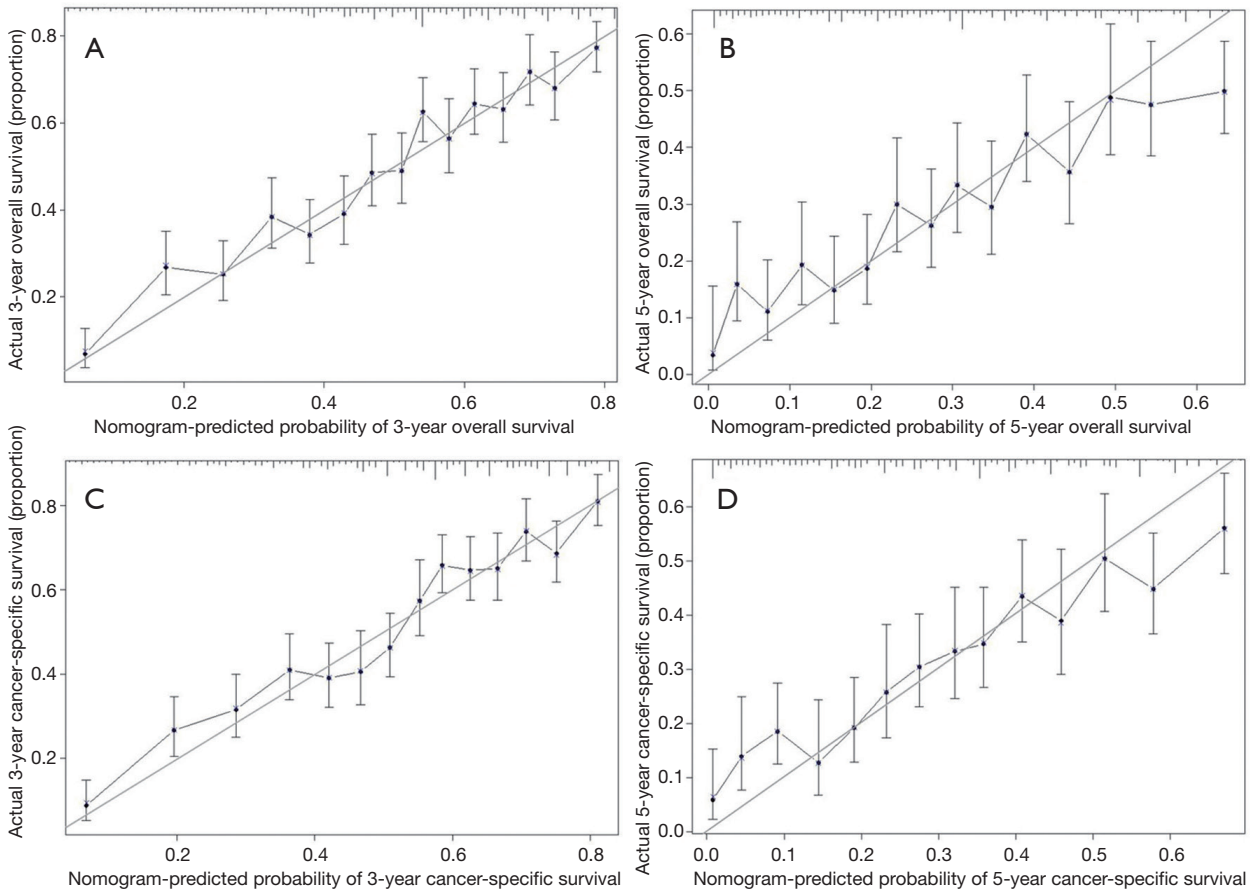

Figure 4 Calibration curves of the nomogram in the training cohort. Prediction of 3- (A) and 5-year (B) overall survival; and prediction of 3- (C) and 5-year (D) cancer-specific survival.

chemotherapy can achieve survival benefits. It is generally accepted that radiotherapy has the potential to alleviate pain and achieve good local control. Some studies reported that breast radiotherapy is associated with improved survival in metastatic patients (42,43). However, our multivariate analysis failed to identify radiotherapy as a significant predictor of either OS or CSS. Roayaei *et al.* (44) also supported this finding and showed no effect of radiotherapy of the breast on survival in metastatic disease.

In order to maximize prognostic ability, we established the nomograms (*Figures 2,3*) based on these independent variables. Our developed nomograms presented adequate discriminatory ability and obvious correlation between prediction and actual observation. Clinicians can refer to our nomograms to recommend appropriate treatment for BC patients with bone metastasis. Nomograms are widely constructed for predicting the outcome of other different BC populations and showed advantage in their management (45-47). Additionally, Yang *et al.* (48) established a user-friendly nomogram to preoperatively predict axillary lymph node metastasis, which is helpful to optimize treatment methods of BC patients. Delpech *et al.* (49) developed a clinical nomogram for probability prediction of bone-only metastasis among non-metastatic BC patients based on five independent predictors.

Several limitations in this research should be acknowledged. One limitation was that this was a retrospective study, which may generate inevitable biases. Second, the SEER database does not contain data about recurrence or specific treatment, which may affect the clinical outcome. The third limitation was that other important factors such as specific site of bone metastasis, treatment for bone metastasis, were not included in the database. Those important variables should be considered in the future research.

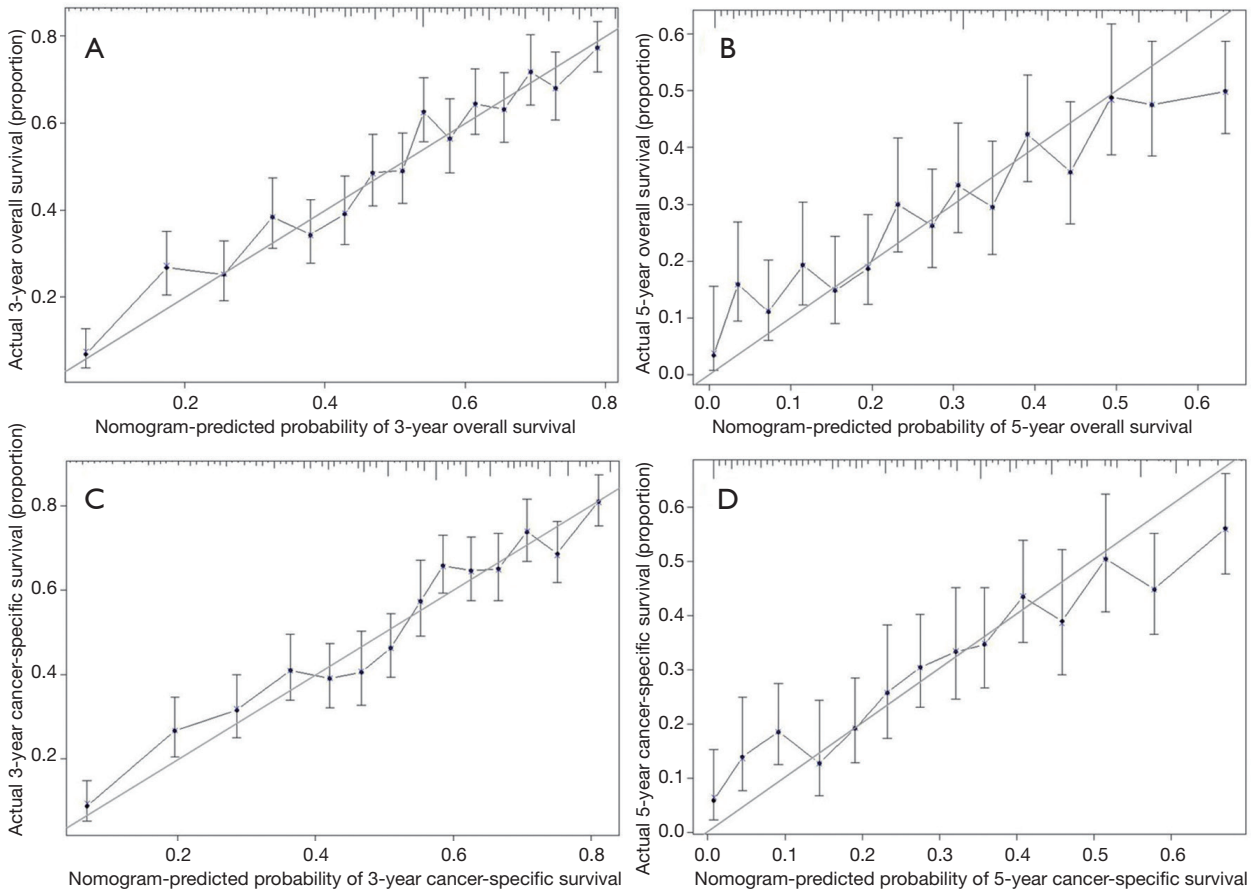

Figure 5 Calibration curves of the nomogram in the validation cohort. Prediction of 3- (A) and 5-year (B) overall survival; and prediction of 3- (C) and 5-year (D) cancer-specific survival.

Conclusions

Our novel prognostic nomograms for BC patients with bone metastasis can provide more accurate survival information for clinicians and facilitate them to provide appropriate treatment measures for metastatic lesions. Meanwhile, we propose more external validation to further refine our conclusions.

Acknowledgments

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Footnote

Conflicts of Interest: 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. This study was undertaken in accordance of standard guidelines and the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

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