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Risk factors and nomogram for newly diagnosis of bone metastasis in bladder cancer

A SEER-based study

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Abstract

Bladder cancer (BC) is the second most common urogenital malignant tumor. Bone metastasis (BM) is not common in BC patients, and there are only few studies on it. However, it was found in a clinical study that BM was related to the occurrence of bone complications and the decrease in survival rate. Early diagnosis of BC with BM is important for timely intervention and prevention of pathological fracture, which is of great significance for improving the quality of life of BC patients. This study aimed to identify the risk factors of BM and establish a predictive nomogram for the early diagnosis of BM in BC.

The medical records of the newly diagnosed BC patients were extracted from the database of Surveillance, Epidemiology, and End Results (SEER) during 2010 to 2016. The risk factors of BC with BM were evaluated using multivariate logistic regression analysis. Then a nomogram was established to predict the risk of BC with BM.

This study included 35,506 patients identified in the SEER database as diagnosed with BC, 796 of whom had BM. Grade, T stage, N stage, liver metastasis, race, brain metastasis, lung metastasis, histologic type, primary site, and age were risk predictors of BC with BM. Using Harrell's concordance index, calibration curve, and decision curve analyses, we found that the nomogram for predicting the risk of BC metastasis performed well internally.

The nomogram developed in this study is expected to become an accurate and personalized tool for predicting risks of BC with BM in patients. It may be of great significance for clinicians to formulate more reasonable and effective treatment strategies. As the first study, we established a predictive nomogram for BC with BM based on the retrospective analysis of data of BC patients from the SEER database.

Abbreviations: AJCC = American Joint Committee on Cancer, BC = bladder cancer, BM = bone metastasis, C-index = Harrell's concordance index, DCA = decision curve analyses, SCC = squamous cell carcinoma, SEER = Surveillance, Epidemiology, and End Results, SRE = skeletal-related event, TCC = transitional cell carcinoma.

Keywords: bladder cancer, bone metastasis, Surveillance, epidemiology, and end results, nomogram, risk factors, predictor

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ZF, ZH, and CH contributed equally to this work.

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The data corresponding to patient records were obtained from the SEER database, and owing to the retrospective study design, the study was exempted from the need for an informed patient consent by the SEER database administrators.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Bladder cancer (BC) is the second most common urogenital cancer. The initial site of BC metastasis is usually the pelvic lymph nodes, but this cancer often spreads to other organs, most commonly the lungs and bones, through lymph and blood channels. BC has a poor prognosis and is rarely cured.[1] Without treatment, bone metastasis (BM) may lead to the skeletal-related event (SRE), such as pathological fracture, spinal cord compression, and malignant tumor hypercalcemia.[2,3] SRE is still the leading cause of mortality and morbidity and often leads to a decline in patients quality of life.[4] At present, surgery is the first choice for BC; however, most BC patients with BM receive palliative treatment instead of undergoing a radical surgery. The latter may be related to the fact that surgery does not necessarily prolong the survival time in patients. Of course, surgical treatment is not suitable for patients with multiple metastases or those with poor general conditions. All in all, there is no particular effective treatment for BC patients with BM.

Thus far, there are few studies that investigated the risk factors of developing BM in patients with primary BC. Therefore, it is necessary to analyze the epidemiological characteristics of BC with BM comprehensively and identify the risk factors of BM. The TNM staging system of the American Joint Committee on Cancer (AJCC) is publicly recognized and widely used to predict the metastatic risks and prognosis in patients with various cancers. While these staging systems have provided useful

estimates for recurrence risks and survival outcomes, the heterogeneity in tumor biology and patient characteristics within each prognostic group lead to significant variations. This highlights the ultimate limitations of the categorical risk grouping models because specific risk factors are defined in a manner that includes patients with varying degrees of risk.[5] In addition, TNM staging does not include other factors such as age, gender, comorbidity, previous treatment, imaging, and molecular characteristics. The TNM staging system is convenient to use, and it is used as a common language to communicate with patients and describe their illness. However, clinicians often combine the TNM staging system with personal experience to predict the prognosis of cancer patients. In view of the inaccuracy of personal judgment, modern statistical methods and computer prediction models should be incorporated into clinical decision-making more frequently.

As a statistical tool, a nomogram can solve the above problems in a more accurate way. A large number of studies showed that a nomogram can predict the prognosis of some malignant tumors. Compared with the traditional AJCC TNM staging system, the nomogram is simpler and more accurate tool and is a good substitute for the TNM staging system. As a result, a number of cancer-related nomograms have been developed. For example, BH et al established and verified a nomogram to predict the risk of recurrence after radical cystectomy for BC.[6] A good nomogram can be used to predict personal results, which is beneficial to both patients and clinicians. However, to the best of our knowledge, there is no research that constructed a nomogram to estimate the risk of BC with BM. This study had 2 main objectives: to identify the significant variables, mainly the risk factors that may affect BC with BM, and to construct a prediction model based on these variables. Therefore, the purpose of this study was to construct and validate the prediction model of BC with BM by analyzing the patient data extracted from the database of Surveillance, Epidemiology, and End Results (SEER).

2. Methods

2.1. Ethics statement

We obtained approval from the Ethics Committee of the Affiliated Hospital of Chengde Medical University before carrying out this study. The content of this study did not involve human subjects or personal privacy; hence, informed consent from patients was not required in this study.

2.2. Patients and data collection

The SEER database is a program of the National Cancer Institute. In brief, it contains data related to cancer incidence and survival outcomes from population-based cancer registries, covering 28% of the US population. In our study, we included patients who were newly diagnosed with BC from 2010 to 2016 in the SEER database. Patients meeting the following criteria were included in our analysis:

1. site record: trigon of bladder, dome of the bladder, bladder wall (lateral wall of the bladder, anterior wall of the bladder, posterior wall of the bladder), bladder neck, ureteral associated tissue (ureteric orifice, urachus), overlapping lesion of the bladder, and bladder, NOS according to the Third Edition of International Classification of Diseases for Oncology (ICD-O-3);
2. pathological type: transitional cell carcinoma (TCC), squamous cell carcinoma (SCC), adenocarcinoma;
3. complete information preservation about T and N classification.

Exclusion criteria were as follows:

1. information on survival rate, follow-up time or cause of death was missing or insufficient,
2. diagnosis was based on only autopsy results or certificates of death,
3. multiple primary tumors and patients with unknown metastatic status.

A total of 35,506 BC patients were included in this study, 796 (2.24%) of whom had BM and 34,710 (97.76%) had no BM.

2.3. Statistical analysis

All statistical analyses in our research were carried out using R software (Version 3.6.1). Receiver operating characteristic curve analysis was used to convert age data into categorical data, and the cut-off was determined based on the maximum of Youdens index. To evaluate the risk factors of BC with BM, the difference in continuous variables between patients with BM and those without BM was compared using Student *t* test. All BM patients were randomly divided into training and validation cohorts at a ratio of 7:3. In addition, the risk factors of classification variables were identified using the Chi-Squared test or Fisher extraction test. Multivariate logistic analysis included variables with $P < .05$ in univariate analysis. Then, the independent risk factors of BC with BM in patients were determined, and based on these independent risk factors, a nomogram was established using and RMS packet in R software. Harrell's concordance index (C-index) represented the discrimination of the nomogram. Furthermore, the nomogram was evaluated using calibration curve analysis and decision curve analysis (DCA).

3. Results

3.1. Baseline characteristics of the study population

According to our criteria, 35,506 BC patients whose records were extracted from the SEER database were included. The patients were divided into the training cohort (24,856) and the validation cohort (10,650). As shown in Table 1, in the training cohort, 70.45% of patients were aged $\leq$80, mostly white (89.55%). Differentiation in grades III-IV (88.34%) was the most common among tumor classifications. T1-2 (83.65%) and N0-1 (93.90%) phases were common. Distant metastasis was observed in the following cases: 510 (2.05%) had tumor metastasis to the lung, 324 (1.30%) to the liver, and 46 (0.19%) to the brain.

3.2. Risk factors for developing BM

As shown in Table 2, grade, T stage, N stage, brain, liver and lung metastases, age, race, histologic type, and primary site were related to BC with BM. The variables with *P* value $< .05$ in univariate analysis were included in multivariate logistic regression analysis to determine the risk factors of BC with BM. The results showed that grade, T stage, N stage, brain metastasis, lung metastasis, liver metastasis, race, age, histologic type, and primary site were independent predictors of BC with BM (Table 2).

Table 1

Bladder cancer patients' demographics and clinicopathological characteristic.

	Training cohort		Validation cohort	
	N = 24856		N = 10650	
Variables	n	%	n	%
Age				
≤80	17511	70.45	7677	72.08
>80	7345	29.55	2973	27.92
Race				
Black	1524	6.13	690	6.48
Other	1073	4.32	485	4.55
White	22259	89.55	9475	88.97
Sex				
Female	5724	23.03	2467	23.16
Male	19132	76.97	8183	76.84
Primary site				
Trigon of bladder	1462	5.88	634	5.95
Dome of bladder	1205	4.85	505	4.74
Bladder wall	7438	29.92	3160	29.67
Bladder neck	838	3.37	387	3.63
Ureteral associated tissue	619	2.49	266	2.50
Overlapping lesion of bladder	3432	13.81	1519	14.26
Bladder, NOS	9862	39.68	4179	39.24
Histologic type				
Transitional cell carcinoma	23263	93.59	9941	93.34
squamous cell carcinoma	346	1.39	160	1.50
Adenocarcinoma	594	2.39	262	2.46
Other	653	2.63	287	2.69
Grade				
I-II	2898	11.66	1245	11.69
III-IV	21958	88.34	9405	88.31
T stage				
T1-T2	20791	83.65	8855	83.15
T3-T4	3938	15.84	1735	16.29
TX	127	0.51	60	0.56
N stage				
N0-N1	23340	93.90	9948	93.41
N2-N3	1357	5.46	628	5.90
NX	159	0.64	74	0.69
Brain metastasis				
No	24810	99.81	10635	99.86
Yes	46	0.19	15	0.14
Liver metastasis				
No	24532	98.70	10492	98.52
Yes	324	1.30	158	1.48
Lung metastasis				
No	24346	97.95	10419	97.83
Yes	510	2.05	231	2.17

Table 2

Univariate analysis and multivariate logistic analysis (Training Cohort).

	Univariate analysis	Multivariate logistic analysis	
Variables	*P* value	HR (95% CI)	*P* value
Age			
≤80	<.001	Reference	
>80		1.410 (1.128–1.762)	<.05
Race			
Black	<.001	Reference	
Other		0.567 (0.335–0.960)	<.05
White		0.564 (0.422–0.754)	<.001
Sex			
Female	.972		
Male			
Primary site			
Trigon of bladder	<.001	Reference	
Dome of bladder		0.650(0.342–1.239)	0.191
Bladder wall		0.853(0.553–1.316)	.473
Bladder neck		1.523 (0.861–2.695)	.148
Ureteral associated tissue		0.580 (0.250–1.343)	.203
Overlapping lesion of bladder		1.369 (0.882–2.126)	.161
Bladder, NOS		1.028 (0.679–1.557)	.894
Histologic type			
Transitional cell carcinoma	<.001	Reference	
Squamous cell carcinoma		2.717 (1.628–4.535)	<.001
Adenocarcinoma		0.962 (0.522–1.773)	.901
Other		1.657 (1.128-2.434)	<.05
Grade			
I-II	<.001	Reference	
III-IV		2.618 (1.676–4.089)	<.001
T stage			
T1-T2	<.001	Reference	
T3-T4		1.102 (0.876–1.386)	.408
TX		4.900 (2.949–8.141)	<.001
N stage			
N0-N1	<.001	Reference	
N2-N3		3.584 (2.794–4.598)	<.001
NX		4.193 (2.652–6.630)	<.001
Brain metastasis			
No	<.001	Reference	
Yes		5.342 (2.412–11.828)	<.001
Liver metastasis			
No	<.001	Reference	
Yes		4.815 (3.478–6.665)	<.001
Lung metastasis			
No	<.001	Reference	
Yes		8.112 (6.229–10.564)	<.001

3.3. Diagnostic nomogram development and validation

The risk assessment model of the nomogram was based on logistic regression analysis (Fig. 1). The C-index of the nomogram reached 0.812 and 0.806 in the training and validation cohorts, respectively, showing better discrimination ability. The calibration curve showed a high degree of consistency between the observed and predicted results (Fig. 2). In addition, DCA showed that the nomogram had an excellent performance in clinical practice (Fig. 3).

4. Discussion

It is estimated that 12,500 people die due to metastatic BC every year in the United States.[7] Lymph nodes are the most common metastatic site of BC, but studies have shown that bones can be even considered as the most common sites for distant metastasis in BC, and approximately 30% to 40% of metastatic BC patients have BM.[8,9] SRE caused by these metastases directly affect the prognosis in BC patients. Therefore, it is crucial to identify the risk factors of BC with BM in patients and to carry out early preventive intervention in patients with a high risk of BM. However, there were few detailed studies on risk factors of BC with BM, and there was no study that established a BM prediction model with a nomogram. BC is a heterogeneous disease. For each patient, there may be many possible treatment methods and prognostic outcomes. Therefore, the TNM staging system alone cannot predict the BM risks individually, visually, and quantitatively. As a reliable graphical calculation model, the

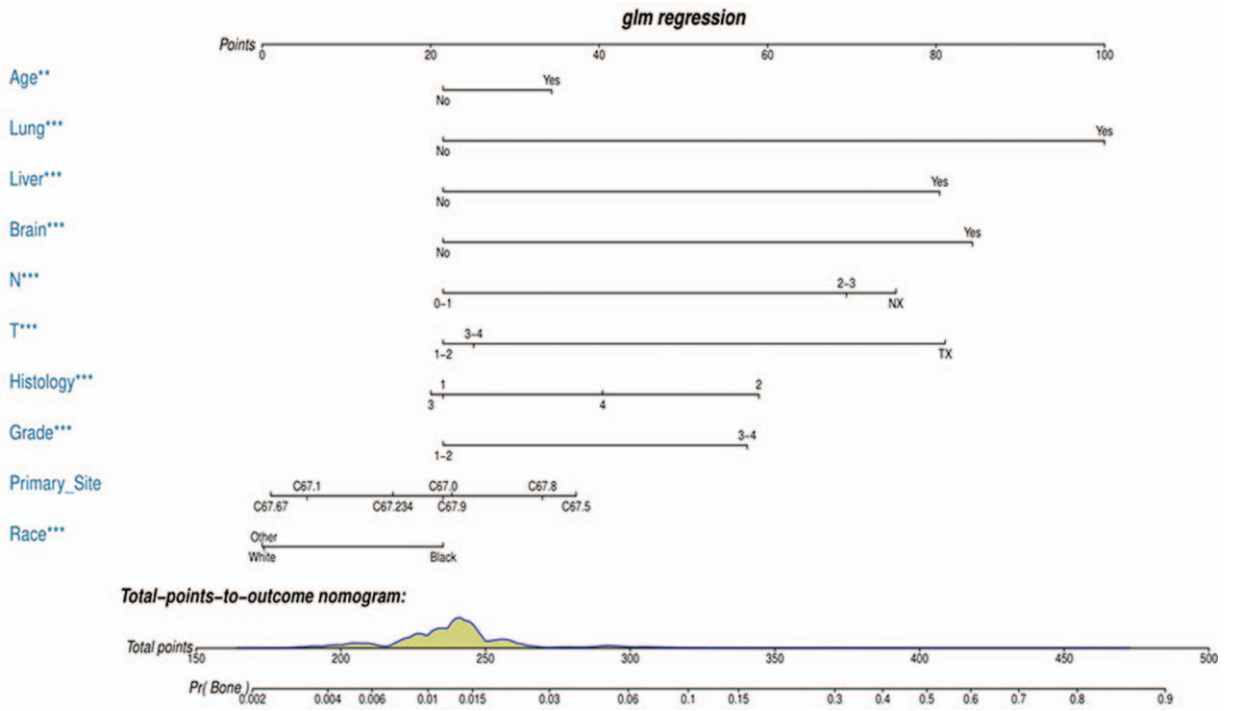

Figure 1. Nomogram to estimate the risk of BM in patients with BC. Lung = lung metastasis; Liver = liver metastasis; Brain = brain metastasis; C67.67 = ureteral-associated tissue; C67.1 = dome of the bladder; C67.234 = bladder wall; C67.0 = trigon of bladder; C67.9 = Bladder; NOS, C67.8 = overlapping lesion of the bladder; C67.5 = bladder neck.

nomogram is used to integrate all risk factors of tumor occurrence and predict individual risks of specific events.[10,11] This is a tool that can evaluate the possibility of metastasis progress, tumor specificity, mortality rate, and long-term quality of life accurately. Therefore, nomogram is an important tool to assist clinicians during patient consultation and decision making on treatment options.

Therefore, for the first time, we have established the predictive nomogram for BC with BM based on the retrospective analysis of data of BC patients from the SEER database. We determined the

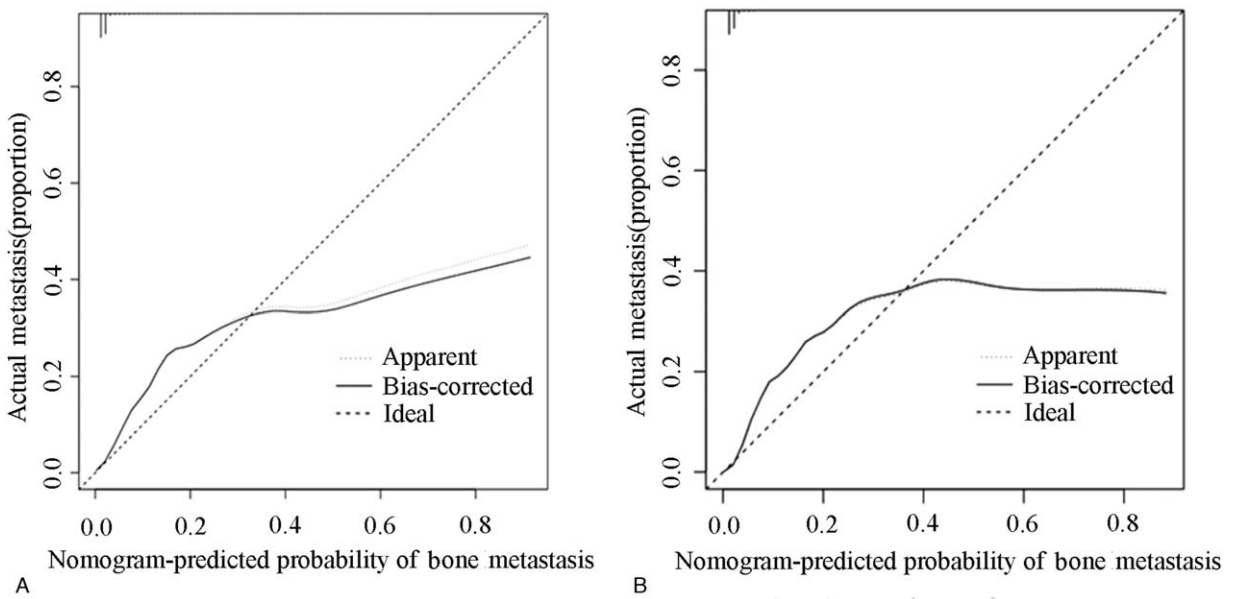

Figure 2. Calibration curves of the nomogram for the risk of bladder cancer with brain metastasis in the training cohort (A) and the validation cohort (B), respectively.

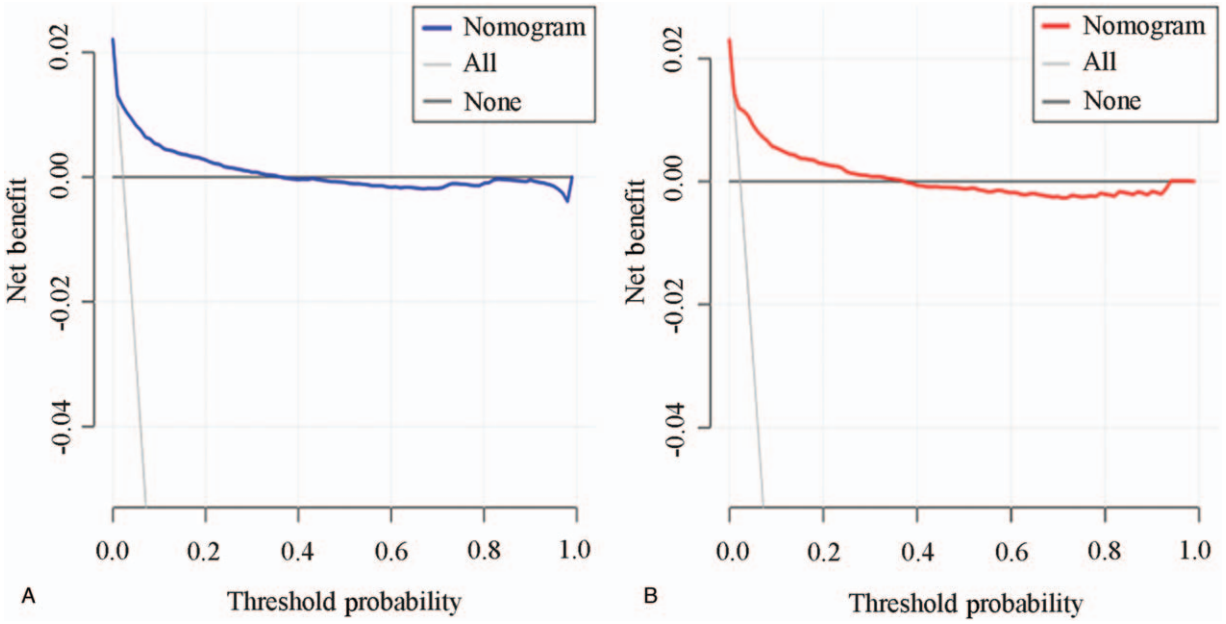

Figure 3. Decision curve analysis of the nomogram for estimating the risk of bladder cancer with brain metastasis in the training cohort (A) and validation cohort (B), respectively.

risk factors that may lead to BC with BM in patients, including age, race, T and N stage, grade, lung, liver and brain metastases, primary site, and histologic type. Among them, histologic type and primary site have not been examined as BM risk factors in previous similar studies. For example, Zhang et al studied and analyzed the risk factors of BC with BM, including age, race, marital status, insurance status, T and N stage, tumor grade, liver, lung, and brain metastases.[12] SCC accounts for only 2% to 5% of BC, but bladder SCC has the characteristics of high malignant degree and high recurrence rate.[13] SCC has a faster disease progression than TCC in BC patients with stage III or IV.[14] Therefore, there may be differences in BC with BM between the 2 tissue types. Previous studies by Weiner et al have shown that triangular and bladder neck tumors were associated with higher lymph node involvement rates, indicating that they had higher invasion and metastasis potential.[15] Animal experiments showed that urothelial stem cells were mainly located in the bladder triangle and bladder neck, and cancer stem cells may be highly distributed in these areas of the bladder.[16] Therefore, BM risks in different locations may also be different, and BM risk is added as a study variable. Fortunately, our study results also confirmed that histological type and primary site were BM risk factors; SCC is indeed more likely to cause BM than other BC types, and the possibility of BM was highest when the tumor was located in the bladder neck. Other BM risk factors included age, race, T and N stage, grade, lung, liver, and brain metastases, which were the same as those reported in the literature. Most importantly, we have successfully established the prediction model of BC with BM, which was done for the first time in the field for the BC with multiple BM risk factors. Second, Zhang et al have only studied the risk factors of BC with BM, but no prediction model has been established. We believe that our study is more accurate and more convenient to apply in clinical work.

In addition to the newly discovered risk factors, we have also studied several other risk factors and analyzed the possible reasons for them to become risk factors. The increase in T and N stage and grade was an independent risk factor of BC with BM. As shown in previous studies, the increase in T and N stage in patients with malignant tumors may mean the increase in tumor volume and the involvement degree and range of adjacent tissues and lymph nodes, while the increase in grade may mean the increase in the malignant degree of a tumor, which are all manifestations of further progression of the malignant tumor. Among BC patients with cancer progression, 40% of those with advanced disease will have BM.[17,18] Therefore, effective treatment as early as possible and intervention with tumor progression to prevent or delay the increase of T and N stage and grade are essential means to prevent BM in BC patients. Black race has been proven to be one of the risk factors for BM diagnosis, which was consistent with other reported cancer types.[19–21] Previous studies also reported that black patients showed higher stage disease and worse disease-specific survival rate than white race.[22,23] There are also studies showing that SCC is more common in blacks than in whites,[24] while our study and previous studies showed that SCC is more malignant, leading to a higher risk of BC with BM, which, we believe, may be the reason why black BC patients were more prone to develop BM. Finally, age as a continuous variable had an odds ratio value of $0.983 < 1$ in our study, indicating that the lower the age of the BC patients, the higher was the risk of BM. This also indicates the importance of paying close attention to BC patients in low age group in clinical work. Finally, we also confirmed that BC patients were more likely to have BM if accompanied by liver, lung, brain, and other metastases. Most people think that once a tumor metastasizes to a distant area in an organ, it may accelerate metastasis in other parts, which is in agreement with our observations in this study. Therefore, controlling tumor metastasis in other body parts is also important for preventing BM. To sum up, the prediction model that we have established is of great help to predict BC with BM risks in patients in the clinical

setting and to formulate treatment plans according to the patients physical conditions.

5. Conclusion

The nomogram developed in this study can be used as an auxiliary graphical tool for patients with BC to help clinicians evaluate the risks of BC combined with BM and predict prognosis. Verification and application in an independent population showed that the prediction model had excellent performance and clinical application value.

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