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Original Article

Survival nomogram for osteosarcoma patients: SEER data retrospective analysis with external validation

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Abstract: This study aimed to develop a nomogram based on the clinicopathological factors affecting the prognosis of osteosarcoma patients to help clinicians predict the overall survival of osteosarcoma patients. A total of 1362 patients diagnosed with osteosarcoma were enrolled in this study, among which, 1081 cases were enrolled from the SEER (Surveillance, Epidemiology, and End Results) database as training group, while 281 patients from two Clinical Medicine Center database were used in validation group. Univariate and multivariate Cox analyses were performed to identify the independent prognostic factors for overall survival. Nomogram predicting the 3- and 5-year overall survival probability was constructed and validated. Multiple validation methods, including calibration plots, consistency indices (C-index), and area under the receiver operating characteristic curve (AUC) were used to validate the accuracy and the reliability of the prediction models. Decision curve analysis (DCA) was conducted to validate the clinical application of the prediction model. Furthermore, all patients were divided into low- and high-risk groups based on their nomogram scores. Kaplan-Meier (KM) curves were applied to compare the difference in survival between the two groups. Predictors in the prediction model included age, sex, tumor size, primary site, grade, M stage, and surgery. Our results showed that the model displayed good prediction ability, and the calibration plots demonstrated great power both in the training and the validation groups. In the training group, C-index was 0.80, and the 3- and 5-year AUCs of the nomogram were 0.82 and 0.81, respectively. In the validation group, C-index was 0.79, and the 3- and 5-year AUCs of the nomogram were 0.85 and 0.83, respectively. Furthermore, DCA data indicated the potential clinical application of this model. Therefore, our prediction model could help clinicians evaluate prognoses, identify high-risk individuals, and provide individualized treatment recommendation for patients with osteosarcoma.

Keywords: Osteosarcoma, clinical prediction model, nomogram, R software

Introduction

Osteosarcoma is the most common malignant bone tumor [1, 2], accounting for 35% of all primary malignant bone tumors. The diagnosis rate of osteosarcoma is relatively consistent across the world, and the onset of osteosarcoma is often located in the distal femur, proximal tibia, or humerus. The typical clinical symptoms of osteosarcoma include pain and swelling of the affected bone, with approximately 15 to 20% of patients presented metastases to the lungs and, to a lesser extent, to other bones at the time of diagosis [3].

Data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program show that the 5-year survival rate for patients with osteosarcoma was 60.6-68.1% between 1987 to 2002 [4]. However, the prognosis for patients with metastatic and recurrent osteosarcoma remains unsatisfied, with an overall 5-year survival rate of approximately 20% [5, 6]. Unfortunately, the overall survival rate of patients with osteosarcoma has not improved significantly, despite the advances in medical technology over the past 30 years [7, 8].

Predicting risk factors for osteosarcoma could thus significantly improve the prognosis and increase the survival of patients. Therefore, identifying risk factors for osteosarcoma is urgently needed. In our study, we constructed a

nomogram using reliable osteosarcoma patient data in SEER and further used data from two Clinical Medicine Center to independently validate the nomogram. As a clinical prediction tool, nomogram can be used to generate a clinical profile by integrating different prognostic variables, which could help clinicians predict the outcomes of patients and select the appropriate treatment options [9]. Therefore, this study will contribute to the improvement in patient care and predicting the prognoses of patients.

Methods

Data collection

In this study, the clinical information of patients diagnosed with osteosarcoma between 2010 and 2015 was collected. For training group, the patient data were extracted from the SEER database with the SEER*Stat software version 8.3.9.2 (NCI, Bethesda, MD, USA), and the third edition of the International Taxonomy of Oncology (ICDO-3) was used to identify osteosarcoma that was histologically confirmed as primary osteosarcoma. The exclusion criteria of patients in the training group were: (1) with other primary neoplastic diseases; (2) incomplete tumor information in pathological histological typing, tumor size, primary site; (3) incomplete treatment information such as surgery, radiotherapy, and chemotherapy; (4) incomplete follow-up information.

The clinical data used in the validation group were obtained from patients who were treated in the General Hospital of Ningxia Medical University and the People's Hospital of Ningxia Hui Autonomous Region from 2018 to 2021. During the period of this study, each center was responsible for the acquisition of data by three independent investigators, in which two were responsible for data extraction, while the third person examined the accuracy of the data acquisition. All patients' data are anonymous, and hence the requirement for informed consent was waived.

Variables included in this study

The potential prognostic variables for this study mainly included Age, Sex, Race, Tumor size, Primary site, Grade, Metastases information (Bone, Brain, Liver, and Lung metastases), AJCC 7th stage, Surgery, Radiation, Chemotherapy, Survival months, and Survival status. The X-tile software (Yale University, New Haven, CT, USA) was utilized to identify the optimal cut-off values to categorize continuous variables of age and tumor size.

Identification of prognosis predictive factors for survival

Univariate and multivariate Cox proportional hazards regression analyses were performed to identify independent prognostic factors for overall survival from the potential prognostic factors. The hazard ratio and its corresponding 95% confidence interval of each variable were also calculated.

Establishment and validation of the predictive models for over survival

The prognostic nomogram for 3- and 5-year over survival was established based on the prognostic factors identified in univariate and multivariate Cox analyses. External validation was performed with 1000 bootstrap resamples to prevent overfitting and to get a relatively unbiased estimation. C-index was utilized to evaluate the performance of these established predictive nomograms. Calibration curves were also constructed to assess the consistency between the predicted and the actual survival.

Statistical analysis

X-tile software was used to categorize continuous variables of age and tumor size. Categorical variables were presented as frequencies. The chi-square test or Fisher exact test was used to compare the differences of variables of cohorts. Survival was analyzed using the Kaplan-Meier method and compared through log-rank tests. All analyses were performed using R software version 4.1.2 (http://www.r-project.org) including multiple R packages (Including rms, foreign, and survival). A two-sided P-value < 0.05 was considered statistically significant.

Results

Demographic baseline characteristics

As shown in **Table 1**, a total of 1,362 patients were enrolled in this study. There was no statistically significant difference between the train-

Table 1. Baseline data table of the training group and the validation group

Demographic characteristics	Development cohort/[n (%)]	Validation cohort/[n (%)]	*P*
Age			
≤20	485 (44.87%)	129 (45.91%)	0.840
21-55	379 (35.06%)	100 (35.59%)	
≥56	217 (20.07%)	52 (18.50%)	
Sex			
Male	576 (53.28%)	152 (54.09%)	0.809
Female	505 (46.72%)	129 (45.91%)	
Race			
White	804 (74.38%)	0 (0.00%)	< 0.001
Black	174 (16.10%)	0 (0.00%)	
Other	103 (9.52%)	281 (100.00%)	
Tumor size			
≤70 mm	368 (34.04%)	90 (32.03%)	0.748
71-119 mm	389 (35.99%)	101 (35.94%)	
≥120 mm	324 (29.97%)	90 (32.03%)	
Primary site			
Axis bone	243 (22.48%)	59 (21.00%)	0.844
Limb bone	763 (70.58%)	201 (71.53%)	
Other	75 (6.94%)	21 (7.47%)	
Grade			
Well differentiated	53 (4.90%)	9 (3.20%)	
Moderately differentiated	80 (7.40%)	15 (5.34%)	0.218
Poorly differentiated	340 (31.45%)	102 (36.30%)	
Undifferentiated; anaplastic	608 (56.25%)	155 (55.16%)	
Bone_ metastases			
No	1042 (96.39%)	270 (96.09%)	0.807
Yes	39 (3.61%)	11 (3.91%)	
Brain_ metastases			
No	1077 (99.63%)	278 (98.93%)	0.159
Yes	4 (0.37%)	3 (1.07%)	
Liver_ metastases			
No	1079 (99.81%)	280 (99.64%)	0.500
Yes	2 (0.19%)	1 (0.36%)	
Lung_ metastases			
No	928 (85.85%)	233 (82.92%)	0.218
Yes	153 (14.15%)	48 (17.08%)	
AJCC_7th			
I+II	834 (77.15%)	208 (74.02%)	0.270
III+IV	247 (22.85%)	73 (25.98%)	
T stage			
T0-1	434 (40.15%)	112 (39.86%)	
T2	617 (57.08%)	159 (56.58%)	0.877
T3	23 (2.12%)	7 (2.49%)	
Tx	7 (0.65%)	3 (1.07%)	
N stage			
N0	1030 (95.28%)	265 (94.31%)	0.500
N1a-N2	51 (4.72%)	16 (5.69%)	

M stage			
M0	897 (82.98%)	225 (80.07%)	0.254
M1a/M1b/M1NOS	184 (17.02%)	56 (19.93%)	
Surgery			
No	104 (9.62%)	30 (10.68%)	0.597
Yes	977 (90.38%)	251 (89.32%)	
Radiation			
No	956 (88.44%)	245 (87.19%)	0.564
Yes	125 (11.56%)	36 (12.81%)	
Chemotherapy			
No	225 (20.81%)	46 (16.37%)	0.096
Yes	856 (79.19%)	235 (83.63%)	

ing group (n = 1,081) and the validation group (n = 281) in clinicopathological features except the race ($P < 0.001$) which may be due to the demographic differences and healthcare disparities between the USA and China. The optimal cut-off values for age and tumor size identified by X-tile software were 21 and 55 years, and 71 and 119 mm, respectively.

Identification of prognostic factors for osteosarcoma

As shown in **Table 2**, a univariate Cox regression analysis was conducted to search for osteosarcoma-related prognosis factors. Based to univariate Cox regression analyses, age, sex, tumor size, primary site, grade, bone metastases, brain metastases, liver metastases, lung metastases, AJCC 7th stage, T stage, N stage, M stage, surgery, radiation, and chemotherapy were significantly associated with prognosis ($P < 0.05$). Subsequently, based on the above results, multivariable Cox logistics regression analysis showed that age, sex, tumor size, primary site, grade, M stage, and surgery were significantly associated with osteosarcoma over survival ($P < 0.05$); therefore, these seven variables were defined as independent prognostic factors of osteosarcoma.

Nomogram construction

Using the independent risk factors obtained by univariate and multivariate Cox regression analyses, we constructed a nomogram to predict the 3- and 5-year OS of patients with osteosarcoma. The nomogram consisted of seven risk factors that were confirmed to be statistically significant by logistic regression analysis, including age, sex, tumor size, primary site, grade, M stage, and surgery (**Figure 1**). Each variable was distributed on the nomogram according to its weight to obtain different lines, and the points of each variable corresponded to a point. The sum of the points of all the variables in the nomogram equaled to an overall point, thus obtaining survival rates at different point of time.

Nomogram validation

Importantly, we applied a series of validation methods, including the consistency index (C-index), the calibration curve, and the area under the receiver operating characteristic curve (AUC) to confirm the accuracy and reliability of our nomogram. Similarly, the C-index of the training set and the validation set were 0.80 (95% CI 0.75-0.84) and 0.79 (95% CI 0.76-0.81), respectively, indicating that the nomogram has a good discrimination. In addition, the accuracy of the nomogram was tested by the calibration curve, which was used to compare the relationship between the observed value and the actual value through 1,000 bootstrap sampling. The calibration curves of the training and the validation group demonstrated that the predicted value of the nomogram was highly consistent with the observed value (**Figure 2**). In the training group, the 3- and 5-year AUCs of the nomogram were 0.82 (95% CI 0.79-0.85) and 0.81 (95% CI 0.78-0.84), respectively. Consistently, the 3- and 5-year AUCs of the nomogram were 0.85 (95% CI 0.80-0.90) and 0.83 (95% CI 0.78-0.88), respectively, in the validation group (**Figure 3**). Furthermore, the ROC curve demonstrated a superior performance of the nomogram com-

Table 2. Univariate and multifactorial logistic regression analysis of risk factors for patients with osteosarcoma

Variables	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Age				
≤20	Reference	Ref	Reference	Ref
21-55	1.287 (1.024, 1.619)	0.030	1.855 (1.449, 2.376)	< 0.001
≥56	3.341 (2.662, 4.193)	< 0.001	3.920 (2.909, 5.281)	< 0.001
Sex				
Male	Reference	Ref	Reference	Ref
Female	0.746 (0.617, 0.902)	0.003	0.801 (0.657, 0.978)	0.029
Race				
White	Reference	Ref		
Black	1.168 (0.913, 1.494)	0.216		
Other	0.932 (0.669, 1.300)	0.679		
Tumor size				
71-119 mm	Reference	Ref	Reference	Ref
≤70 mm	0.654 (0.512, 0.835)	0.001	0.547 (0.377, 0.795)	0.002
≥120 mm	1.463 (1.180, 1.815)	0.001	1.468 (1.160, 1.858)	0.001
Primary site				
Limb bone	Reference	Ref	Reference	Ref
Axis bone	1.831 (1.484, 2.259)	< 0.001	1.573 (1.210, 2.045)	0.001
Other	2.105 (1.525, 2.906)	< 0.001	0.938 (0.589, 1.492)	0.787
Grade				
Moderately differentiated	Reference	Ref	Reference	Ref
Well differentiated	0.230 (0.122, 0.431)	< 0.001	0.251 (0.130, 0.484)	< 0.001
Poorly differentiated	0.926 (0.759, 1.131)	0.452	0.958 (0.779, 1.178)	0.684
Undifferentiated	0.096 (0.031, 0.300)	< 0.001	0.076 (0.024, 0.242)	< 0.001
Bone metastases				
No	Reference	Ref	Reference	Ref
Yes	4.058 (2.823, 5.834)	< 0.001	1.191 (0.729, 1.945)	0.486
Brain metastases				
No	Reference	Ref	Reference	Ref
Yes	11.149 (4.13, 30.09)	< 0.001	1.365 (0.468, 3.977)	0.569
Liver metastases				
No	Reference	Ref	Reference	Ref
Yes	82.74 (18.67, 366.7)	< 0.001	10.863 (2.00, 58.9)	0.500
Lung metastases				
No	Reference	Ref	Reference	Ref
Yes	3.316 (2.666, 4.124)	< 0.001	1.096 (0.647, 1.855)	0.734
AJCC 7th				
I+II	Reference	Ref	Reference	Ref
III+IV	3.591 (2.961, 4.354)	< 0.001	1.370 (0.841, 2.231)	0.206
T stage				
T2	Reference	Ref	Reference	Ref
T0-1	0.636 (0.519, 0.780)	< 0.001	1.169 (0.811, 1.684)	0.403
T3	2.158 (1.339, 3.478)	0.002	1.507 (0.848, 2.681)	0.162
Tx	9.998 (4.659, 21.45)	< 0.001	1.280 (0.556, 2.948)	0.561
N stage				
N0	Reference	Ref	Reference	Ref
N1a-N2	2.464 (1.744, 3.481)	< 0.001	1.128 (0.776, 1.642)	0.528

M stage				
M0	Reference	Ref	Reference	Ref
M1a/M1b/M1NOS	3.694 (3.010, 4.535)	< 0.001	2.465 (1.215, 5.000)	0.012
Surgery				
Yes	Reference	Ref	Reference	Ref
No	5.083 (3.989, 6.476)	< 0.001	2.722 (1.996, 3.711)	< 0.001
Radiation				
No	Reference	Ref	Reference	Ref
Yes	2.133 (1.667, 2.730)	< 0.001	0.775 (0.578, 1.040)	0.090
Chemotherapy				
No	Reference	Ref		
Yes	0.913(0.725, 1.150)	0.436		

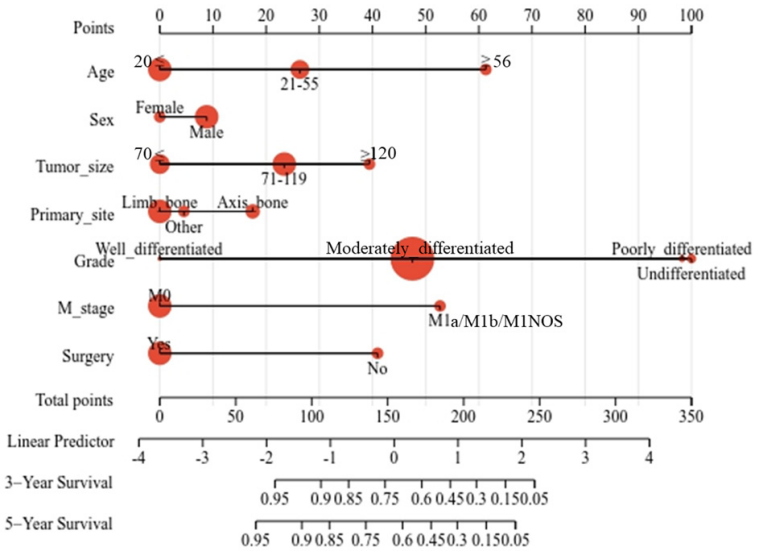

Figure 1. Nomogram predicting the 3- and 5-year Overall survival rates of patients with Osteosarcoma.

pared to the single variable, including T-stage (AUC = 0.585, 95% CI 0.555 to 0.614), N-stage (0.527, 0.497 to 0.557), M-stage (AUC = 0.617, 95% CI 0.587 to 0.646), and AJCC 7th stage (AUC = 0.645, 95% CI 0.615 to 0.673). The statistical results of the validation group were consistent with the training group, including T-stage (AUC = 0.578, 95% CI 0.518 to 0.637), N-stage (0.530, 0.470 to 0.590), M-stage (AUC = 0.621, 95% CI 0.561 to 0.678) and AJCC 7th stage (AUC = 0.669, 95% CI 0.611 to 0.724) (**Figure 4**). The AUC results once again proved the accuracy and the discrimination of the nomogram. These validations showed that the nomogram was at least 75% accurate, especially for predicting medium-term survival.

Clinical application of the nomogram

Moreover, the decision curve analysis (DCA) showed that the overall net benefit of this nomogram in 3- and 5-years is substantial over most of the range of reasonable threshold probabilities both in the training set and validation set (**Figure 5**). Specifically, the DCA of the training group and the validation group indicated that the clinical value of the nomogram was higher than that of the TNM stage and AJCC 7th stage (**Figure 6**). According to the score of the nomogram, the patients were divided into low- and high-risk groups. As expected, the Kaplan-Meier curve showed that patients in the high-risk group had lower survival rates than those in the low-risk group (**Figure 7**).

Discussion

Although the improvements in chemotherapy regimens and surgical treatment have improved the 5-year overall survival rate for nonmetastatic osteosarcoma from 22% in 1950 to 70% currently [10], approximately 30% of the locally advanced and 80% of the metastatic osteosarcoma still experience recurrence, and surgery and chemotherapy have limited therapeutic efficacy for recurrent osteosarcoma. Therefore, there is an urgent need to identify risk factors for osteosarcoma patients to improve their

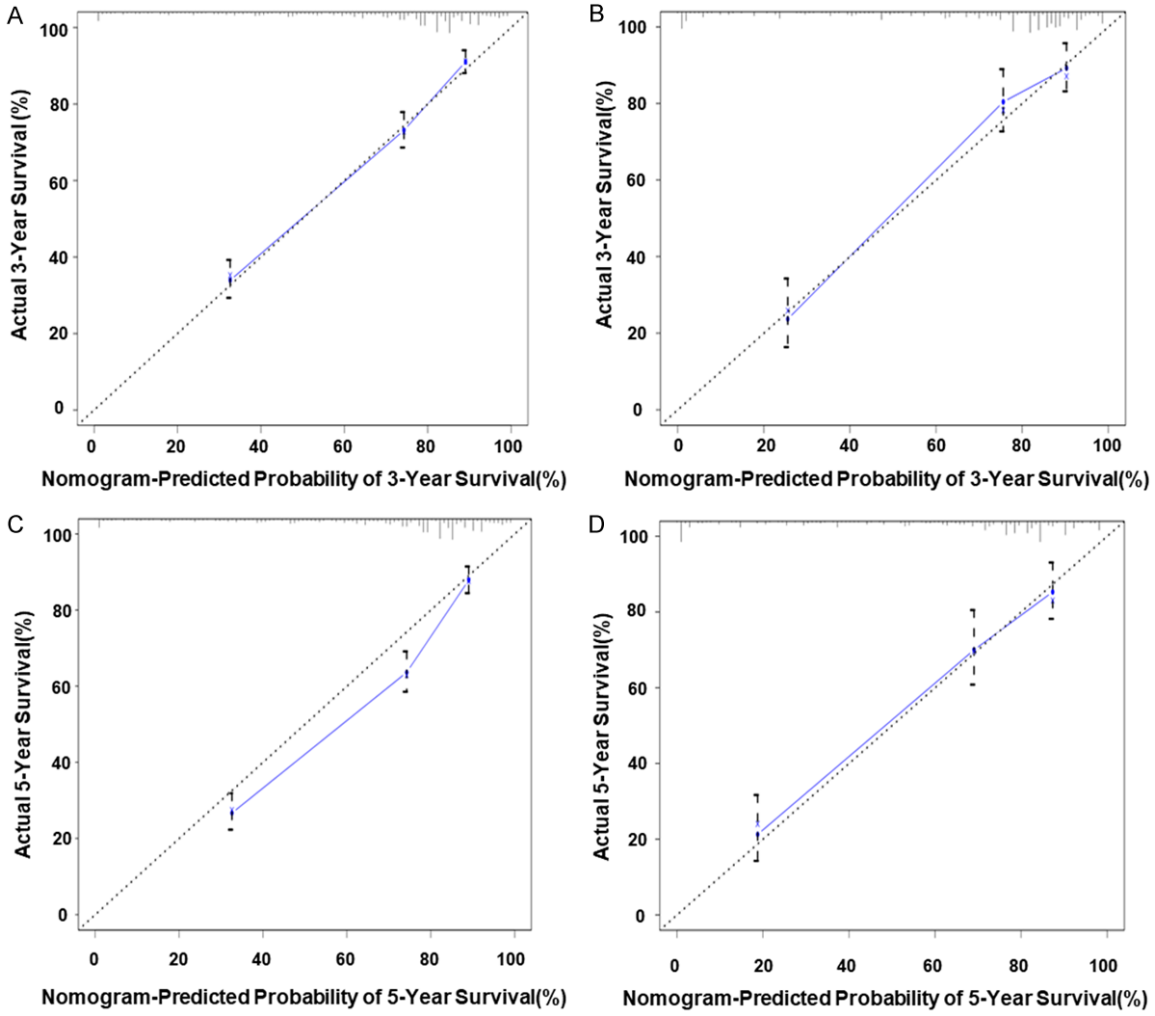

Figure 2. Calibration curve of the nomogram. A, C. For 3-, 5-year in the training set; B, D. For 3-, 5-year in the validation set.

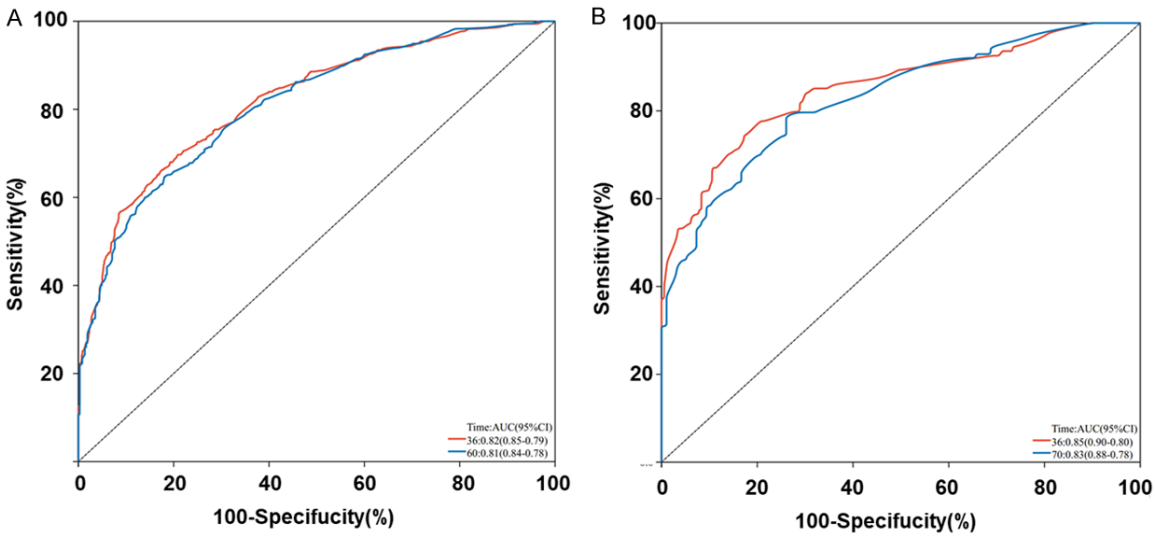

Figure 3. The ROC of 3- and 5-year of the training (A) and validation (B) sets.

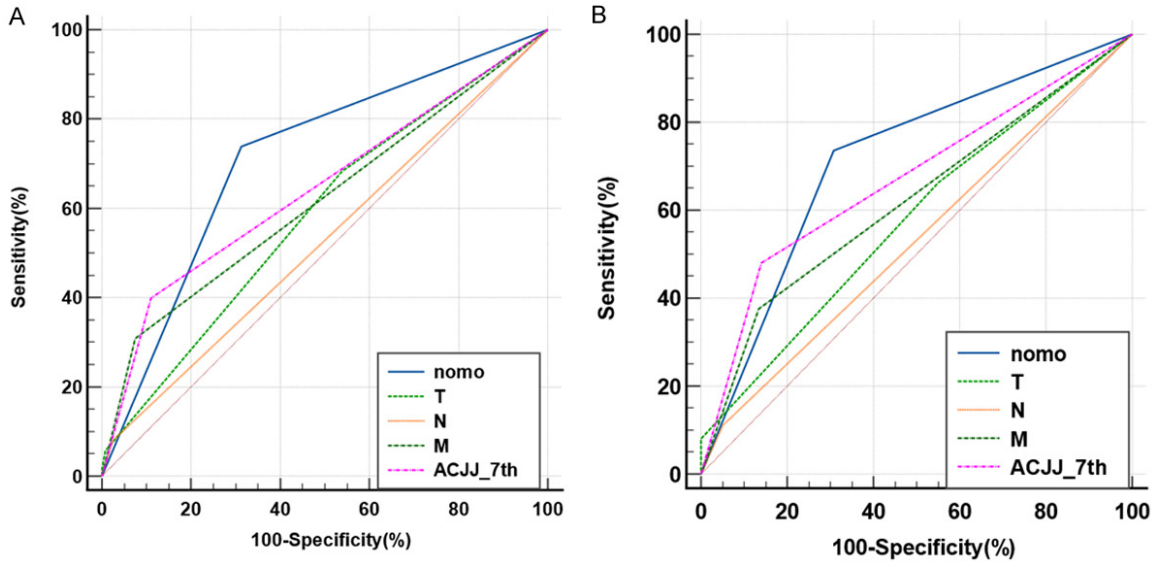

Figure 4. ROC curves of the nomogram TNM stage and AJCC 7th in the training and validation group. A. Training group; B. Validation group.

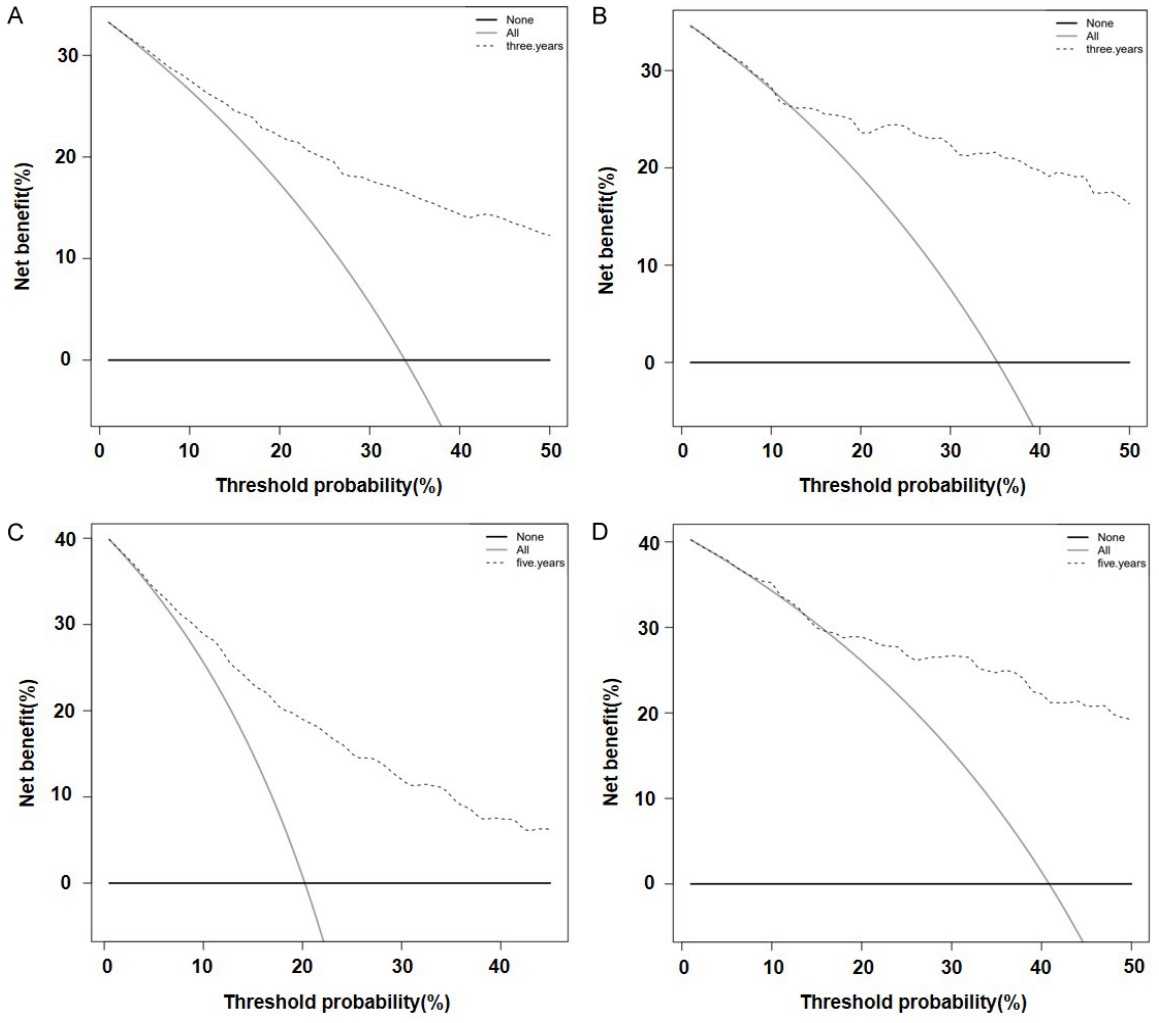

Figure 5. The DCA of 3-, 5-year in the training set (A, C); 3-, 5-year in the validation set (B, D).

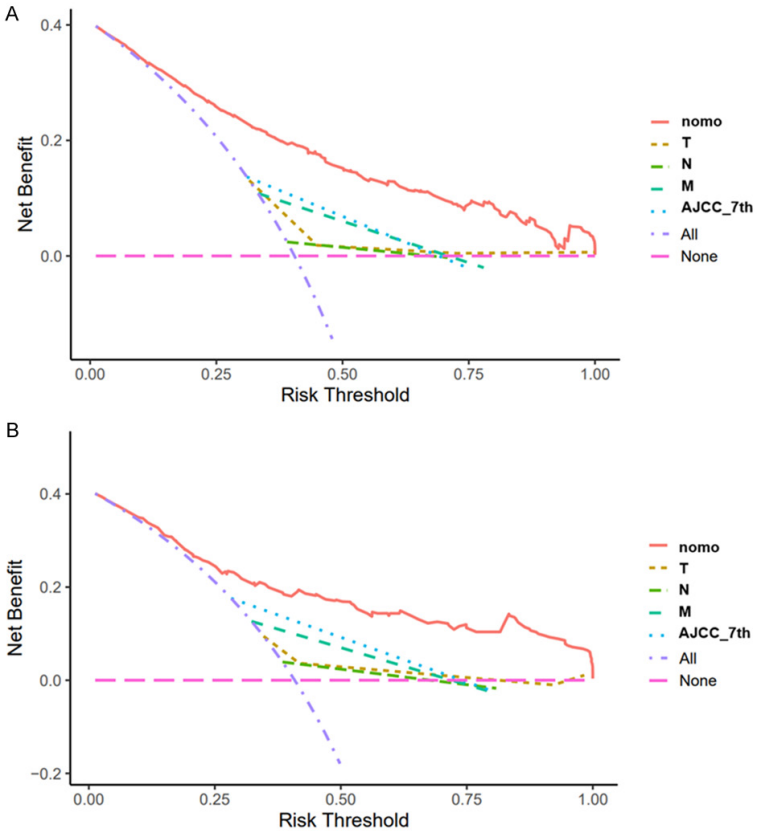

Figure 6. Decision curves of the nomogram, TNM Stage, and AJCC 7th in the training set (A) and the validation set (B).

prognosis. Nomogram is a reliable and simple intuitive predictive tool with excellent discrimination and excellent calibration [11]. It can reduce the statistical prediction models to a single numerical estimate of the probability of an event (e.g., Death or Recurrence) for an individual patient profile, which can be used effectively in the clinic and to facilitate physician decision-making [12]. Indeed, Zheng et al. [13] used nomogram plots to provide individual predictions of OS for secondary osteosarcoma patients and concluded that secondary osteosarcoma patients had worse OS than primary osteosarcoma patients; however, no external data validation was performed in their study.

In this study, age, sex, tumor size, primary site, grade, surgery of primary site, bone metastases, brain metastases, liver metastases, lung metastases, AJCC 7th stage, T stage, N stage, M stage, surgery, and chemotherapy were risk factors for osteosarcoma in univariate Cox logistic regression analysis. After stepwise logistic regression analysis, age, sex, tumor size, primary site, grade, liver metastases, M-stage, and surgery were identified as the most significant risk factors. It is not surprising that age is usually considered to be a factor that affects prognosis [14, 15], as aging process triggers many physiological changes in a body. Aging is accompanied by changes in genomic stability as well as in protein and metabolism function [16, 17]. All these changes are known to be involved in the development and progression of tumors [18]. On the hand, the relationship between gender and the prognosis of patient with osteosarcoma is controversial. Several studies have concluded that gender has an impact on patient survival, although it is less important than age [19, 20]. This may be because osteosarcoma is not a sex hormone-secreting tumor. However, the effect of gender on the survival of patients with osteosarcoma might be biased by the data used. Hence, the effect of gender on the survival of patients with osteosarcoma remains to be further clarified. As for tumor size, we found a larger Tumor size indicated a worse prognosis, consistent with previous studies [21, 22]. It is conceivable that the larger the tumor, the more extensive the involvement and the increased physiological spacing of the tumor, resulting in a greater likelihood of vascular nerve invasion, with results similar to those of tumor progression staging affecting survival outcomes. In addition, it is known that the larger the tumor the greater the surgical trauma, the greater the corresponding complications, and the corresponding decrease in the likelihood of complete margin negativity [23]. Furthermore, we found that the tumor location near the central axis (spine, pelvis, thorax) has a significantly higher risk of mortality than that near the limbs. Similar to previous studies, axial tumor location predicts the worst prognosis [24, 25]. For example, Picci et al. [26] have reported that tumors at the limbs can be removed by surgery, but it is more difficult to

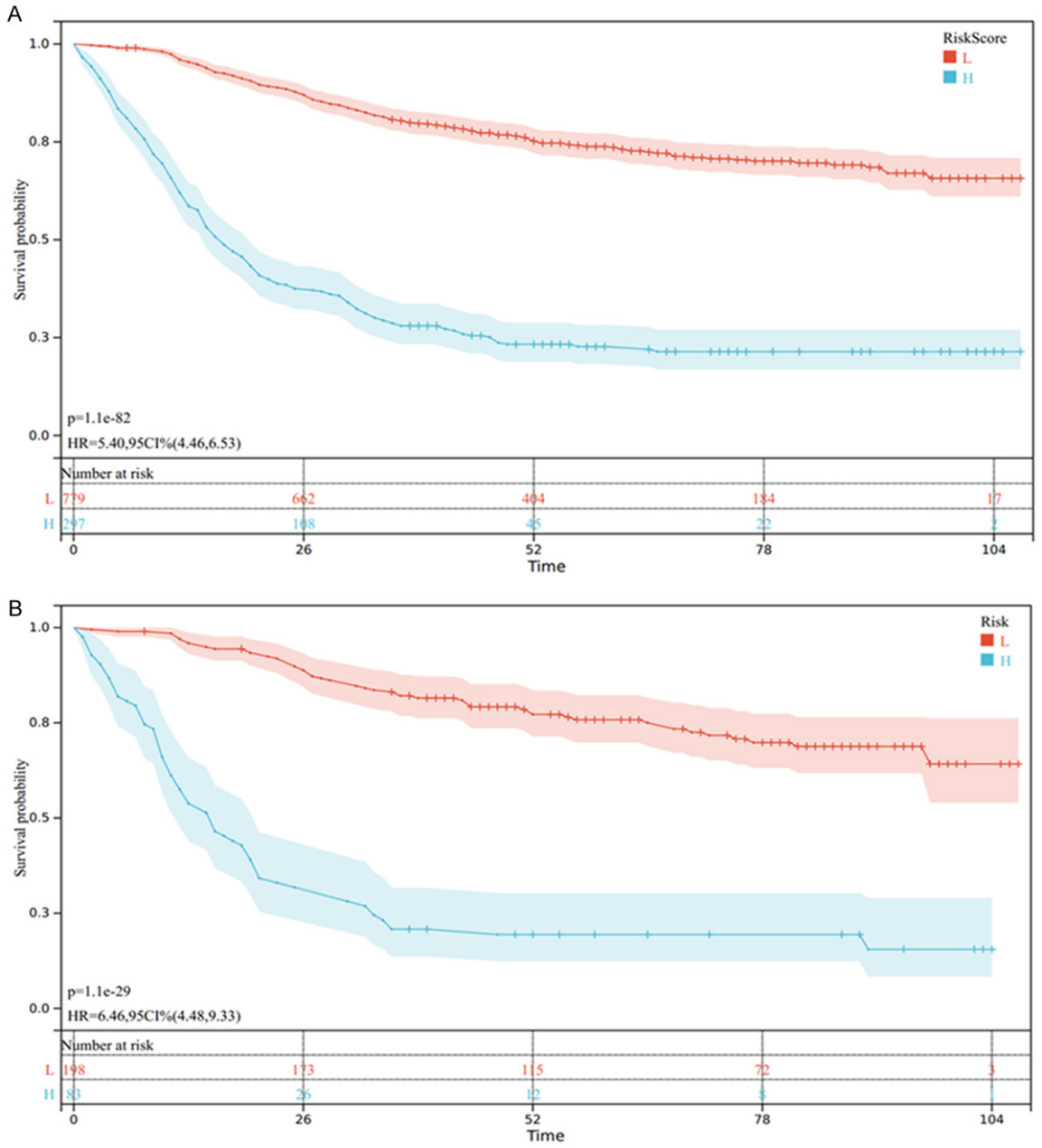

Figure 7. Kaplan-Meier curves of Overall survival in the low- and high-risk groups in the training set (A) and validation set (B).

remove tumors at the axial bones. As we know, tumor grade is the description of a tumor based on how abnormal the tumor cells and the tumor tissue look under a microscope, which is an indicator of how quickly a tumor is likely to grow and spread according to the National Cancer Institute (https://www.cancer.gov/about-cancer/diagnosis-staging/prognosis/tumor-grade-fact-sheet). In this study, patients with distant metastasis showed worse survival. In line with this finding, a previous study reported that the survival of patients with primary metastatic osteosarcoma was significantly correlated with age, primary tumor site, response to neoadjuvant chemotherapy, numbers and sites of metastasis, and surgical resection of the tumor sites. Notably, surgery is the core treatment for osteosarcoma [27]. Although the outcome of surgery is influenced by many factors, a complete resection of the primary tumor can block

the progression of tumors including metastases to some extent [28, 29]. In consistent with this notion, our results showed that surgery was a protective factor. Nevertheless, the ability of a single factor to affect the overall survival of osteosarcoma is limited; hence, we combined multiple prognostic factors to construct a nomogram for the prediction of the overall survival, and in fact, the application of nomogram to predict tumor risk has long been widely accepted.

The nomogram we constructed was accurate and reliable, suggesting that the nomogram model is a promising tool in tumor surveillance and clinical decision-making. Although some predictive nomograms have been reported in previous studies, our investigation complemented the previous studies. Compared to previous studies, in this study, we used external independent validation cohorts consisting of patients from multiple medical centers to confirm the findings from testing cohort. Furthermore, the inclusion of multiple ethnic groups in this study enhanced the credibility of the results. Nonetheless, our study has certain limitations. First, because our study is a retrospective study based on information from the SEER database, some possible variables such as surgical margins, tumor recurrence, genetic factors were not available. Second, we only included patients from 2010 to 2015, because AJCC 7th version staging information was missing for patients with osteosarcoma before 2010. With the improvement of treatment methods, the survival rate of patients in different years could be different. However, our validation group data were collected from 2018 to 2021, due to incomplete record in the early years, which supported the findings from samples collected in earlier years. Third, genetic data were not included in this study, although the combination of clinical data and genetic data might enhance the predictive ability of the model. Our future will incorporate the genetic variables in the model construction. Moreover, in our follow-up study, we will apply this nomogram in the clinical process to further validate and refine our model.

Conclusion

In summary, this study constructed a reliable nomogram by using the clinical factors including age, sex, tumor size, primary site, grade, M stage, and surgery to predict the prognosis of patients with osteosarcoma. The discovery of risk factors and the construction of nomograms can help clinicians evaluate the prognosis of patients, choose the appropriate treatment options.

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Disclosure of conflict of interest

None.

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