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ORIGINAL ARTICLE

Development and validation of a nomogram for specific survival in osteosarcoma patients less than 60 years old: a population-based study

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Summary

Purpose: *The present study aimed to develop a nomogram to predict the overall survival of patients with osteosarcoma, especially those less than 60 years old.*

Methods: *903 osteosarcoma patients less than 60 years old were collected from the Surveillance, Epidemiology, and End Results (SEER) database.Univariate and multivariate analyses identified the independent prognostic factors of osteosarcoma. Nomogram was used to predict 3- and 5-year overall survival (OS) of osteosarcoma.The accuracy of the model was determined using the concordance index (C-index), calibration curves, the area under the receiver operating characteristic curves (ROC),as well as decision curve analysis (DCA).*

Results: *Osteosarcoma patients less than 60 years old were randomly assigned into a training cohort (n=635) or validation cohort (n=268). Age, tumor site, tumor grade, tumor size, and tumor stage were identified as independent prognostic factors via univariate and multivariate Cox analyses (all p<0.05) and then included in the prognostic nomogram. The concordance indices(C-index) for OS prediction in the training cohort was 0.788 (95% CI 0.751-0.852) and in the external validation cohort was 0.779 (95% CI 0.712-0.846). Calibration plots and the area under the ROC revealed excellent consistency between actual survival and nomogram prediction. Finally, DCA demonstrated that the prognostic nomogram was clinically meaningful.*

Conclusions: *A nomogram could accurately predict the OS of osteosarcoma patients less than 60 years old and contribute to making better clinical treatment decisions for the treating doctors.*

Key words: *osteosarcoma, nomogram, overall survival, prognosis, SEER*

Introduction

Osteosarcoma is the most common primary malignant bone tumor, which mainly affects children and adolescents [1,2]. Approximately 400 new cases are confirmed annually in the United States [1]. Patients with untreated osteosarcoma rapidly deteriorate and develop distant metastases and more than 90% died of them [3]. With the continuous improvement of treatment, although about 90% of patients underwent surgery and postoperative chemotherapy [4] the cure rate of limited non-metastatic osteosarcoma was close to 70% [5] and less than 30% of patients with metastatic disease were still alive within five years after diagnosis [2]. Therefore, larger population-based studies are needed to assess the survival rate of osteosarcoma patients to identify prognostic factors. Although the prognosis of patients less than 60 years old is better than that of patients over 60 years [6], and previous studies suggested that many prognostic factors were related to the survival outcome of pa-

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tients older than 60 years, such as tumor size, race, metastasis, tumor grade and treatment methods [7,8], studies on osteosarcoma patients less than 60 years have not been reported. Therefore, the integration of a variety of prognostic factors to accurately predict the survival of osteosarcoma patients less than 60 years may assist to guide clinical treatment, and establish standard treatment strategy.

As a statistical prediction tool, a nomogram can integrate a variety of prognostic factors to predict the survival outcome accurately [9] and has been widely demonstrated in colorectal cancer [10], hepatocellular carcinoma [11], gastric cancer [12], and pelvic chondrosarcoma [13]. Therefore, the nomogram association with multiple prognostic factors would be desirable to estimate the survival of osteosarcoma patients, which is beneficial to individualized treatment. Although prognostic nomograms of osteosarcoma patients were constructed and showed excellent predictive abilities [14,15], they did not evaluate prognostic factors such as lung metastasis, tumor differentiation, tumor stage, and tumor size in patients less than 60 years. Therefore, this study aimed to determine the independent prognostic factors of patients with osteosarcoma less than 60 years based on the SEER database and constructed a nomogram to evaluate the 3- and 5-year overall survival (OS).

Methods

Data source and selection

All osteosarcoma patients listed were collected from the SEER database, which comprises 18 population-based cancer registries. SEERStat software (version 8.3.6.1) was used to acquire patient information. The inclusion criteria were all patients diagnosed with osteosarcoma less than 60 years old. The exclusion criteria were as follows: unknown tumor stage (stage T, stage N, stage M), tumor grade, lung metastasis, race and uncertain tumor size.

Study variables

Clinicopathological features, including vital status, OS, age, race, gender, tumor site, tumor grade, tumor stage, tumor size, and lung metastasis, were collected. OS was used as primary endpoint and defined as the interval from the time of diagnosis to death or last follow-up. The optimal cutoff value of tumor size was determined using the X-tile software [16] (Yale University, New Haven, CT, USA), as shown in Figure 1,so patients were divided into three groups (≤92mm, 92-147mm, and ≥147mm). Patient age at diagnosis was categorized into three groups (0-19 years, 20-39 years, and 40-59 years). Tumor grade was categorized into two groups [poorly differentiated (ICD-O-3grade III and IV) and well differentiated (ICD-O-3 grade I and II)]. Race was categorized into 3 groups: white, black, and others. Specific osteosarcoma site was categorized as extremity (long or short bones of lower or upper limb and associated joints, limb bone), axial (rib, sternum, clavicle and associated joints, pelvic bones, sacrum, coccyx and associated joints, vertebral column) and others (heart, bones of skull and face and associated joints, mandible, etc.). Patients coded with stage T were classified as T1 (T1, T1a, T1b, T1NOS), T2 (T2, T2a, T2b, T2NOS), T3, and Tx; stage N were classified as N0, N1, and Nx; stage M was classified as M0 and M1(M1, M1a, M1b, M1NOS).

Statistics

In the training and validation cohorts, the prognostic factors (race, gender, tumor site, tumor grade, tumor size, tumor stage, etc.) were further evaluated via univariate and multivariate Cox proportional hazards regression analyses. The nomogram for 3- and 5-year OS was built with potential risk factors based on Cox analysis. We used C-index to evaluate the prediction performance of the nomogram. In general, the C-index of the nomogram greater than 0.7 indicates good predictive ability [17]. Calibration plots and the ROC (Receiver operating characteristic) curves were used to evaluate the precision of the nomogram. The average mean and range were used to present continuous variables; counts and percentages were used to present distributed variables. We used the Kaplan-Meier method to construct the cumulative survival curve. Finally, the clinical net benefit and usefulness of the prognostic model were evaluated

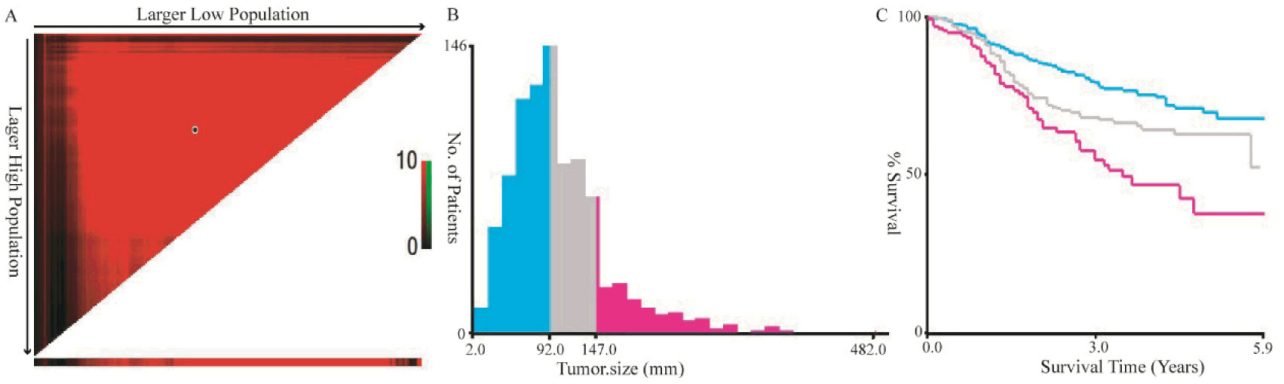

Figure 1. The optimal cut-off value of tumor size via X-tile analysis **(A–C)**. Based on overall survival, the optimal cutoff value of tumor size was 92mm or 147mm.

using DCA [18]. SPSS 22.0 (IBM Corp.) was used to evaluate the prognostic effect and to compare it with the x^2 test. P<0.05 was considered statistically significant.

Results

Patient baseline characteristics

According to the inclusion and exclusion criteria we collected 903 patients diagnosed with osteosarcoma less than 60 years between 1973 and 2015, including 635 patients in the training cohort and 268 patients in the validation cohort, from the SEER database. The clinical characteristics of the patients were summarized, as shown in Table 1. Among those patients, 484 (53.6%) were male and 419 (46.4%) female. With regard to tumor grade, poorly differentiated (grade III and IV) (87.8%) was most frequent, followed by well-differentiated (grade I and II) (12.2%). The majority of patients were white (73.5%, 73.1%); in the training and vali-

Table 1. Baseline characteristics of the included patients

Characteristic	*Total (n=903)* *n (%)*	*Training cohort (n=635)* *n (%)*	*Validation cohort (n=268)* *n (%)*	*p*
Age (years)				0.164
0~20	485(53.7)	337(53.1)	148(55.2)	
20~40	255(28.2)	179(28.2)	76(28.4)	
40~60	163(18.1)	119(18.7)	44(16.4)	
Race				0.951
White	663 (73.4)	467 (73.5)	196 (73.1)	
Black	150 (16.6)	104 (16.4)	46 (17.2)	
Others	90 (10.0)	64 (10.1)	26 (9.7)	
Gender				0.264
Female	419 (46.4)	287 (45.2)	132 (49.3)	
Male	484 (53.6)	348 (54.8)	136(50.7)	
Tumor site				0.567
Extremity	718 (79.5)	509 (80.2)	209 (78.0)	
Axial	89 (9.9)	63 (9.9)	26 (9.7)	
Others	96 (10.6)	63 (9.9)	33 (12.3)	
Grade				0.714
Poorly	793 (87.8)	556 (87.6)	237 (88.4)	
Well	110 (12.2)	79 (12.4)	31 (11.6)	
T Stage				0.329
T1	352 (39.0)	248 (39.1)	104 (38.8)	
T2	525 (58.1)	368 (58.0)	157 (58.6)	
T3	19 (2.1)	12 (1.9)	7 (2.6)	
Tx	7 (0.8)	7 (1.1)	0 (0)	
N Stage				0.836
N0	864 (95.7)	607 (95.6)	257 (95.9)	
N1	17 (1.9)	13 (2.1)	4 (1.5)	
Nx	22 (2.4)	15 (2.4)	7 (2.6)	
M Stage				0.508
M0	750 (83.1)	524 (82.5)	226 (84.3)	
M1	153 (16.9)	111 (17.5)	42 (15.7)	
Tumor size (mm)				0.574
≤92	475 (52.6)	327 (51.5)	148 (55.2)	
92~147	284 (31.6)	204 (32.1)	81 (30.2)	
≥147	144 (15.8)	104 (16.4)	39 (14.6)	
Lung metastasis				0.313
No	772 (85.5)	538 (84.7)	234 (87.3)	
Yes	131 (14.5)	97 (15.3)	34 (12.7)	

dation cohorts of the extremity there were 80.2%, 78.0%, stage T2 (58.0%, 58.6%), stage N0 (95.6%, 95.9%) and stage M0 (82.5%, 84.3%). The 3- and 5-year OS rates were 71.1% and 63.2%, respectively.

Kaplan-Meier survival analysis and prognostic factors of OS results

The specific survival curves of osteosarcoma were calculated by Kaplan-Meier method for all variables (Figure 2). Univariate and multivariate analysis were conducted for the OS to analyze prognostic factors. As shown in Table 2, it demonstrated that age (p<0.001), tumor site (p<0.05), tumor grade (p<0.001), T stage (p<0.001), N stage (p<0.05), M stage (p<0.001), tumor size (p<0.001) and lung metastasis (p<0.001) were associated with OS based on the univariate analysis, which was consistent with the results of Kaplan-Meier survival analysis. However, there was no significant difference in race and gender (p>0.05). Meanwhile, multivariate analyses demonstrated that age (p<0.001), tumor site (axial, p<0.05), tumor grade (p<0.001), T stage (Tx, p<0.05), N stage (N1, p<0.001), M stage (p<0.001), tumor size (p<0.05) were independent prognostic factors of OS.

Prognostic nomogram construction and validation

Based on the significant independent prognostic factors of age, tumor site, tumor grade, T stage, N stage, M stage and tumor size, the nomogram was established to predict 3- and 5-year OS. Each prognostic variable was scored on the nomogram. As shown in Figure 3, tumor grade made the most significant contribution to prognosis, followed by N stage, T stage, M stage and age. Internal validation in the training cohort and external in the validation cohort showed that the C-index value of nomogram predictions of OS were 0.788 (95% CI 0.751-0.852) and 0.779 (95% CI 0.712-0.846). Besides, the AUC values of ROC curves and the calibration curves for 3-y and 5-year OS demonstrated excellent consistency between nomogram prediction and actual survival, as shown in Figure 4 (the training cohort)

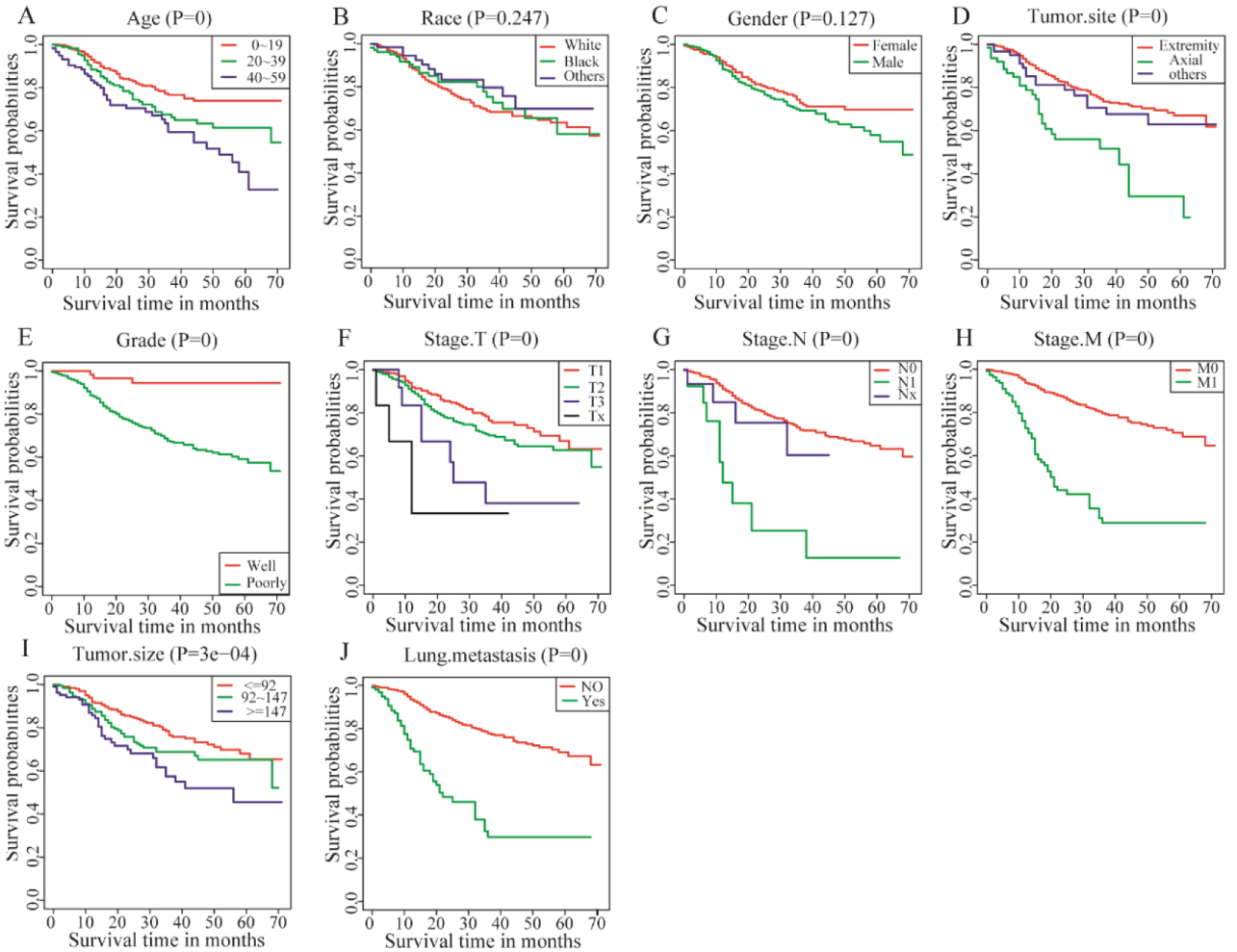

Figure 2. Kaplan-Meier overall survival analyses for osteosarcoma patients based on **A:** age (p=0), **B:** race (p=0.247), **C:** gender (p=0.127), **D:** tumor site (p=0), **E:** grade (p=0), **F:** T stage (p=0), **G:** N stage (p=0), **H:** M stage (p=0), **I:** tumor size (p<0.001), and **J:** lung metastasis (p=0).

and Figure 5 (the validation cohort). All those suggested that this model made accurate predictions.

Clinical use

In addition, the clinical validity of the nomogram of the training cohort was analyzed using DCA. Because of the extensive and practical ranges of threshold probabilities, the results strengthened the excellent clinical applicability of the nomogram in predicting OS in patients with osteosarcoma less than 60 years. When comparing with the traditional AJCC stages, the nomogram we constructed increased the patient net benefits within a considerable range of threshold probabilities (Figure 6).

Discussion

Based on the SEER dataset, we established a novel and convenient nomogram for estimating individual OS outcomes for patients with osteo-

Table 2. Univariate and multivariate analyses of overall survival in the training cohort

Characteristics	*Univariate analysis*	*Multivariate analysis*	
	p	*HR (95%CI)*	*p*
Age (years)	< 0.001		
0~19		Reference	
20~39		2.570(1.682-3.928)	< 0.001
40~59		4.272(2.707-6.744)	< 0.001
Race	0.262	NI	
White			
Black			
Others			
Gender	0.127	NI	
Female			
Male			
Tumor site	0.022		
Extremity		Reference	
Axial		2.312(1.442-3.708)	< 0.001
Others		1.695 (0.935-3.074)	0.082
Grade	< 0.001		
Poorly	Reference		
Well	9.784 (3.05-31.385)	< 0.001	
T Stage	< 0.001		
T1		Reference	
T2		0.813 (0.429-1.541)	0.526
T3		1.873 (0.701-5.006)	0.211
Tx		3.672 (1.020-13.220)	0.047
N Stage	0.047		
N0		Reference	
N1		3.816 (1.852-7.863)	< 0.001
Nx		0.630 (0.195-2.037)	0.44
M Stage	< 0.001		
M0		Reference	
M1		4.776 (2.330-9.788)	< 0.001
Tumor size (mm)	< 0.001		
≤92		Reference	
92~147		1.923 (1.022-3.617)	0.0425
≥147		2.586 (1.322-5.060)	0.006
Lung metastasis	< 0.001		
No		Reference	
Yes		1.170 (0.560-2.444)	0.676

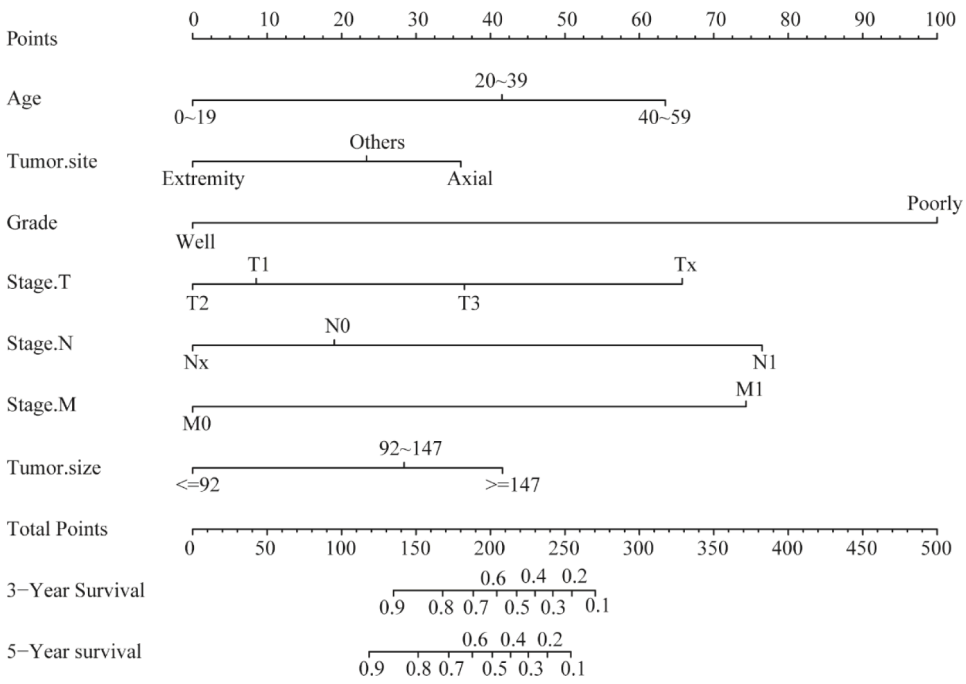

Figure 3. Nomogram for osteosarcoma patients to predict the probability of 3- and 5-year OS.

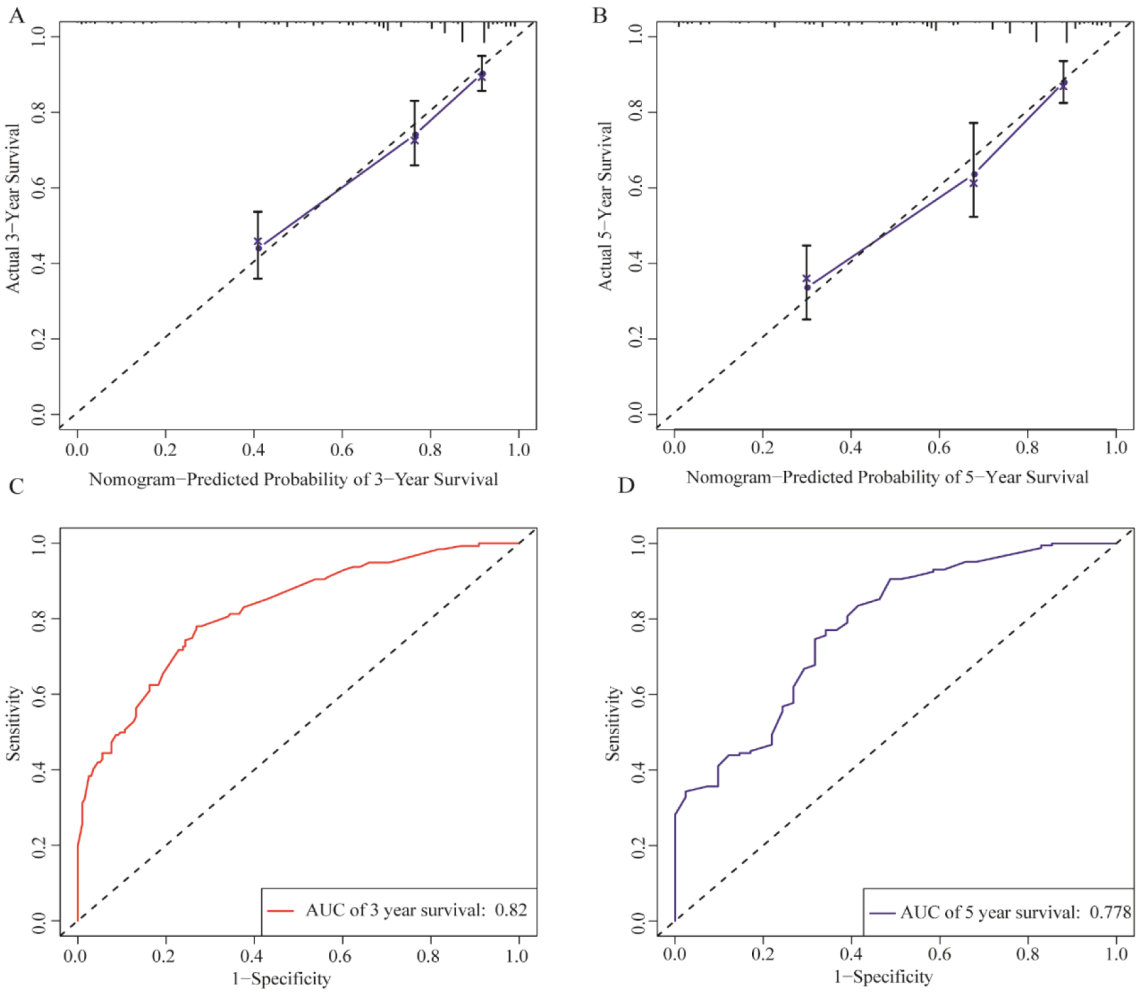

Figure 4. ROC curves and calibration plots of the nomogram in the training cohort. **A** and **B:** The calibration curves of 3- and 5-year OS. **C** and **D:** The AUC values of ROC curves for 3-year OS (AUC=0.82) and 5-year OS (AUC=0.778). AUC: area under the receiver operating characteristic curve.

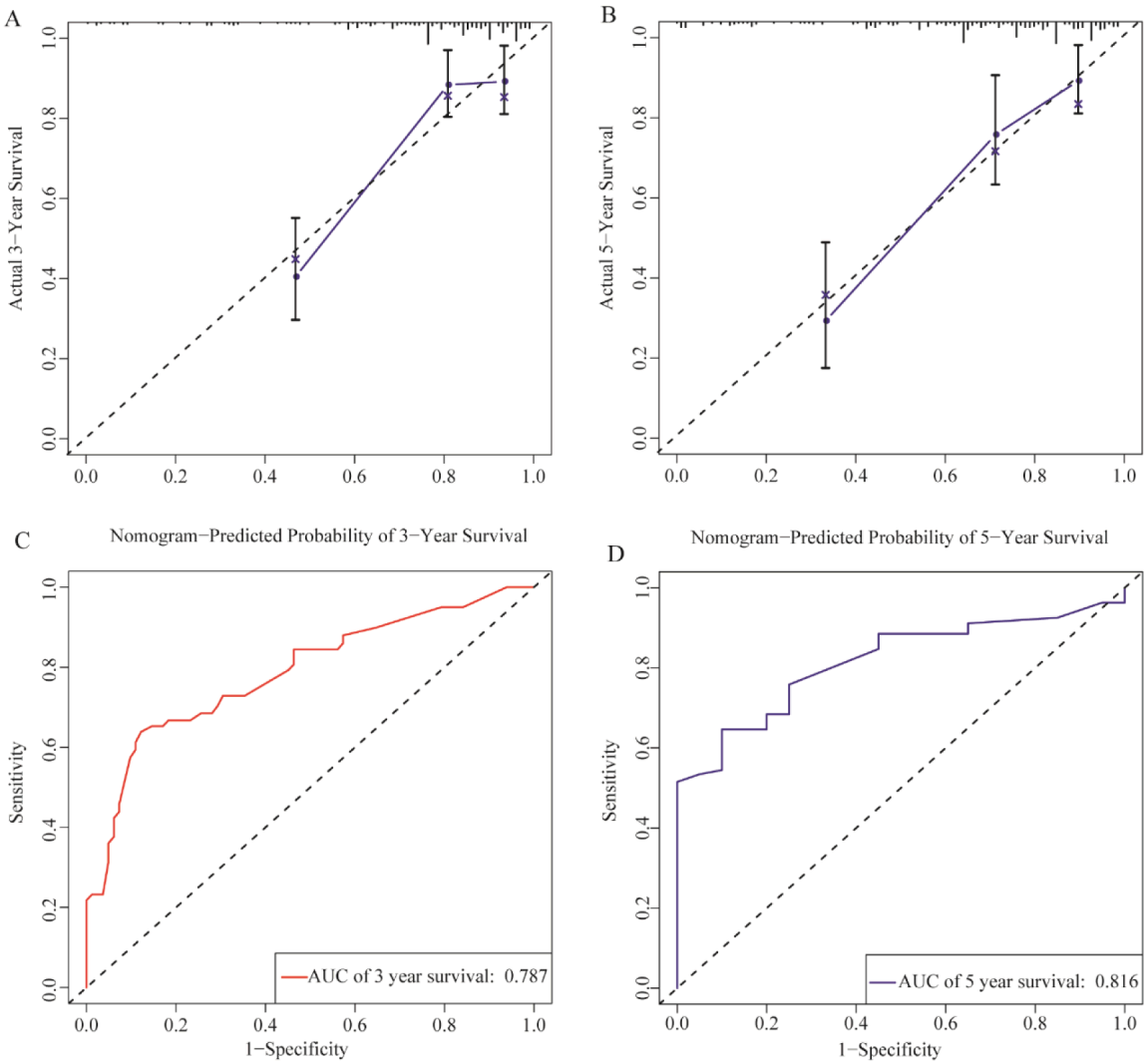

Figure 5. ROC curves and calibration plots of the nomogram in the validation cohort. **A** and **B:** The calibration curves of 3- and 5-year OS. **C** and **D:** The AUC values of ROC curves for 3-year OS (AUC=0.787) and 5-year OS (AUC=0.816). AUC: area under the receiver operating characteristic curve.

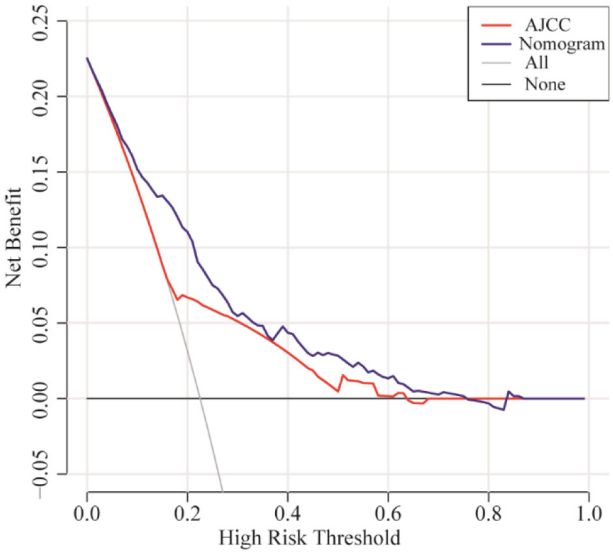

Figure 6. Decision curve analysis for the prognostic nomogram. AJCC: American Joint Committee on Cancer.

sarcoma, which might be considered a complement of the previous researches that failed to establish a prognostic prediction model for patients less than 60 years [8,14]. In the training and validation cohorts, the nomogram showed satisfactory consistency, which indicated good clinical applicability. Our study demonstrated that age, tumor site, tumor grade, T stage, N stage, M stage, and tumor size were independent prognostic factors for patients with osteosarcoma less than 60 years. Then, the prognostic nomogram was developed and validated by integrating these independent factors to predict 3- and 5-year OS. Multivariate analysis showed that age 20-39 years (HR=2.570, 95% CI=1.682-3.928, p<0.001, 40-59 years HR=4.272, 95% CI=2.707-6.744, p<0.001), tumor grade (HR=9.784, 95% CI=3.05-31.385, p<0.001), N stage (N1, HR=3.816, 95% CI=1.852-7.863, p<0.001) and M stage (HR=4.776, 95% CI=2.330-9.788, p<0.001)

resulted in higher HRs than other variables (tumor size and T stage) did, which was consistent with the results of many studies [19,20]. TNM stage and tumor grade are considered to be the very important factors in predicting OS and are valuable in predicting the survival of patients with osteosarcoma [21].

The nomogram is a new form of disease risk assessment, which is widely used as a prognostic tool in medicine and oncology and can help clinical decision making [22]. In this study, age was one of the independent prognostic factors of the nomogram, and Kaplan-Meier analysis showed that the prognosis of osteosarcoma patients was worse with increasing age, which was consistent with previous studies [15,23,24]. In addition, to obtain the best cut-off points of tumor size, we analyzed the data with X-Tiles software and found that 92 mm and 147 mm were the best cut-off values. Similarly, the results showed that tumor size was also one of the important indicators of prognosis in patients with osteosarcoma younger than 60 years. Combined with Kaplan-Meier analysis, it was found that the larger the tumor, the worse the prognosis and the lower the survival rate, which were consistent with previous studies [15,25]. In this study, tumor site was a significant prognostic factor for osteosarcoma. Compared with extremity tumors, the OS rate of osteosarcoma patients with non-extremity tumors was significantly lower, which was consistent with the results of Seker et al [26] and Sun et al [27]. Of note, the site of osteosarcoma was associated with lung metastasis, while osteosarcoma patients with non-extremity tumors had a higher risk of lung metastasis [28]. Non-extremity osteosarcomas are usually closer to large blood vessels, which may increase the likelihood of metastasis [29]. This may explain the significant difference of lung metastasis in univariate analysis ($p< 0.001$), but lung metastasis was not identified as an independent survival risk factor after the multivariate regression analysis ($p=0.676$). In addition, in the disease course, non-extremity osteosarcomas tend to be diagnosed late because of lack of positive symptoms or signs [30]. For example, it was reported that the 5-year survival rate of osteosarcoma of the pelvis was less than 30% [29,31], which was close to the results of our survival analysis.

Then, the results of calibration plots and ROC curve analysis of 3- and 5-year survival (the AUC values of ROC curves were 0.82, 0.778 and 0.787, 0.816) indicated that the newly established nomogram had good prediction performance in the training and verification set. Besides, compared with the traditional AJCC stage, DCA demonstrated that the OS of patients with osteosarcoma less than 60 years provided an ideal net benefit, which should show its clinical use and impact on actual decision-making.

In conclusion, based on the SEER database, this study identified age, tumor site, tumor grade, T stage, N stage, M stage and tumor size as independent prognostic factors for patients with osteosarcoma younger than 60 years. Although the nomogram could individually estimate the 3- and 5-year OS rates according to C-indexes, calibration plots, the AUC values of ROC curves and DCA, the performance of nomogram did not provide an absolutely accurate prognosis and may only be used as a reference for clinicians. The development of osteosarcoma risk prediction tool is still an important task.

Conflict of interests

The authors declare no conflict of interests.

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