Translational Oncology 18 (2022) 101349

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Original Research

A predictive model with a risk-classification system for cancer-specific survival in patients with primary osteosarcoma of long bone

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ARTICLE INFO

Keywords:
Osteosarcoma
Nomogram
Long bone
Risk classification system
Prognosis

ABSTRACT

Background: Osteosarcoma (OS), most commonly occurring in long bone, is a group of malignant tumors with high incidence in adolescents. No individualized model has been developed to predict the prognosis of primary long bone osteosarcoma (PLBOS) and the current AJCC TNM staging system lacks accuracy in prognosis prediction. We aimed to develop a nomogram based on the clinicopathological factors affecting the prognosis of PLBOS patients to help clinicians predict the cancer-specific survival (CSS) of PLBOS patients.

Method: We studied 1199 PLBOS patients from the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2015 and randomly divided the dataset into training and validation cohorts at a proportion of 7:3. Independent prognostic factors determined by stepwise multivariate Cox analysis were included in the nomogram and risk-stratification system. C-index, calibration curve, and decision curve analysis (DCA) were used to verify the performance of the nomogram.

Results: Age, Histological type, Surgery of primary site, Tumor size, Local extension, Regional lymph node (LN) invasion, and Distant metastasis were identified as independent prognostic factors. C-indexes, calibration curves and DCAs of the nomogram indicating that the nomogram had good discrimination and validity. The risk-stratification system based on the nomogram showed significant differences ($P < 0.05$) in CSS among different risk groups.

Conclusion: We established a nomogram with risk-stratification system to predict CSS in PLBOS patients and demonstrated that the nomogram had good performance. This model can help clinicians evaluate prognoses, identify high-risk individuals, and give individualized treatment recommendation of PLBOS patients.

Introduction

Osteosarcoma (OS) is an aggressive malignant neoplasm originating from mesenchymal cells with heterogeneous biological and clinical behaviors [1,2]. OS is the most frequent primary malignant tumor of bone with a bimodal distribution concerning age [3], however, the incidence of it is higher in adolescence and childhood [4]. Although OS is rare in the general population (2–3 affected individuals per million person-years), it is the third most common tumor in the adolescent age group [5–7]. Standard treatments such as radical surgery and multi-agent chemotherapy have increased long-term survival from 20% to approximately 70%, markedly improving OS prognosis [8]. MAP (cisplatin, methotrexate, doxorubicin) chemotherapy has become the most commonly used chemotherapy regimen in North America; however, little progress has been made to improve the survival of OS patients in the past 40 years [4,9]. Therefore, further investigations into more clinical features are required.

Several studies have demonstrated the limitations of the AJCC system in predicting the prognoses of OS patients [2]. The TNM staging system only considers tumor size, regional lymph node (LN) invasion, and distant metastasis, ignoring individualized factors such as age [10]. Moreover, although primary OS most commonly occurs in the metaphysis of long bones such as the distal femur, proximal tibia, and proximal humerus [11], it can be found in any part of the body [12]. OS from different sites shows different prognoses, indicating that tumors in different anatomical sites have heterogeneous clinical behaviors. Past studies have suggested that not only staging systems such as TNM [13] but many other clinicopathological factors, such as age, tumor size, histological type, serological treatment options, and biomarkers such as ALP, are closely associated with clinical prognosis in OS patients

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https://doi.org/10.1016/j.tranon.2022.101349
Received 12 October 2021; Received in revised form 7 December 2021; Accepted 18 January 2022

[14–16]. Therefore, to assess the individual risk more accurately, a reliable prognosis tool based on multiple clinicopathologic factors is required.

A nomogram is a graphical representation of a statistical predictive model based on clinical and biological variables [10]. A nomogram based on a clinical prediction model can take full advantage of diverse clinicopathologic factors and give a more precise prediction of patients' individualized risk, compensating for the shortcomings of the TNM system [10,17,18]. To focus on the effect of the tumor itself, we chose cancer-specific survival (CSS) as the main end event, which was different from other existing nomograms, to predict different clinical outcomes for patients with OS [19–21]. Furthermore, to exclude effects caused by tumor primary sites and multiple tumors, it is necessary to establish a nomogram predicting CSS in primary long bone osteosarcoma (PLBOS), which would predict the prognosis of patients with OS more accurately.

In this study, we obtained eligible PLBOS case data from the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2015; the subset of clinical factors strongly associated with CSS was mined to make a clinical prediction model using Cox regression. A nomogram was drawn based on the model to predict the CSS of PLBOS patients. This nomogram presented non-inferior performance to the TNM system, showing that it can help clinicians make more accurate prognostic predictions and individual risk evaluations, which may improve the ability to make prospective decisions.

Methods

Study design and patient selection

The SEER database contains cancer incidence, demographic, clinicopathologic characteristics, treatment information, and survival outcomes of tumor patients based on 28% of the US population (https://seer.cancer.gov). SEER*Stat 8.3.9 was used to obtain population incidence and OS patient data from Incidence-SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000–2018). The SEER database provides open and free online access and all data was anonymized and deidentified, so the need for informed consent was waived. To assure that all patients were followed up for at least 36 months and as many variables as possible were obtained, we only selected cases diagnosed between 2004 and 2015 whose last follow-up year was 2018. The inclusion criteria were as follows: (1) Patients with a confirmed diagnosis of OS according to the AYA site record 2020 version, 4.1 Osteosarcoma. (2) Long bones as the primary site (Primary site = C40.0, C40.2). (3) OS was identified as the first primary tumor (First malignant primary indicator = Yes). The exclusion criteria were as follows: (1) Patients with incomplete prognosis information. (2) Patients with recurrent Paget's disease. (3) Survival time less than 1 month.

Covariates and endpoints

Demographic and clinical variables were extracted as follows: Age, Gender, Marital status, Histological type, Race, Primary site, Grade, Surgery of primary site, Surgery of local LN, Surgery of other sites, Sequence of systemic therapy and surgery, Radiation, Chemotherapy, Tumor size, Local extension, Regional LN invasion, Distant metastasis, and AJCC 6th T/N/M stage. We combined some categories in "Histological type," "Local extension," and "Surgery of primary site" due to the limited case numbers. For "Histological type," all histological types were combined into "Central type" and "Peripheral type" by the relative position of the tumor [22]. For "Local extension," descriptions "Skin," "Further contiguous extension," "Discontinuous tumors in the primary bone site," and "Stated as T3 with no other information on extension" were combined into "Further extension," indicating that the tumor had invaded other tissue/organs or jump metastasis had occurred. For "Surgery of primary site," categories "Local tumor destruction or excision, NOS," "Local tumor destruction," "Local excision," and "Partial resection" were combined into "Local treatment," indicating that these cases had undergone local non-radical surgery. X-tile program (X-tile software version 3.6.1) was used to establish the best cut-off values for age and tumor size [23]. Cancer-specific death (SEER cause-specific death classification = Dead (attributable to this cancer dx)) was defined as the primary endpoint.

Statistical analysis

Statistical analysis was performed using R (version 4.0.5; http://www.r-project.org) and *R* studio (version 1.4.1717; https://www.rstudio.com). All cases were randomly divided into training and validation cohorts at a proportion of 7:3 so that outcome events were distributed randomly between the two cohorts. Descriptive statistics were used for clinical and demographic variables. Categorical variables were described as frequencies (%) and compared with Chi-Square tests. Continuous variables were expressed as a median [first quartile; third quartile] and compared with Kruskal-Wallis rank-sum tests. Survival was analyzed using the Kaplan-Meier method and compared through log-rank tests. Two-tailed p values < 0.05 were considered significant.

Construction and validation of the nomogram

The association between clinicopathological variables and CSS was estimated using univariate and multivariate Cox proportional hazard analyses. Then hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated. Variables with P value < 0.05 in the univariate Cox regression analyses were enrolled in the multivariable Cox regression analysis. Independent prognostic factors were included in the nomogram and screened using the Akaike information criterion (AIC) [24]. The concordance index (C-index) and calibration curve with 1000 bootstrap resampling were used to assess the discrimination and accuracy of the nomogram. Decision curve analysis (DCA) was established to determine clinical usefulness [25]. All statistical analyses were done using R packages survival, rms, nomogramFormula, ggDCA, etc.

Results

Baseline characteristics of patients

From the SEER population data, the incidence and mortality rates of OS remained stable from 2004 to 2015 in the US (Fig. 1A,B) and the proportion of "Long bone" steadily occupied first place out of the primary sites (Fig. 1C). The screening process for patient data is presented in Fig. 1D. In this study, 1199 patients were identified as PLBOS, 840 patients were assigned to the training cohort, and 359 patients to the validation cohort. The median follow-up time of the overall cohort was 65 (1–179) months; it was 64 (1–179) months in the training cohort and 65 (3–178) months in the validation cohort. The determination process for the best cut-off values for age and tumor size is presented in Fig. S1. Clinicopathological variables for all cohorts are shown in Table 1; there was no significant difference between the training and validation cohorts ($P > 0.05$). The median age of the training cohort was 17 years [interquartile range (IQR):12–29 years]; most of the patients (525, 62.5%) were younger than 20 years old. The median tumor size was 95 mm [interquartile range (IQR):70–130 mm]; over half of the cases (431, 51.3%) had a tumor sized between 70 and 139 mm. The histological type could not be determined for most patients (533, 63.5%) and patients with undifferentiated grades (520, 61.9%) constituted the majority of the cohort; 533 (63.5%) patients underwent radical surgery with limb salvage of the primary site, 729 (86.8%) patients underwent chemotherapy, and 34 (4.0%) patients underwent radiation treatment. Only a few patients developed regional LN invasion (16, 1.9%) and distant metastasis, among which lung metastasis was the most common site for metastasis (87, 10.4%). In most patients, the tumor extended

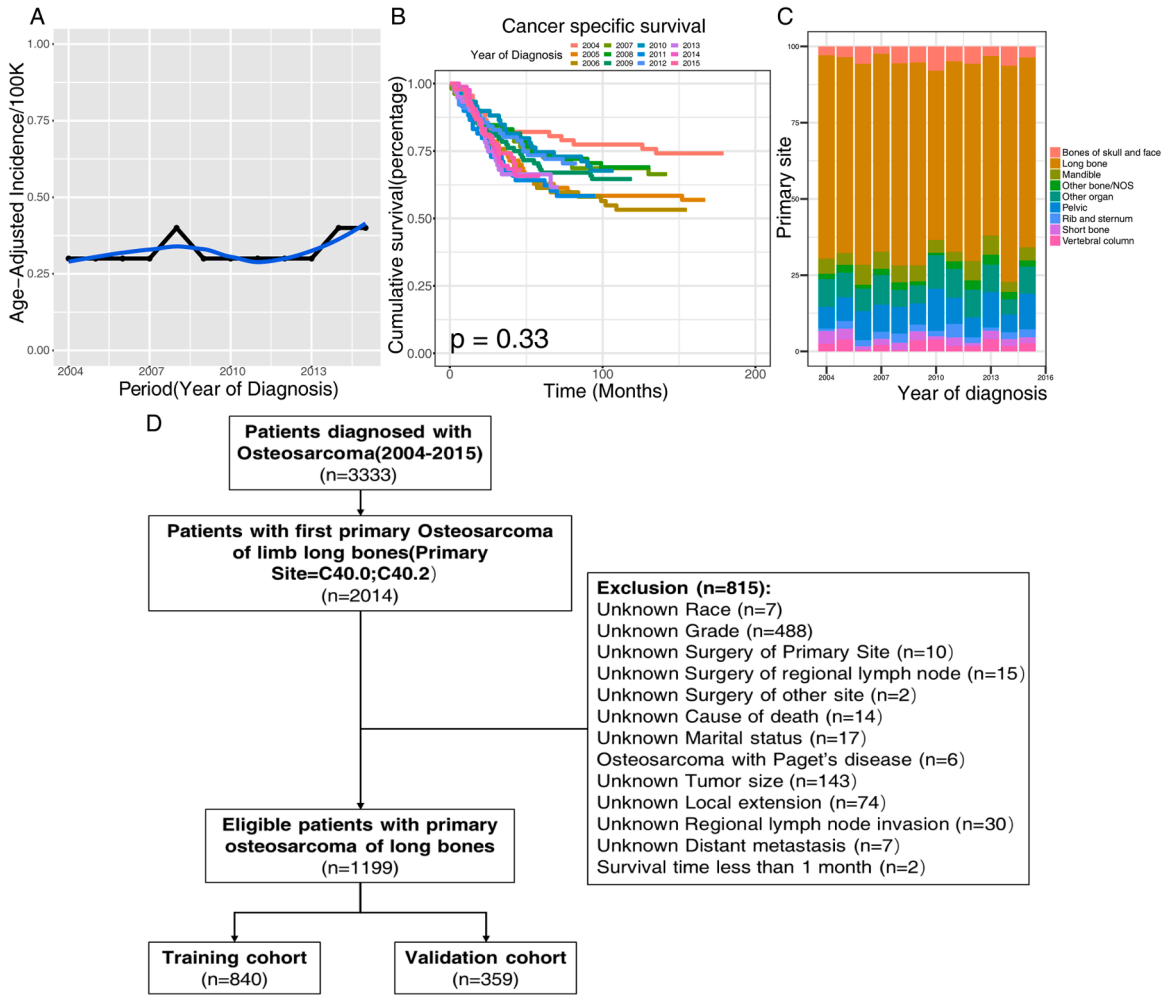

Fig. 1. Cross-sectional data of PLBOS patients. (A) Incidence of PLBOS from 2004 to 2015 in SEER database. (B) Kaplan-Meier survival curves of PLBOS patients by diagnosis year. (C) Distribution of different primary sites in PLBOS. (D) Flow chart of eligible cases screening, 1199 eligible patients were selected. Abbreviations: PLBOS: Primary long bone osteosarcoma. SEER: Surveillance epidemiology and end results.

beyond the periosteum (507, 60.4%). Results were similar for the validation cohort.

Identification of independent prognostic factors

A univariate Cox regression model was used to search for CSS-related prognosis factors (Table 2). According to univariate Cox analyses, age, gender, marital status, histological type, grade, surgery of primary site, surgery of regional LN, surgery of another site, radiation, systemic therapy/surgery sequence, tumor size, local extension, regional LN invasion, and distant metastasis were significantly associated ($p < 0.05$) with prognosis. These factors and chemotherapy (as a part of standard OS therapy protocol [4]) were included in the subsequent multivariate Cox analysis (Table 2). According to the stepwise regression results based on the minimum AIC value, age, histological type, surgery of primary site, tumor size, local extension, regional LN invasion, and distant metastasis were found to be significantly associated ($p < 0.05$) with CSS. These seven variables were defined as independent prognostic factors of PLBOS.

Construction of the nomogram and risk stratification

Based on the above seven independent prognostic factors (Age, Histological type, Surgery of primary site, Tumor size, Local extension, Regional LN invasion, Distant metastasis), the nomogram predicted the CSS for PLBOS patients (Fig. 2). In this nomogram, histological type, age, and distant metastasis had the most significant contribution to the prognoses of PLBOS patients, followed by surgery of primary site, local extension, regional LN invasion, and tumor size. The variables were mapped onto the score-axis and all points were summarized to obtain a total score. Then, 3-year and 5-year CSS probability was obtained according to the total score. After calculating the total points of all patients (Table S1), X-tile was used to select the optimal cut-off value (Fig. S2). Next, all patients were divided into low-risk (0–162), medium-risk (162–215.8), and high-risk (> 215.8) prognostic groups, according to their score. Kaplan-Meier analyses indicated a significant difference ($p < 0.0001$) among three risk stratification groups in the training cohort (Fig. 3A). The validation dataset was used to confirm the conclusion (Fig. 3B). The difference among the three groups remained significant ($p < 0.0001$), which preliminarily indicated the effectiveness of the nomogram and risk stratification system. We also compared the clinical information of the three risk groups (Fig. 3B). Consistent with the distribution of risk factors shown in the nomogram compared to the low-risk group, the medium and high-risk groups had older ages, larger tumor sizes, fewer peripheral types, more local extension, more LN invasion and distant metastasis, and a lower rate of surgery. In addition to these significant prognostic factors, we observed that the proportion of males in the medium- and high-risk groups was higher than that in the low-risk group and the grade of the high-risk group was overall biased toward poor differentiation. More patients (although still a small total

Table 1
Baseline demographics and clinicopathologic characteristics of patients with PLBOS.

Characteristic		All cohort $n = 1199$,n(%)	Training cohort $n = 840$,n(%)	Validation cohort $n = 359$,n(%)	*P* value
Age (median [IQR])	**17.00 [12.00, 28.00]**	**17.00 [12.00, 29.00]**	**16.00 [12.00, 23.00]**	**0.265**	
Age (%)				**0.31**	
	≤ 20	766 (63.9)	525 (62.5)	241 (67.1)	
	20–45	285 (23.8)	207 (24.6)	78 (21.7)	
	> 45	148 (12.3)	108 (12.9)	40 (11.1)	
Gender (%)					**0.276**
	Female	538 (44.9)	386 (46.0)	152 (42.3)	
	Male	661 (55.1)	454 (54.0)	207 (57.7)	
Marital status (%)				**0.187**	
	Single	950 (79.2)	655 (78.0)	295 (82.2)	
	Married	207 (17.3)	156 (18.6)	51 (14.2)	
	Separated/Divorced/Widowed	42 (3.5)	29 (3.5)	13 (3.6)	
Histological type[†] (%)				**0.753**	
	Osteosarcoma,NOS	758 (63.2)	533 (63.5)	225 (62.7)	
	Central osteosarcoma	329 (27.4)	232 (27.6)	97 (27.0)	
	Peripheral osteosarcoma	112 (9.3)	75 (8.9)	37 (10.3)	
Race (%)					**0.309**
	White	891 (74.3)	633 (75.4)	258 (71.9)	
	Black	191 (15.9)	125 (14.9)	66 (18.4)	
	Other	117 (9.8)	82 (9.8)	35 (9.7)	
Primary Site (%)					**0.316**
	Lower limb	1018 (84.9)	707 (84.2)	311 (86.6)	
	Upper limb	181 (15.1)	133 (15.8)	48 (13.4)	
Grade (%)					**0.224**
	Well differentiated	43 (3.6)	36 (4.3)	7 (1.9)	
	Moderately differentiated	84 (7.0)	57 (6.8)	27 (7.5)	
	Poorly differentiated	331 (27.6)	227 (27.0)	104 (29.0)	
	Undifferentiated	741 (61.8)	520 (61.9)	221 (61.6)	
Surgery of primary site[‡] (%)				**0.739**	
	None	69 (5.8)	48 (5.7)	21 (5.8)	
	Local treatment	102 (8.5)	68 (8.1)	34 (9.5)	
	Radical treatment with limb salvage	764 (63.7)	533 (63.5)	231 (64.3)	
	Amputation	264 (22.0)	191 (22.7)	73 (20.3)	
Surgery of regional LN (%)				**0.586**	
	None	1092 (91.1)	768 (91.4)	324 (90.3)	
	Removement/Biopsy/Aspiration	107 (8.9)	72 (8.6)	35 (9.7)	
Surgery of other site (%)				**0.265**	
	None	1145 (95.5)	798 (95.0)	347 (96.7)	
	Yes	54 (4.5)	42 (5.0)	12 (3.3)	
Radiation (%)				**0.867**	
	None/Unknown	1149 (95.8)	806 (96.0)	343 (95.5)	
	Yes	50 (4.2)	34 (4.0)	16 (4.5)	
Chemotherapy (%)				**0.113**	
	None/Unknown	146 (12.2)	111 (13.2)	35 (9.7)	
	Yes	1053 (87.8)	729 (86.8)	324 (90.3)	
Systemic therapy/surgery sequence (%)				**0.428**	
	None	163 (13.6)	119 (14.2)	44 (12.3)	
	Systemic therapy before surgery	243 (20.3)	159 (18.9)	84 (23.4)	
	Systemic therapy after surgery	97 (8.1)	68 (8.1)	29 (8.1)	
	Systemic therapy both before and after surgery	440 (36.7)	316 (37.6)	124 (34.5)	
	Other	256 (21.4)	178 (21.2)	78 (21.7)	
Tumor size (median [IQR])	**95.00 [70.00, 130.00]**	**95.00 [70.00, 130.00]**	**93.00 [70.00, 130.00]**	**0.708**	
Tumor size (%)					**0.798**
	≤ 70 mm	325 (27.1)	232 (27.6)	93 (25.9)	
	70–139 mm	622 (51.9)	431 (51.3)	191 (53.2)	
	> 139 mm	252 (21.0)	177 (21.1)	75 (20.9)	
Local extension[§] (%)				**0.327**	
	No break in periosteum	417 (34.8)	291 (34.6)	126 (35.1)	
	Extension beyond periosteum	729 (60.8)	507 (60.4)	222 (61.8)	
	Further extension	53 (4.4)	42 (5.0)	11 (3.1)	
Regional LN invasion (%)				**1**	
	No	1176 (98.1)	824 (98.1)	352 (98.1)	
	Yes	23 (1.9)	16 (1.9)	7 (1.9)	
Distant metastasis (%)				**0.993**	
	None	997 (83.2)	699 (83.2)	298 (83.0)	
	Lung only	125 (10.4)	87 (10.4)	38 (10.6)	
	Other distant organ	77 (6.4)	54 (6.4)	23 (6.4)	

[†] Central osteosarcoma: Including ICD-O-3 code 9181/3,9182/3,9183/3,9185/3,9186/3,9187/3
Peripheral osteosarcoma: Including ICD-O-3 code 9192/3,9193/3,9194/3.

‡ Local treatment: Including code Partial resection; Local excision; Local tumor destruction; Local tumor destruction or excision, NOS
Amputation: Including code Major amputation; Amputation of limb.
§ Further extension: Including code Skin; Further contiguous extension; Discontinuous tumors in the primary bone site; Stated as T3 with no other information on extension.

Table 2
Univariate and stepwise multivariate Cox regression analysis of the potential independent prognostic factors in the training cohort.

Characteristics	Univariate Cox analysis			Characteristics	Multivariate Cox analysis		
	HR†	95%CI‡	*P* Value		HR	95%CI	*P* Value
Age				**Age**			
≤20	1.00	Reference	Reference	≤ 20	1	Reference	Reference
20–45	1.35	1.02–1.79	0.036	20–45	1.89	1.41–2.52	< 0.001
>45	3.04	2.26–4.09	< 0.001	> 45	3.69	2.69–5.05	< 0.001
Gender							
Female	1.00	Reference	Reference				
Male	1.48	1.16–1.88	0.001				
Marital status							
Single	1.00	Reference	Reference				
Married	1.65	1.25–2.16	< 0.001				
Separated/Divorced/Widowed	1.54	0.84–2.83	0.161				
Histological type				**Histological type**			
Osteosarcoma,NOS	1.00	Reference	Reference	Osteosarcoma,NOS	1	Reference	Reference
Central osteosarcoma	0.79	0.6–1.03	0.08	Central osteosarcoma	0.92	0.70–1.21	0.538
Peripheral osteosarcoma	0.18	0.08–0.4	< 0.001	Peripheral osteosarcoma	0.23	0.10–0.53	0.001
Race							
White	1.00	Reference	Reference				
Black	1.06	0.77–1.47	0.718				
Other	1.16	0.79–1.7	0.447				
Primary site							
Lower limb	1.00	Reference	Reference				
Upper limb	1.08	0.79–1.48	0.641				
Grade							
Well differentiated	1.00	Reference	Reference				
Moderately differentiated	1.22	0.37–4.05	0.746				
Poorly differentiated	3.72	1.36–10.15	0.01				
Undifferentiated	3.62	1.34–9.73	0.011				
Surgery of primary site			**Surgery of primary site**				
None	1.00	Reference	Reference	None	1	Reference	Reference
Local treatment	0.33	0.2–0.55	< 0.001	Local treatment	0.61	0.36–1.04	0.071
Radical treatment with limb salvage	0.19	0.13–0.28	< 0.001	Radical treatment with limb salvage	0.34	0.22–0.51	< 0.001
Amputation	0.37	0.25–0.56	< 0.001	Amputation	0.51	0.33–0.80	0.003
Surgery of regional LN							
None	1.00	Reference	Reference				
Removement/Biopsy/Aspiration	1.59	1.11–2.29	0.012				
Surgery of other site							
No	1.00	Reference	Reference				
Yes	1.97	1.29–3.02	0.002				
Radiation							
No/Unknown	1.00	Reference	Reference				
Yes	3.10	2–4.79	< 0.001				
Chemotherapy							
No/Unknown	1.00	Reference	Reference				
Yes	1.22	0.84–1.77	0.292				
Systemic therapy/surgery sequence							
None	1.00	Reference	Reference				
Systemic therapy before surgery	0.72	0.49–1.07	0.103				
Systemic therapy after surgery	0.89	0.55–1.44	0.633				
Systemic therapy both before and after surgery	0.58	0.4–0.82	0.002				
Other	0.69	0.47–1.01	0.054				
Tumor size				**Tumor size**			
≤70mm	1.00	Reference	Reference	≤70 mm	1	Reference	Reference
70–139mm	2.00	1.44–2.78	< 0.001	70–139 mm	1.52	1.08–2.12	0.015
>139mm	2.92	2.04–4.18	< 0.001	>139 mm	1.78	1.21–2.61	0.003
Local extension				**Local extension**			
No break in periosteum	1.00	Reference	Reference	No break in periosteum	1	Reference	Reference
Extension beyond periosteum	1.96	1.48–2.61	< 0.001	Extension beyond periosteum	1.48	1.10–1.99	0.01
Further extension	5.14	3.32–7.95	< 0.001	Further extension	2.49	1.56–3.97	< 0.001
Regional LN invasion			**Regional LN invasion**				
No	1.00	Reference	Reference	No	1	Reference	Reference
Yes	6.81	3.96–11.71	< 0.001	Yes	2	1.07–3.73	0.03
Distant metastasis				**Distant metastasis**			
None	1.00	Reference	Reference	None	1	Reference	Reference
Lung only	4.00	2.97–5.38	< 0.001	Lung only	3.52	2.56–4.84	< 0.001
Other distant organ	4.77	3.36–6.77	< 0.001	Other distant organ	2.98	1.99–4.47	< 0.001

† HR: Hazard ratio.
‡ CI: Confidence interval.

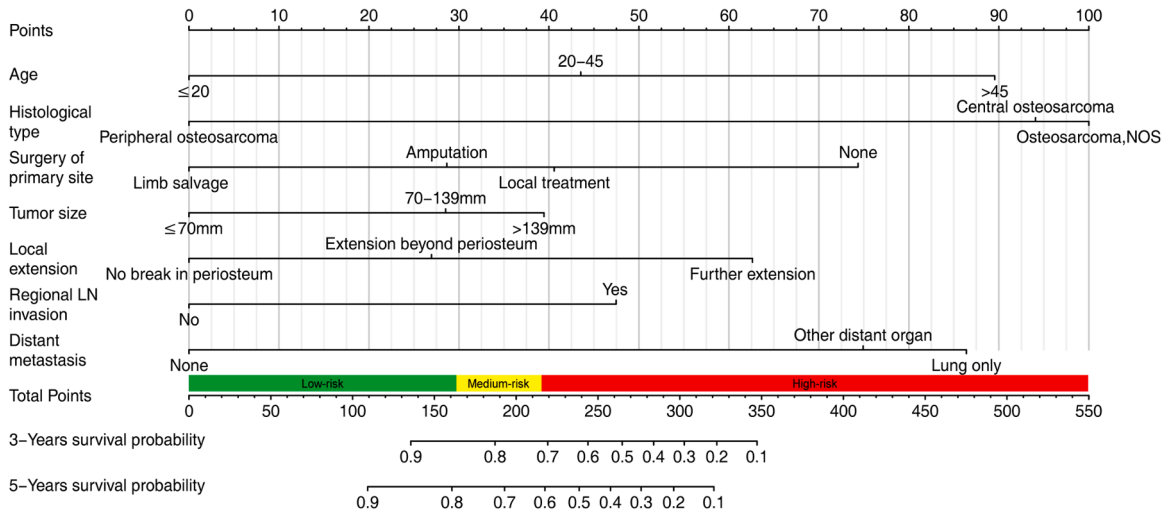

Fig. 2. Nomogram predicting the 3- and 5-year CSS rates of patients with PLBOS. The corresponding score is obtained by projecting each variable on the sub-axis, and the total score is obtained by adding the score of each variable. Mapping the position of the score on total score axis onto the corresponding position of the survival axis, then 3-year or 5-year CSS probability can be obtained.

number) underwent radiotherapy in the high-risk group (Table S2).

Validation of the nomogram

C-index, calibration curve, and DCA were used to evaluate the performance of the nomogram. The nomogram had a higher C-index (0.767 (0.74–0.795) in the training cohort and 0.715 (0.665–0.764) in the validation cohort) than the TNM system (0.676 (0.645–0.707) and 0.644 (0.596–0.692)) in both cohorts, indicating that the nomogram had better accuracy than the TNM system. Calibration curves showed good consistency in 3- and 5-year CSS rates between nomogram prediction and actual observation, proving the robustness and confidence of the nomogram (Fig. 4A,B). The DCA of the nomogram and TNM system predicting for 3- and 5-year CSS rates of the training and validation cohorts (Fig. 4C–F) showed that nomogram-related DCA had more positive net benefits than TNM-related DCA. Therefore, we considered the nomogram to be stable with excellent prediction performance, better than the TNM system.

Discussion

OS is the most common malignant bone tumor with a poor prognosis and unsatisfactory treatment and mainly affects adolescents and children. Due to the rarity of OS cases [26], we used the SEER database [27] as our data source to ensure that sufficient data was obtained. Different sites with anatomical and clinical heterogeneity may cause biased results [28]. For example, primary limb tumors have better prognoses than non-limb tumors [12]. Additionally, studies have shown that patients with a second primary malignancy have higher mortality rates than those with a single tumor [29]. These confounders may interfere with the prognosis predictions of OS patients. To make the conclusion more persuasive and reduce heterogeneity, we restricted our study subjects to patients with first primary OS of long bones.

To identify independent prognostic factors as precisely as possible, we explored as many clinical variables as possible. The optimal cut-off values for age and tumor size were identified as 20/45 (year) and 70/139 (mm). After converting the continuous variables into categorical variables, all the clinical features were integrated into univariate and multivariate Cox regression models. We confirmed seven clinicopathological characteristics (Age, Histological type, Surgery of primary site, Tumor size, Local extension, Regional LN invasion, Distant metastasis) as independent prognostic factors of PLBOS patients. Then, we built a nomogram and relative risk-stratification system. This system, based on the risk score calculated by the multivariable cox model and risk group, was divided using X-tile. We found that all independent prognostic factors in the three risk groups showed the same concentration trends as in the nomogram. Interestingly, patients who underwent radiation therapy were concentrated in the high-risk group. This may be because OS is a relatively radiation-resistant tumor and radiotherapy was often used for palliative treatment on unresectable OS; patients with this kind of OS often have a poor prognosis [30].

Histological type had the most significant contribution in the nomogram. In this study, some histological types had few cases, so we merged all subtypes into “Central Osteosarcoma” and “Peripheral osteosarcoma” [22]. In line with previous studies, patients with peripheral OS had better prognoses than those with central OS [31]. This may be because the classical central OS subtype was always WHO III grade and most peripheral OS subtypes were WHO I&II grade [32], meaning that the peripheral subtype often exhibited an indolent biologic behavior [33]. The location and biological behavior of the tumor subtype may be the reason for its relatively good prognosis. Due to the constraints of the SEER database, many patients were annotated as “Osteosarcoma, NOS.” However, the differences in HR between “Osteosarcoma, NOS” and “Central osteosarcoma” were not significant. This may be partly because the majority of patients with “Osteosarcoma, NOS” had central osteosarcoma.

Older patients (> 45) were associated with worse prognoses and this finding was consistent with the results of previous studies [2,14,31,34–36]. In our study and previous report, OS had two incidence peaks with the second peak in the elders. The elders’ poor prognoses may be due to intolerance of the treatment, poor general health, or chronic comorbidities [37].

The traditional AJCC staging system lacks accuracy in predicting prognoses [38], however, some metrics of it have good predictive performance. In this study, larger tumor sizes (70–139 mm; > 139 mm), regional LN invasion (AJCC N stage), and distant metastasis (AJCC M stage) were independent risk factors for the CSS of PLBOS patients; this result corresponded with the fact that patients with metastasis and large tumors have worse prognoses [14,39,40]. AJCC T includes three parts—T1, T2 (representing tumor size), and T3 (meaning the patient has developed a discontinuous tumor), however, none of them consider the effect of local tumor invasion. Therefore, we examined the effect of the local extension of the tumor on the prognosis. Due to the lack of cases, variables named “skin, further continuous extension, discontinuous tumor” were merged with “further extension,” representing further local invasion of the tumor. With increasing levels of local extensions,

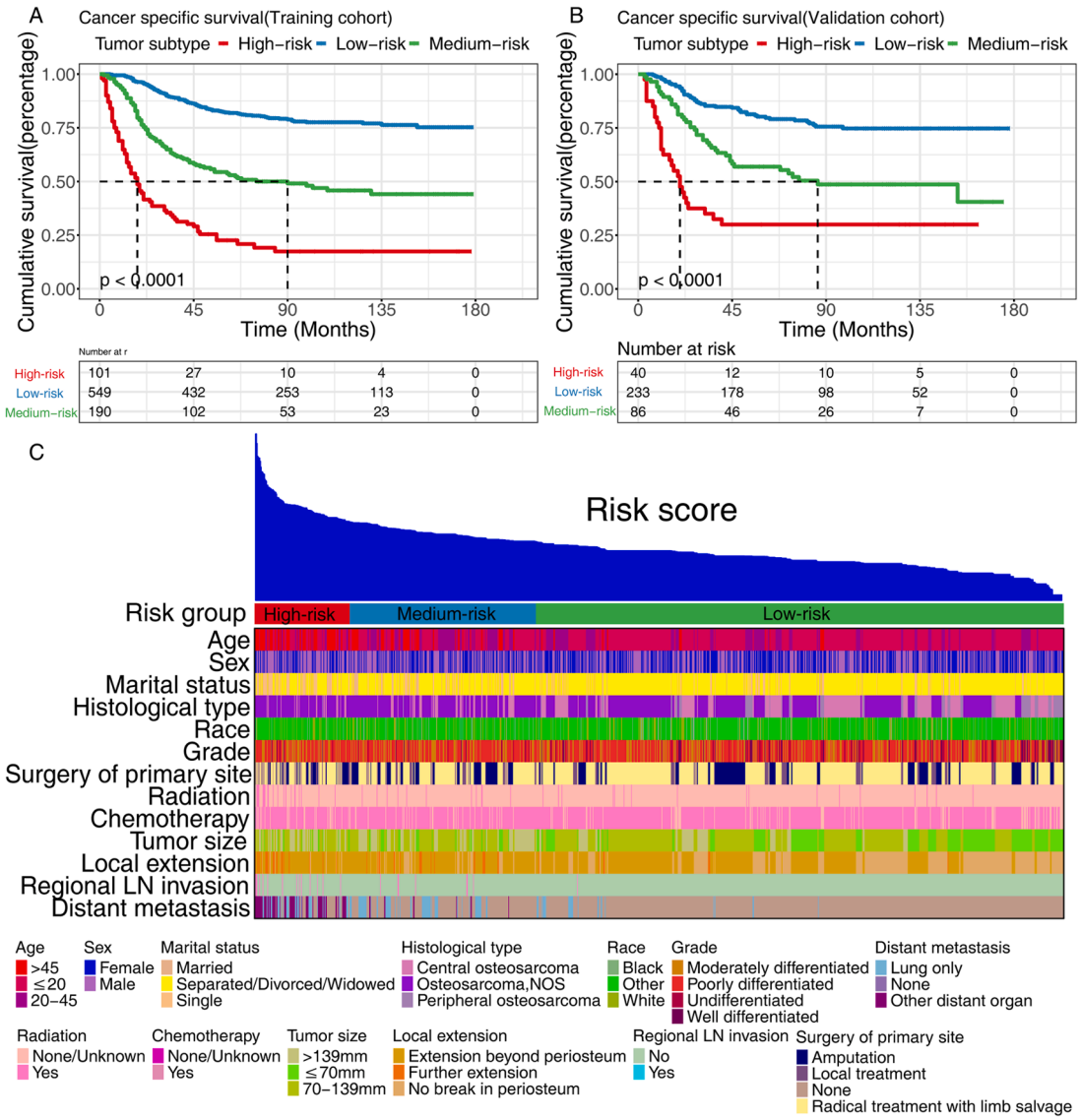

Fig. 3. Overview of risk-stratification system according to risk points calculated by nomogram. Kaplan–Meier survival analysis of the training cohort (A) and validation cohort (B) by risk group. (C) The distribution of clinicopathological features in different risk groups.

patient prognosis became gradually worse, confirming that local extension of the tumor was an independent risk factor for PLBOS patients, which is consistent with the results of previous studies [13].

Surgery of primary site greatly improved the prognosis of PLBOS. Currently, surgical resection is the final treatment for OS [41] and is closely related to patient survival time [42]. However, prognoses vary according to the type of surgery. In this nomogram, radical treatment with limb salvage was the best surgical method for prognosis, while amputation and local treatment were worse. Previous studies [43,44] have shown that radical limb salvage surgery has an advantage over amputation. For instance, limb salvage surgery leads to better survival rates without increasing the risk of local recurrence [45]. One possible explanation for this is that amputation is commonly used in patients with poor disease states [46], which harms the disease progression and chances for survival of patients. It should be noted that, although the introduction of chemotherapy significantly improved the prognosis of patients with local OS [47], the presence or absence of chemotherapy was not included in the independent prognostic factors of this study. This is because we could not know the specific chemotherapy regimen and adherence of each patient. Moreover, the No/Unknown option in the Chemotherapy variable provided ambiguous information so that we could not confirm whether the patient underwent chemotherapy, which limited the statistical effectiveness of this study.

We identified seven independent prognostic factors and built a nomogram with a risk-stratification system based on these factors for predicting 3- and 5-year CSS rates of PLBOS. Similar works have been done by Zhang et al. established a model consisting of seven factors (Age, Sex, Primary site, Decade of diagnosis, Extent of disease, Tumor size, Tri-modality therapy) with the longest follow-up being from 1973 to 2015 [48]. Zheng et al. firstly established a model with seven factors (Age, Tumor site, Histology, Tumor size, Tumor stage, Surgery, Grade) and predicted OS and CSS for patients with positive histological confirmation of OS in an extremity or axial location [49]. Their work included more cases and established predicting models with good performance; results for three factors (Age, Tumor size, and Surgery) are consistent with our results. Compared to their studies, our work included fewer samples but considered as many potential factors as possible and controlled the heterogeneity of each variable. We only focused on the first primary OS located in long bone, by which we could describe the categories under clinical variables (e.g., surgical methods, local extension) based on the criteria of the same anatomical structure. This avoided the heterogeneity caused by different tumor locations and

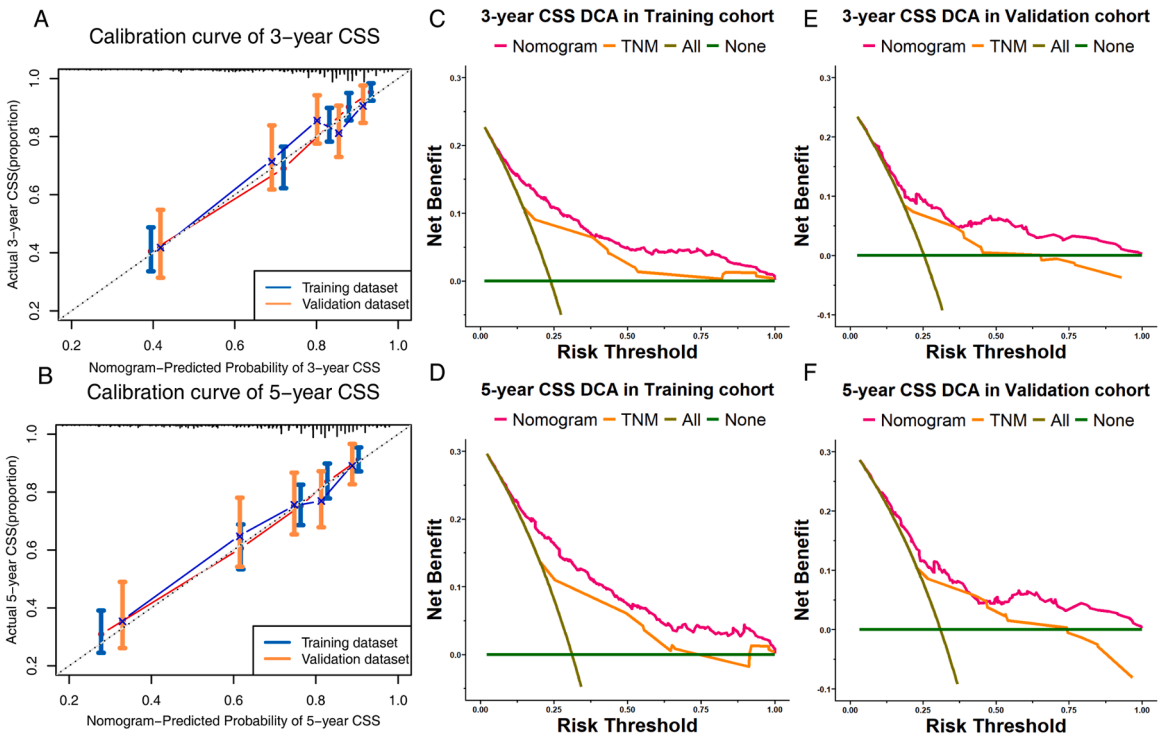

Fig. 4. Validation of the prognostic nomogram in predicting 3- and 5- year CSS of PLBOS patients. (A) Calibration curve for 3-year CSS of prognostic nomogram in training and validation cohort. (B) Calibration curve for 5-year CSS of prognostic nomogram in training and validation cohort. (C–D) DCA plot for 3- and 5-year CSS of nomogram and AJCC TNM system in training cohort. (E–F) DCA plot for 3- and 5-year CSS of nomogram and AJCC TNM system in validation cohort.

excluded the influence of other primary tumors and Paget's disease, which made the model more specific and robust. Furthermore, long bone is the most common site of OS; therefore, the focus on long bone OS could potentially yield more benefits for OS patients. We chose 2004 to 2015 as our study period. Although we lost some cases, we could include as many potential clinical variables as possible (e.g., Marital status, Surgery sequence) and guarantee a 3-year follow-up. We fully investigated each variable and combined some categories with too few cases according to their commonness, to improve the statistical efficiency and better mine the prognostic factors affecting PLBOS. In summary, our work confirmed the clinical factors affecting the prognosis of patients with PLBOS. Then, we developed a more targeted nomogram with a risk-stratification system to better identify high-risk PLBOS patients, give individualized treatment regimens, and avoid too frequent medical examinations [28].

Although the nomogram showed good predictive performance, it had some limitations. Firstly, the data included in this study were from the SEER database, which only represents 30% of the American population and lacks validation for other populations. Secondly, this study was designed to be retrospective and inevitably had a selection bias. Thirdly, known prognostic factors such as local recurrence [50], serum markers (LDH, ALP, etc. [51]), and chemotherapy response [14] were not incorporated in the current datasets. Additionally, treatment-related information such as radiation, chemotherapy, and surgery of primary site was limited and lacked details such as the specific primary site of the tumor, treatment plan, and therapeutic effects. The nomogram hypothesized that the results remained stable over time although this study only included data from 2004 to 2015. As time was prolonged, prognosis factors such as treatment methods may change, which may decrease the accuracy of this nomogram. In future studies, we will follow up at our center and try to apply this nomogram to the clinical process to further validate and refine our model.

Conclusion

Our research identified Age, Histological type, Surgery of primary site, Tumor size, Local extension, Regional LN invasion, and Distant metastasis as independent prognostic factors of PLBOS patients. Based on these factors, we established and validated a nomogram with a risk-stratification system that can effectively predict the 3- and 5-year CSS rates of patients with PLBOS. This nomogram had good predictive performance and showed non-inferior performance to the traditional TNM staging system. Our nomogram can help clinicians to evaluate the prognoses of patients with OS in the most common site and assess the individual risk of patients. Our goal is to collect more high-quality data sets in the future to improve our model and achieve more reliable results.

Submission declaration and verification

All authors read and approved the final manuscript, and promise that this article has not been published previously.

Ethical approval statement

This study involved the analysis of public-use data, for which formal ethical approval is not required.

Data availability statement

The data that support the findings of this study are openly available in https://seer.cancer.gov

CRediT authorship contribution statement

Shuo Tian: Conceptualization, Formal analysis, Writing – original draft. **Sheng Liu:** Software, Methodology. **Xiangcheng Qing:** . **Hui Lin:** . **Yizhong Peng:** Conceptualization, Writing – review & editing.

Baichuan Wang: . **Zengwu Shao:** Supervision, Funding acquisition.

Declaration of Competing Interest

All authors declare that they have no competing interests.

Funding

This work was supported by the Major Research Plan of National Natural Science Foundation of China [No. 91649204]

Acknowledgements

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101349.

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