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ORIGINAL RESEARCH

Nomogram application to predict overall and cancer-specific survival in osteosarcoma

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Purpose: A prognostic nomogram was applied to predict survival in osteosarcoma patients.

Patients and methods: Data collected from 2,195 osteosarcoma patients in the Surveillance, Epidemiology, and End Results (SEER) database between 1983 and 2014 were analyzed. Independent prognostic factors were identified via univariate and multivariate Cox analyses. These were incorporated into a nomogram to predict 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) rates. Internal and external data were used for validation. Concordance indices (C-indices) were used to estimate nomogram accuracy.

Results: Patients were randomly assigned into a training cohort (n=1,098) or validation cohort (n=1,097). Age at diagnosis, tumor site, histology, tumor size, tumor stage, use of surgery, and tumor grade were identified as independent prognostic factors via univariate and multivariate Cox analyses (all $P<0.05$) and then included in the prognostic nomogram. C-indices for OS and CSS prediction in the training cohort were 0.763 (95% CI 0.761–0.764) and 0.764 (95% CI 0.762–0.765), respectively. C-indices for OS and CSS prediction in the external validation cohort were 0.739 (95% CI 0.737–0.740) and 0.740 (95% CI, 0.738–0.741), respectively. Calibration plots revealed excellent consistency between actual survival and nomogram prediction.

Conclusion: Nomograms were constructed to predict OS and CSS for osteosarcoma patients in the SEER database. They provide accurate and individualized survival prediction.

Keywords: cancer-specific survival, nomogram, osteosarcoma, overall survival, prognosis, SEER database

Introduction

Osteosarcoma, mainly originated from primitive malignant mesenchymal cells in bone,[1] is the most common primary malignant bone tumor, typically affecting adolescents under 24 years of age with an estimated incidence of 0.34/100,000 per year.[2] The metaphyses of long bones are the primary sites of most osteosarcomas, including distal femur, proximal humerus, and proximal tibia, with approximately 10% of osteosarcomas derived from the axial skeleton.[3] Local swelling, pain, and restricted joint movement are the most common symptoms. Before the 1970s, amputation was still the main therapeutic measure for high-grade osteosarcoma because of the lack of adjuvant chemotherapy,[4] which seriously affected patient quality of life and reduced the probability of survival. With the introduction of the adjuvant chemotherapy and limb salvage surgery, the survival rate rose from less than 20% to approximately 70%.[5] Currently, wide resection together with adjuvant chemotherapy and limb reconstruction have been widely applied to treat high-grade osteosarcoma.[6,7] Nevertheless, these options are often insufficient for patients with metastatic and recurrent osteosarcoma.[1,8] Better comprehension of

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the prognostic variables of osteosarcoma can provide more assistance to guide therapeutic intervention, which contributes to prolonging survival and enhancing quality of life.

Although previous studies focused on prognostic factors for osteosarcoma patients, including tumor size, response to chemotherapy, recurrence, and metastasis,[9–11] these variables only served as a single index to evaluate prognosis, which limited their impact on a precise individualized survival prediction of osteosarcoma patients. Considering the limitation of the single factor, we sought to develop a novel prognostic model. In the present study, we constructed a nomogram, an efficient prognostic tool, to more precisely estimate an individual patient's survival more precisely by integrating all prognostic factors for osteosarcoma patients. A prognostic nomogram is an ocular and effective tool based on statistical regression models.[12] It can provide a graphic calculating scales method that can be used to estimate the probability of patient survival.[13] A nomogram can improve the predictive accuracy of individual prognosis because of its strong robustness and better predictive accuracy.[12–14] The Surveillance, Epidemiology, and End Results (SEER) dataset between 1983 and 2014 provided clinical information of osteosarcoma patients that allowed detailed analyses of survival of osteosarcoma. This cancer database covers approximately 30% of the overall US population.[12] It is composed of 18 registries that contain clinical information on patients with tumors in the US.[12] The purpose of current study was to construct effective prognostic nomograms to predict 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) rates for osteosarcoma patients.

Patients and methods

Patient eligibility and variables

We identified all osteosarcoma patients listed in the SEER database, which collects anonymized clinical data from population-based cancer registries. Use of these clinical data does not require patients' informed consent since no case-identifying information is provided.[15] No ethics approval was sought for this study as the data used were from the publicly available, de-identified SEER database.[16] All procedures were performed in accordance with the Helsinki Declaration (1964) and its later amendments or comparable ethical standards.[16] SEER*Stat software (version 8.3.5; NCI, Bethesda, MD, USA) was used to acquire patient information.

The inclusion criteria for osteosarcoma patients in the present study were as follows:

1. Diagnosed with osteosarcoma (International Classification of Diseases for Oncology [ICD-O]: 9180, 9181, 9182, 9183, 9184, 9185, 9186, 9187, 9192, 9193, 9194, or 9200) as a primary malignancy between 1983 and 2014.
2. Positive histological confirmation of osteosarcoma.
3. Site limited to extremity (long or short bones of the upper or lower extremities) or axial location (skull, pelvis, spine, or ribs).
4. Confirmation of histologic type of osteosarcoma.
5. Known cause of death and survival months after diagnosis.

The exclusion criteria for osteosarcoma patients in this study were:

1. Unknown use of surgery.
2. Unknown surgical stage.
3. Unknown tumor size.

Clinicopathological features including patient age, gender, histology, surgical stage, tumor size, tumor site, grade, marital status, race, use of surgery, and survival time were collected. The anatomic location of osteosarcoma was categorized as extremity (long or short bones of the upper or lower extremities) or axial (skull, pelvis, spine, or ribs). Low-grade tumors contained well- and moderately differentiated grades (ICD-O-3 Grades 1 and 2), and high-grade tumors contained poorly or undifferentiated grades (ICD-O-3 Grades 3 and 4). Cutoff values of age of diagnosis and tumor size were determined via X-tile software (Yale University, New Haven, CT, USA), which was previously shown to determine best cut-points of tumor variables.[17] The optimal cutoff values of tumor size were categorized as small (<2.9 cm), intermediate (2.9–10.0 cm), and large (>10.0 cm) (Figure 1). The optimal age cutoffs were 25 and 51 years (Figure 1), so patients were categorized into three age groups (0–24 years, 25–51 years, or >51 years). According to American Joint Committee on Cancer (AJCC) staging system for bone sarcomas, surgical stage was categorized as localized, regional, or distant.[18] Patients coded with "localized" disease were classified as disease confined to the periosteum, while those with "regional" disease had tumor extending beyond the periosteum but without distant metastasis. Patients with missing surgical stage data were excluded. Surgical resection was categorized as yes or no; data on the type of resection (eg, wide, marginal, or intralesional) could not be obtained from the SEER database. Race was categorized as white, black, or other (American Indian/Alaskan Native, Asian/Pacific Islander). In terms of chemotherapy and radiation, "No/Unknown" was used in the updated SEER dataset as a single option, impacting data completeness. These patients

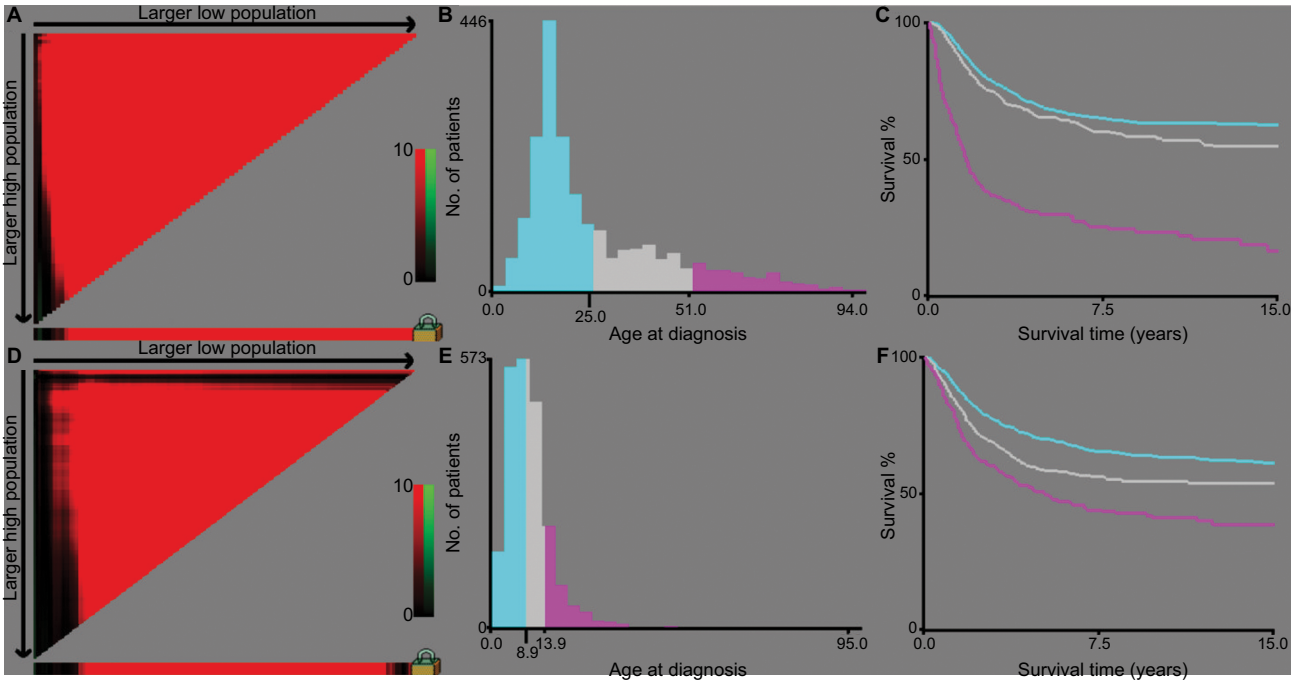

Figure 1 Identification of optimal cutoff values of age of diagnosis (**A–C**) and tumor size (**D–F**) via X-tile analysis.
Notes: Optimal cutoff values of age were identified as 29 and 51 years based on overall survival. Optimal cutoff values of tumor size were identified as 8.9 and 13.9 cm based on overall survival. Histogram and Kaplan–Meier analysis were developed based on these cutoff values.

had no codes for radiation or chemotherapy in their medical records. Adding this information to the nomogram might have introduced relevant bias,[12] so use of chemotherapy and radiation was not included as a variable.

Statistical analysis

Based on the abovementioned inclusion and exclusion criteria, osteosarcoma patients were randomly divided into a training cohort (n=1,098) or validation cohort (n=1,097) to construct and validate nomograms. Chi-squared tests were used to compare clinical characteristics between the cohorts.

Continuous and categorical variables are presented as the number of osteosarcoma patients with respective percentages. X-tile software was applied to calculate cutoff values for tumor size and age of diagnosis based on OS information (Figure 1). The prognostic factors (age at diagnosis, gender, primary site, tumor size, histology, surgical stage, grade, marital status, race, use of surgery, etc) were further evaluated via univariate and multivariate Cox proportional hazards regression analyses. Hazard ratios and corresponding 95% CI of variables were also calculated. OS and CSS were the two primary endpoints. Survival times were calculated from the date of disease diagnosis to the date of death from any disease cause (OS) or death from osteosarcoma (CSS). Prognostic nomograms for 3- and 5-year OS and 3- and 5-year CSS were constructed according to the univariate and multivariate Cox analyses. Internal and external validations of the prognostic nomogram were performed. Harrell's concordance-index (C-index) was applied to evaluate prognostic nomogram performance. This C-index was a useful evaluation value similar to calculating the area under the receiver operating characteristic curve.[19] C-indices range from 0.5 to 1.0, indicating total chance and perfect matching, respectively.[20] Calibration curves were constructed to compare consistency between predicted and observed survival. Chi-squared tests and univariate and multivariate Cox analyses were performed with SPSS 22.0 software (IBM Corp, Armonk, NY, USA). rms Package in R software (version 3.3.1) was used to construct and validate prognostic nomograms. Differences were considered significant at two-sided $P<0.05$.

Results

Patient baseline characteristics

The SEER database contained 2,195 osteosarcoma patients between 1983 and 2014, including 1,098 patients in the training cohort and 1,097 patients in the validation cohort. The training cohort was used to construct and internally validate the nomogram, and the validation cohort was used for external validation. In the training cohort, 363 patients died from

osteosarcoma, and 32 patients died from other causes. In the validation cohort, 356 patients died from osteosarcoma, and 37 patients died from other causes.

The osteosarcoma patients' characteristics are listed in Table 1. Of these patients, 981 (44.7%) patients were females and 1,214 (55.3%) patients were males. The most common primary location of these osteosarcoma patients was an extremity (80.8%), and 19.2% had a primary axial site. With regard to tumor stage, regional disease (48.0%) was most frequent, followed by localized disease (32.8%) and distant

Table 1 Baseline demographic and clinical characteristics of patients with osteosarcoma

Variables	Training cohort (n=1,098)		Validation cohort (n=1,097)		Total (n=2,195)		*P*
Surgery, n, %							0.399
No	89	8.1%	100	9.1%	189	8.6%	
Yes	1,009	91.9%	997	90.9%	2006	91.4%	
Sex, n, %							0.507
Female	483	44.0%	498	45.4%	981	44.7%	
Male	615	56.0%	599	54.6%	1,214	55.3%	
Age (years), n, %							0.592
<25	693	63.1%	694	63.3%	1,387	63.2%	
>51	127	11.6%	140	12.8%	267	12.2%	
25–51	278	25.3%	263	24.0%	541	24.6%	
Tumor site, n, %							0.118
Axial	225	20.5%	196	17.9%	421	19.2%	
Extremity	873	79.5%	901	82.1%	1,774	80.8%	
Histology, n, %							0.176
Conventional osteosarcoma	663	60.4%	692	63.1%	1,355	61.7%	
Chondroblastic osteosarcoma	186	16.9%	143	13.0%	329	15.0%	
Fibroblastic osteosarcoma	78	7.1%	65	5.9%	143	6.5%	
Telangiectatic osteosarcoma	42	3.8%	39	3.6%	81	3.7%	
Osteosarcoma in Paget disease of bone	8	0.7%	7	0.6%	15	0.7%	
Small cell osteosarcoma	8	0.7%	13	1.2%	21	1.0%	
Central osteosarcoma	26	2.4%	37	3.4%	63	2.9%	
Intraosseous well differentiated osteosarcoma	2	0.2%	2	0.2%	4	0.2%	
Parosteal osteosarcoma	63	5.7%	80	7.3%	143	6.5%	
Periosteal osteosarcoma	18	1.6%	13	1.2%	31	1.4%	
High-grade surface osteosarcoma	4	0.4%	6	0.5%	10	0.5%	
Tumor stage, n, %							0.273
Localized	377	34.3%	344	31.4%	721	32.8%	
Regional	521	47.4%	533	48.6%	1,054	48.0%	
Distant	200	18.2%	220	20.1%	420	19.1%	
Size, n, %							0.373
<8.9	578	52.6%	560	51.0%	1,138	51.8%	
>13.9	184	16.8%	209	19.1%	393	17.9%	
8.9–13.9	336	30.3%	328	29.9%	664	30.3%	
Grade, n, %							0.584
High	938	85.4%	928	84.6%	1,866	85.0%	
Low	160	14.6%	169	15.4%	329	15.0%	
Marital							0.950
Married	842	76.7%	840	76.6%	1,682	76.6%	
Unmarried	256	23.3%	257	23.4%	513	23.4%	
Year of diagnosis							0.810
1983–1992	51	4.6%	47	4.3%	98	4.5%	
1993–2002	274	25.0%	285	26.0%	559	25.5%	
2003–2014	773	70.4%	765	69.7%	1,538	70.1%	
Race							0.341
Black	183	16.7%	167	15.2%	350	15.9%	
Other	115	10.5%	101	9.2%	216	9.8%	
White	800	72.9%	829	75.6%	1,629	74.2%	

disease (19.1%). In both cohorts, the majority of patients were children or adolescents (<25 years; 63.2%). Most tumors were <8.9 cm (51.8%). Most of the patients in our study had received surgical treatment (91.4%). There were no significant differences between the training and validation cohorts.

Prognostic factors for OS and CSS

In the training cohort, data from 1,098 osteosarcoma patients were included in univariate and multivariate analyses to identify independent prognostic factors for OS and CSS. As is shown in Tables 2 and 3, gender, age at diagnosis, tumor site, histol-

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

Characteristics	Univariate analysis *P*	Multivariate analysis		
		HR	95% CI	*P*
Sex	<0.001			
Female		Reference		
Male		1.183	0.954–1.466	0.126
Age (years)	<0.001			
<25		Reference		
>51		2.422	1.718–3.414	<0.001
25–51		1.378	1.009–1.883	0.044
Tumor site	<0.001			
Axial		Reference		
Extremity		0.572	0.442–0.740	<0.001
Histology	<0.001			
Conventional osteosarcoma		Reference		
Chondroblastic osteosarcoma		0.802	0.605–1.064	0.125
Fibroblastic osteosarcoma		0.803	0.537–1.200	0.285
Telangiectatic osteosarcoma		1.336	0.844–2.117	0.217
Osteosarcoma in Paget disease of bone		2.375	1.121–5.032	0.024
Small cell osteosarcoma		0.337	0.047–2.409	0.278
Central osteosarcoma		0.634	0.281–1.430	0.272
Intraosseous well-differentiated osteosarcoma		<0.001	0.000–7.603E+80	0.933
Parosteal osteosarcoma		1.001	0.487–2.058	0.998
Periosteal osteosarcoma		0.201	0.028–1.441	0.110
High grade surface osteosarcoma		1.040	0.145–7.459	0.969
Tumor stage	<0.001			
Localized		Reference		
Regional		1.647	1.248–2.174	<0.001
Distant		4.886	3.580–6.666	<0.001
Surgery	<0.001			
No		Reference		
Yes		0.460	0.339–0.623	<0.001
Size	<0.001			
<8.9		Reference		
>13.9		2.141	1.617–2.835	<0.001
8.9–13.9		1.391	1.094–1.768	0.008
Grade	<0.001			
High		Reference		
Low		0.446	0.287–0.694	<0.001
Marital	<0.001			
Married		Reference		
Unmarried		1.250	0.930–1.681	0.139
Year of diagnosis	0.427			
1983–1992		NI		
1993–2002				
2003–2014				
Race	0.917			
Black		NI		
Other				
White				

Table 3 Univariate and multivariate analyses of cancer-specific survival in the training cohort

Characteristics	Univariate analysis *P*	Multivariate analysis		
		HR	95% CI	*P*
Sex	<0.001			
Female		Reference		
Male		1.164	0.931–1.456	0.183
Age (years)	<0.001			
<25		Reference		
>51		2.175	1.514–3.124	<0.001
25–51		1.371	0.990–1.899	0.057
Tumor site	<0.001			
Axial		Reference		
Extremity		0.541	0.414–0.708	<0.001
Histology	<0.001			
Conventional osteosarcoma		Reference		
Chondroblastic osteosarcoma		0.782	0.581–1.052	0.104
Fibroblastic osteosarcoma		0.797	0.521–1.220	0.297
Telangiectatic osteosarcoma		1.469	0.925–2.331	0.103
Osteosarcoma in Paget disease of bone		2.791	1.308–5.957	0.008
Small cell osteosarcoma		0.359	0.050–2.570	0.308
Central osteosarcoma		0.683	0.302–1.543	0.360
Intraosseous well-differentiated osteosarcoma		<0.001	0.000–6.386E+85	0.935
Parosteal osteosarcoma		0.943	0.443–2.010	0.880
Periosteal osteosarcoma		0.214	0.030–1.532	0.125
High grade surface osteosarcoma		1.102	0.154–7.906	0.923
Tumor stage	<0.001			
Localized		Reference		
Regional		1.782	1.326–2.397	<0.001
Distant		5.267	3.792–7.316	<0.001
Surgery	<0.001			
No		Reference		
Yes		0.461	0.336–0.633	<0.001
Size	<0.001			
<8.9		Reference		
>13.9		2.232	1.667–2.987	<0.001
8.9–13.9		1.435	1.116–1.845	0.005
Grade	<0.001			
High		Reference		
Low		0.502	0.320–0.787	0.03
Marital	<0.001			
Married		Reference		
Unmarried		1.253	0.918–1.709	0.155
Year of diagnosis	0.552			
1983–1992		NI		
1993–2002				
2003–2014				
Race	0.910			
Black		NI		
Other				
White				

ogy, tumor size, tumor stage, use of surgery, tumor grade, and marital status were significantly associated with OS and CSS in the univariate analysis. These nine factors were further selected to conduct the multivariate Cox analysis in order to control for confounding variables. The multivariate Cox analysis revealed that seven factors including age at diagnosis, tumor site, histology, tumor size, tumor stage, use of surgery, and tumor grade were independent prognostic factors for OS and CSS.

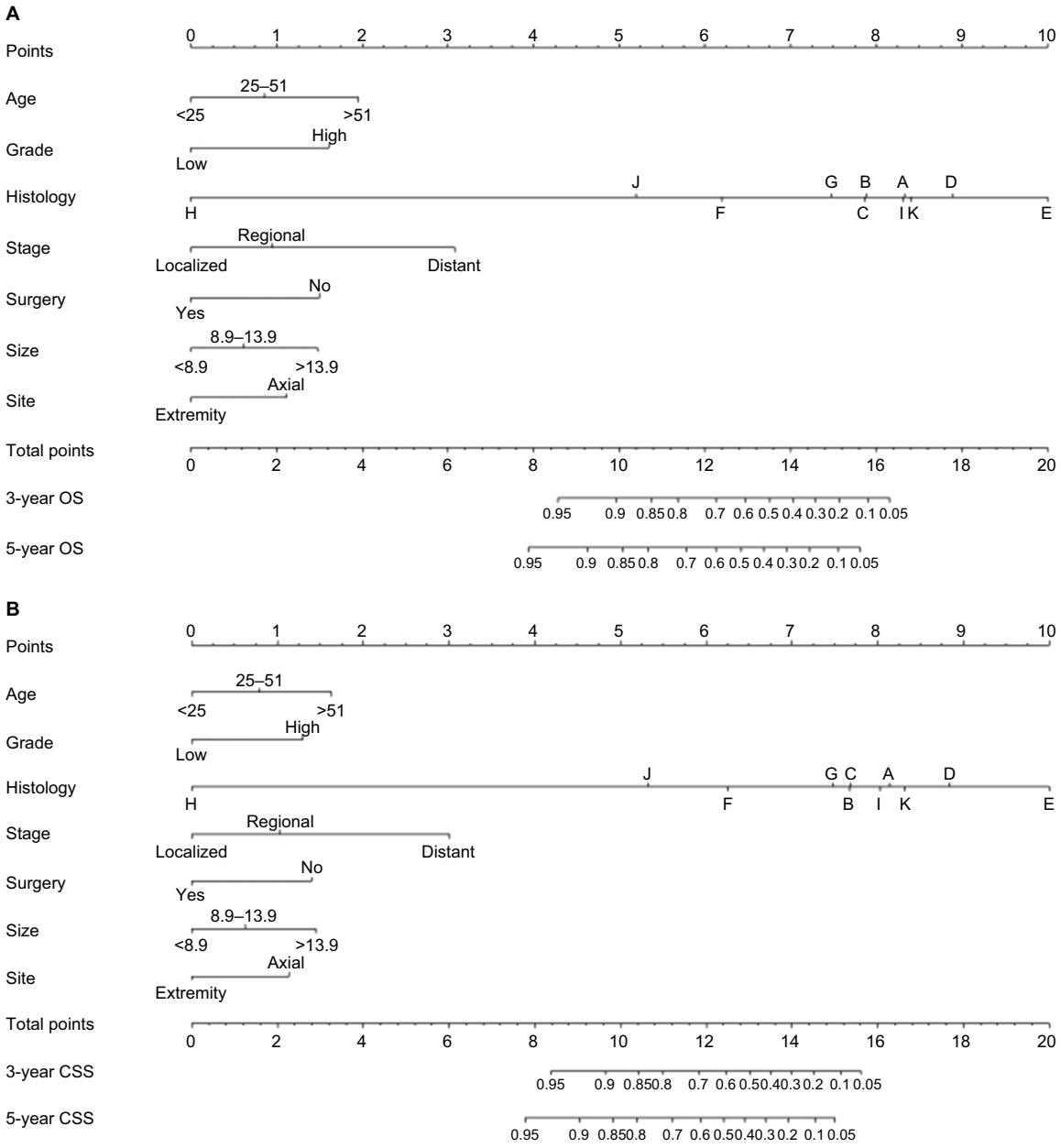

Figure 2 Nomograms to predict 3- and 5-year overall survival (**A**) and cancer-specific survival (**B**) for osteosarcoma patients.
Notes: Vertical line between each variable and points scale can be drawn to acquire points of each variable. Predicted survival rate was calculated according to the total points by drawing a vertical line from Total Points scale to overall survival or cancer-specific survival scale. A, conventional osteosarcoma; B, chondroblastic osteosarcoma; C, fibroblastic osteosarcoma; D, telangiectatic osteosarcoma; E, osteosarcoma in Paget disease of bone; F, small cell osteosarcoma; G, central osteosarcoma; H, intraosseous well-differentiated osteosarcoma; I, parosteal osteosarcoma; J, periosteal osteosarcoma; K, high-grade surface osteosarcoma.

Construction and validation of the OS and CSS nomograms

The significant independent factors of age at diagnosis, tumor site, histology, tumor size, tumor stage, use of surgery, and tumor grade were incorporated to create the prognostic nomograms for estimating the 3- and 5-year OS and CSS of osteosarcoma patients (Figure 2). The nomogram gives every prognostic variable a score on the point scale (Table 4). By adding up these scores to the total on the bottom scale, the 3- and 5-year OS and CSS of osteosarcoma patients can be predicted.

Prognostic nomogram validation was conducted both internally and externally (Figure 3). Internal validation in the training cohort showed that the C-index values for nomogram predictions of OS and CSS were 0.763 (95% CI 0.761–0.764) and 0.764 (95% CI 0.762–0.765), respectively. Similarly, the corresponding C-index values in the external validation cohort were 0.739 (95% CI 0.737–0.740) and 0.740 (95%

Table 4 Detailed scores of prognostic factors in the overall and cancer-specific survival nomograms

Characteristic	OS nomogram	CSS nomogram
Age (years)		
<25	0	0
>51	2.0	1.6
25–51	0.9	0.8
Tumor site		
Axial	1.1	1.1
Extremity	0	0
Histology		
A (9180)	8.3	8.1
B (9181)	7.9	7.7
C (9182)	7.9	7.7
D (9183)	8.9	8.8
E (9184)	10.0	10.0
F (9185)	6.2	6.3
G (9186)	7.5	7.5
H (9187)	0	0
I (9192)	8.3	8.0
J (9193)	5.2	5.3
K (9194)	8.3	8.3
Tumor stage		
Localized	0	0
Regional	0.9	1.0
Distant	3.1	3.0
Surgery		
No	1.5	1.4
Yes	0	0
Size		
<8.9	0	0
>13.9	1.5	1.4
8.9–13.9	0.6	0.6
Grade		
High	1.6	1.3
Low	0	0

Notes: A, conventional osteosarcoma; B, chondroblastic osteosarcoma; C, fibroblastic osteosarcoma; D, telangiectatic osteosarcoma; E, osteosarcoma in Paget disease of bone; F, small cell osteosarcoma; G, central osteosarcoma; H, intraosseous well-differentiated osteosarcoma; I, parosteal osteosarcoma; J, periosteal osteosarcoma; K, high-grade surface osteosarcoma.

CI 0.738–0.741). These results confirm that our prognostic nomograms were reasonably accurate. The calibration plots (Figure 3) demonstrated excellent agreement between actual survival and nomogram prediction.

In summary, we constructed and validated the nomogram to estimate 3- and 5-year OS and CSS for osteosarcoma patients. Based on an individual osteosarcoma patient's prognostic factors, we can obtain a score associated with each prognostic factor on the nomogram point scale and calculate the total score. We can then evaluate 3- and 5-year survival probability by projecting the total points to the total score scale of the nomogram. As an example, an 18-year-old patient was diagnosed with an axial chondroblastic osteosarcoma with a primary tumor size of 10.0 cm that was high grade. This patient was found to have regional disease and underwent surgery. According to our nomograms, the patient has 12.1 and 11.7 points in OS and CSS, respectively. The 3-year OS and CSS rates of this osteosarcoma were 0.72 and 0.69, respectively, while the corresponding 5-year rates were 0.62 and 0.62.

Discussion

Multiple prognostic factors can affect osteosarcoma patient survival, but previous studies did not integrate overall prognostic factors. A single prognostic index may impose limitations on estimating an individual patient's survival prognosis. The nomogram is a common statistical tool that can provide satisfactory accuracy and robustness to precisely predict an individual patient's survival probability.[21] Kim et al constructed a prognostic nomogram for nonmetastatic osteosarcoma patients that could estimate and predict metastasis risk better than the AJCC staging system or tumor necrosis rate alone.[22] Xia et al also devised a nomogram to further predict the survival of osteosarcoma patients after surgical resection.[23] However, these studies were designed without validation, so their results might not be relevant in other populations due to potential bias. Kim et al developed a high-performance nomogram to predict the probability of metastasis in Enneking stage IIB extremity osteosarcoma using the medical records of 91 patients who had undergone surgery.[24] However, the small sample size was a significant limiting factor, and the generalizability of this nomogram should be validated in larger populations. In the present study, we constructed convenient and comprehensive prognostic nomograms using data from 2,195 osteosarcoma cases in the SEER dataset, which allowed us to calculate 3- and 5-year OS and CSS rates for osteosarcoma patients.

To accurately select the prognostic factors, we performed univariate log-rank and multivariate Cox analysis to identify independent prognostic factors. The results showed that age at diagnosis, tumor site, histology, tumor size, tumor stage, use of surgery, and tumor grade are independent prognostic factors for the survival of patients with osteosarcoma. In the current study, within the period from 1984 to 2014, year of diagnosis was not found to be independently associated with OS or CSS. One possible explanation is that progress made in clinical information has not been as successful for osteosarcoma. Similar approach has been taken in previous investigations.[25,26] In previous studies, increasing patient

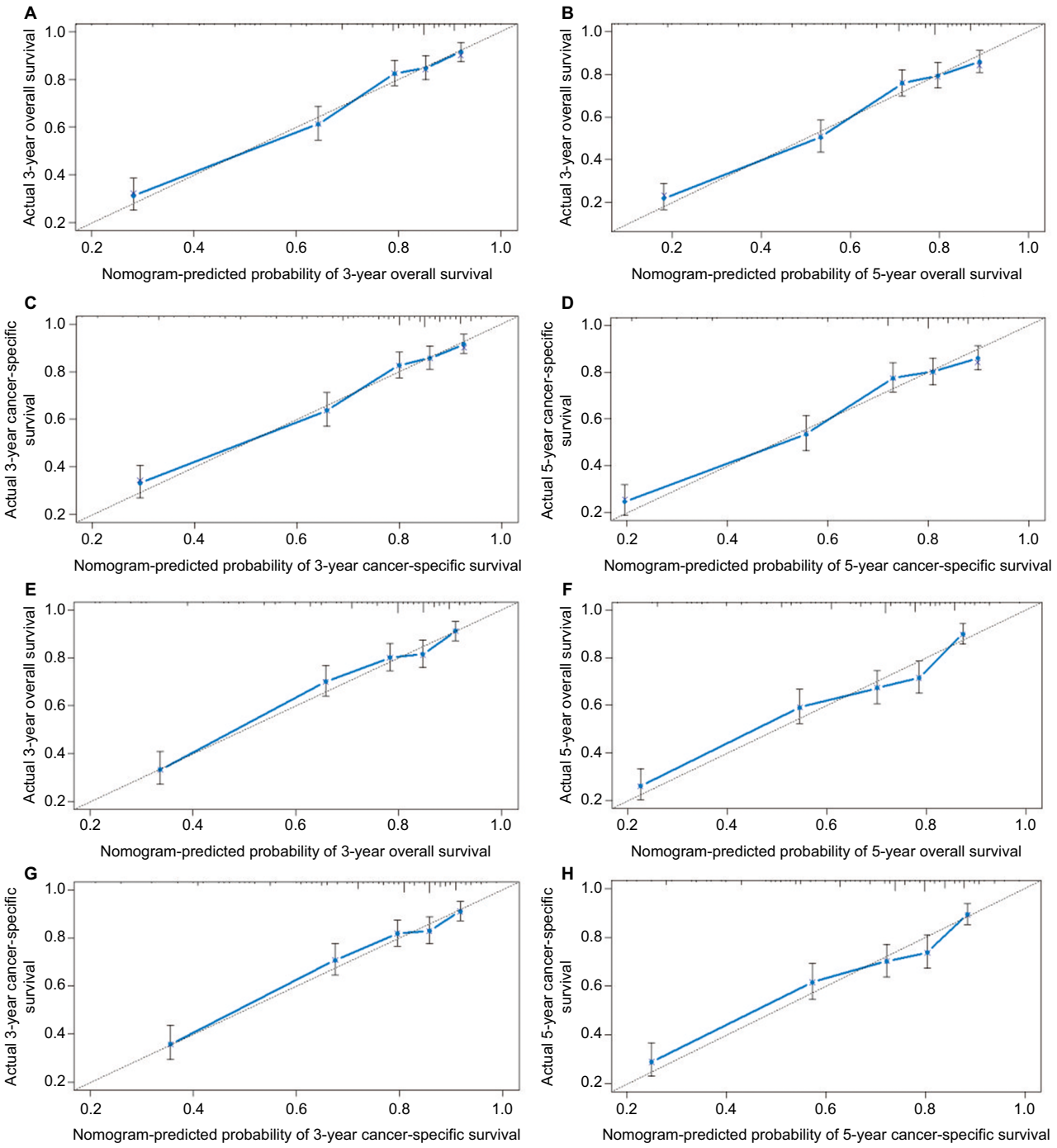

Figure 3 Internal calibration plots of 3-year (**A**) and 5-year (**B**) overall survival nomogram calibration curves; 3-year (**C**) and 5-year (**D**) cancer-specific survival nomogram calibration curves. External calibration plots of 3-year (**E**) and 5-year (**F**) overall survival nomogram calibration curves; 3-year (**G**) and 5-year (**H**) cancer-specific survival nomogram calibration curves.

Notes: The cohort was divided into five subgroups with the equal sample size for present internal validation. The dashed line represents an excellent match between actual survival outcome (Y-axis) and nomogram prediction (X-axis). Closer distances between dashed line and points indicated higher prediction accuracy.

age was associated with a statistically significant decrease in the survival prognosis of osteosarcoma patients.[26–28] Ek et al reported that osteosarcoma patients older than 40 had worse survival outcomes.[29] Similarly, we identified increasing patient age as an independent negative prognostic factor for osteosarcoma patients. Our analysis used X-tile software to stratify the data of age based on status and survival time. It identifies the best cut-points of variables and was initially

applied in breast malignancy. We determined that the optimal age cut-points of osteosarcoma patients were 25 and 51 years. Tumor size was also one of the key measures of survival prognosis of osteosarcoma patients. Several previous studies reported that patients with larger tumors had a poorer prognosis and decreased survival rate.[10,30,31] We also identified larger tumor size as an independent prognostic factor of shorter survival. To obtain the best cut-points for tumor size, we again used X-tile software for data stratification. The results showed that 8.9 and 13.9 cm were the optimal cutoff values. We also observed that adequate use of limb salvage surgery had a significant effect on osteosarcoma patient survival outcomes. Previous studies reported similar results.[9,28,32]

In a previous study, the tumor site and stage were reported as the most significant prognostic factors for osteosarcoma patients.[32] These tumors appear mostly in the metaphyses of long bones, with approximately 10% of osteosarcomas occurring in the axial skeleton.[33] Seker et al reported that osteosarcoma patients with extremity primary tumors have better survival prognoses than those with non-extremity tumors.[32] Other groups also found that an axial primary site of osteosarcoma was associated with considerably worse survival outcomes.[33–35] The present study also demonstrated that tumor site influences the survival of osteosarcoma patients. With regard to the tumor stage at diagnosis, several groups reported that osteosarcoma patients with metastases have a significantly worse survival prognosis.[1,10,36,37] Patients with metastases may have better relative outcomes if they had only lung metastases and underwent curative metastasectomy.[8] Consistent with these findings, we showed that osteosarcoma patients with distant metastases had a higher risk of death. We also identified tumor grade and histology as independent prognostic for osteosarcoma patients, which is in line with previous studies.[38,39] Jawad et al[26] demonstrated that Paget's osteosarcoma had significantly worse prognosis compared with all other histological subtypes. Their analysis of different histological subtypes confirmed the results reported by Damron et al.[40] Jawad et al[26] also reported that fibroblastic osteosarcoma had significantly better prognosis compared with conventional osteosarcoma, which was similar to our results.

By integrating the abovementioned independent prognostic factors, we created prognostic nomograms that offer an effective and functional method to estimate 3- and 5-year OS and CSS for osteosarcoma patients. These nomograms can improve the accuracy of predicting individual survival outcomes of osteosarcoma patients at certain time points.

Although the prognostic nomograms in the present study showed good predictive ability, there are some limitations which should be taken into consideration. First, the data on radiotherapy and chemotherapy were limited in the SEER database, which might have led to incompleteness of several meaningful clinicopathological parameters and caused other relevant bias. For this reason, chemotherapy or radiation use was not incorporated in our study. Second, since our study was retrospective, it is inevitable that certain patient data were missing. This might have decreased the number of eligible cases. Third, our findings will be more reliable if the nomogram model is externally validated using another independent, large-scale dataset; this would verify whether our results are universally applicable. Despite these limitations, our prognostic nomogram is a significant and effective model for accurately predicting the individual survival outcomes of osteosarcoma patients.

Conclusion

The present study identified age at diagnosis, tumor site, histology, tumor size, tumor stage, use of surgery, and tumor grade as independent prognostic variables for both the OS and CSS rates of osteosarcoma patients. These independent prognostic variables were integrated to build a nomogram prognosis evaluation model for osteosarcoma patients. These offer a more reliable and accurate prediction of osteosarcoma patient survival. Utilizing our nomogram, the 3- and 5-year OS and CSS rates for osteosarcoma patients can be estimated, enabling surgeons to assess personalized survival probability and identify mortality risk.

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Disclosure

The authors report no conflicts of interest in this work.

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