



Research Paper

Application of nomograms to predict overall and cancer-specific survival in patients with chordoma

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ABSTRACT

Background: The survival prediction of patients with chordoma is difficult to make due to the rarity of this oncologic disease. Our objective was to apply a nomogram to predict survival outcomes in individuals with chordoma of the skull base, vertebral column, and pelvis.

Methods: A total of 558 patients with chordoma between 1973 and 2014 were collected from the Surveillance, Epidemiology, and End Results (SEER) database. Independent prognostic factors in patients with chordoma were identified via univariate and multivariate Cox analysis. Then these prognostic factors were incorporated into a nomogram to predict 3- and 5-year overall survival and cancer-specific survival rates. Internal and external data were used to validate the nomograms. Concordance indices (C-indices) were used to estimate the accuracy of this nomogram system.

Results: A total of 558 patients were randomly assigned into a training cohort ($n = 372$) and a validation cohort ($n = 186$). Age, surgical stage, tumor size, histology, primary site, and use of surgery were identified as independent prognostic factors via univariate and multivariate Cox analysis (all $p < 0.05$) and further included to establish the nomogram. The C-indices for overall survival and cancer-specific survival prediction of the training cohort were 0.775 (95% confidence interval, 0.770–0.779) and 0.756 (95% confidence interval, 0.749–0.762). The calibration plots both showed an excellent consistency between actual survival and nomogram prediction.

Conclusion: Nomograms were constructed to predict overall survival and cancer-specific survival for patients with chordoma of the skull base, vertebral column, and pelvis. The nomogram could help surgeons to identify high risk of mortality and evaluate prognosis in patients with chordoma.

1. Introduction

Chordomas, which originate from remnants of the embryonic notochord, represent less than 4% of primary bone tumors [1]. Although the chordoma is a slow-growing, low-grade tumor, this aggressive tumor gradually can infiltrate nervous tissue, adjacent muscle, and related joints [2,3]. The growth of a chordoma tumor begins with bony infiltration and proceeds to invasion of endocranium and neurovascular

structures [4]. A high recurrence rate can severely impact the survival rate and reduce the quality of life of patients with this tumor [5]. The location of chordomas is frequently the sacral area (55%), followed by the skull region (35%) and the vertebral column region (10%) [6]. The management of chordoma centers on radical resection when possible [3]. However, the complete surgical resection of aggressive chordomas remains formidable due to the specific location. Adjuvant radiation therapy has been proved to provide benefits in the treatment of skull-

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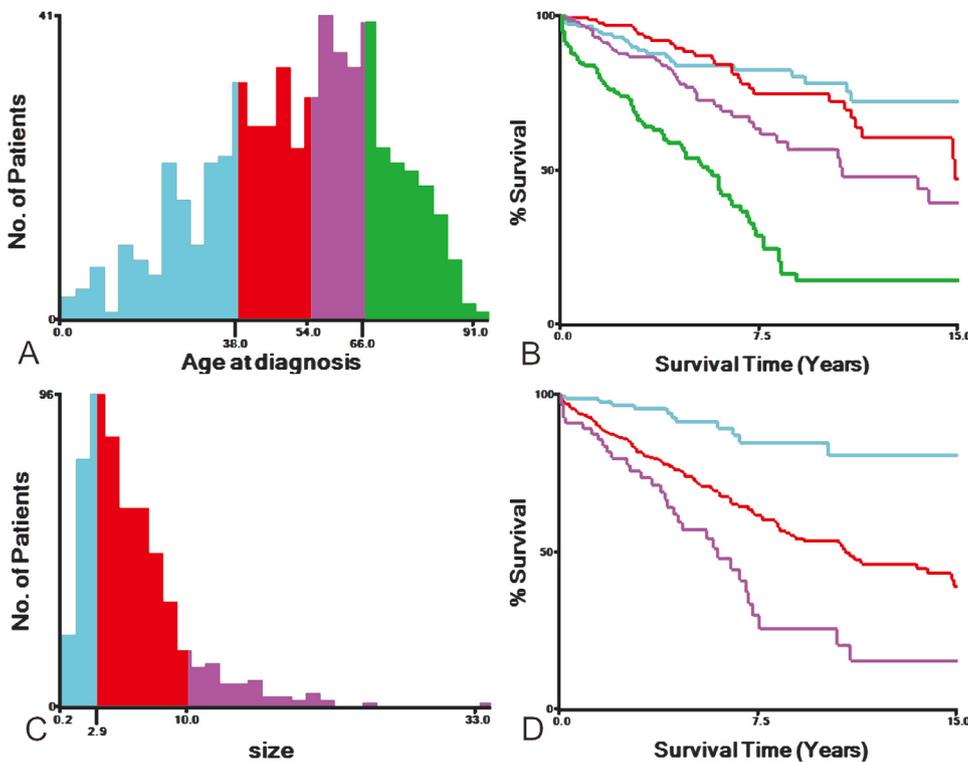


Fig. 1. Identification of optimal cutoff values of age of diagnosis (A, B) and tumor size (C, D) via X-tile analysis.

Optimal cutoff values of age were identified as 38, 54, and 66 years based on overall survival. Optimal cutoff values of tumor size were identified as 2.9 cm and 10.0 cm based on overall survival. Histogram and Kaplan-Meier analysis were developed based on these cutoff values.

Table 1
Baseline demographic and clinical characteristics of patients with chordoma.

Variables	Training cohort		Validation cohort		Total		P
Sex, n,%							0.145
Male	226	60.8%	101	54.3%	327	58.6%	
Female	146	39.2%	85	45.7%	231	41.4%	
Age, n,%							0.923
< 38	85	22.8%	44	23.7%	129	23.1%	
38–54	88	23.7%	48	25.8%	136	24.4%	
55–66	105	28.2%	50	26.9%	155	27.8%	
> 66	94	25.3%	44	23.7%	138	24.7%	
Primary site, n,%							0.872
Bones of skull and face and associated joints	166	44.6%	79	42.5%	245	43.9%	
Vertebral column	60	16.1%	30	16.1%	90	16.1%	
Pelvic bones, sacrum, coccyx and associated joints	146	39.2%	77	41.4%	223	40.0%	
histology, n,%							0.930
Conventional Chordoma	348	93.5%	175	94.1%	523	93.7%	
Chondroid chordoma	21	5.6%	10	5.4%	31	5.6%	
Dedifferentiated chordoma	3	0.8%	1	0.5%	4	0.7%	
Surgical stage, n,%							0.246
Localized	157	42.2%	67	36.0%	224	40.1%	
Regional	185	49.7%	98	52.7%	283	50.7%	
Distant	30	8.1%	21	11.3%	51	9.1%	
Surgery, n,%							0.657
Yes	325	87.4%	160	86.0%	485	86.9%	
No	47	12.6%	26	14.0%	73	13.1%	
Radiation, n,%							0.281
Yes	200	53.8%	91	48.9%	291	52.2%	
No evidence	172	46.2%	95	51.1%	267	47.8%	
Tumor Size, n,%							0.209
< 2.9	90	24.2%	34	18.3%	124	22.2%	
> 10.0	45	12.1%	20	10.8%	65	11.6%	
2.9–10.0	237	63.7%	132	71.0%	369	66.1%	
Chemotherapy, n,%							1.000
Yes	14	3.8%	7	3.8%	21	3.8%	
No evidence	358	96.2%	179	96.2%	537	96.2%	

No significant differences regarding patient age, gender, primary site, tumor size, histology, surgical stage, use of surgery, use of chemotherapy and use of radiation were found between training and validation cohort.

Table 2
Univariate cox regression analysis of cancer-specific survival and Overall survival in the training cohort.

Variables	Cancer-specific survival			Overall survival		
	HR	95%CI	P	HR	95%CI	P
Sex						
Male	Reference			Reference		
Female	1.392	0.894–2.168	0.144	1.155	0.790–1.689	0.456
Age						
< 38	Reference			Reference		
38–54	4.431	2.141–9.171	< 0.001	6.295	3.394–11.676	< 0.001
55–66	1.570	0.737–3.342	0.242	1.227	0.613–2.455	0.564
> 66	2.097	0.979–4.492	0.057	2.262	1.164–4.395	0.016
Primary site						
Bones of skull and face and associated joints	Reference			Reference		
Vertebral column	1.489	0.819–2.709	0.192	1.751	1.038–2.956	0.036
Pelvic bones, sacrum, coccyx and associated joints	1.021	0.625–1.668	0.934	1.426	0.940–2.166	0.095
Histology						
Conventional Chordoma	Reference			Reference		
Chondroid chordoma	1.523	0.660–3.513	0.324	1.033	0.453–2.355	0.939
Dedifferentiated chordoma	14.476	3.391–61.792	< 0.001	9.955	2.376–41.720	0.002
Surgical stage						
Localized	Reference			Reference		
Regional	2.440	1.440–4.135		2.531	1.167–3.961	< 0.001
Distant	3.024	1.401–6.529		2.8775	1.474–5.608	0.002
Surgery						
Yes	Reference			Reference		
No	3.171	1.868–5.380	< 0.001	3.596	2.337–5.533	< 0.001
Radiation						
Yes	Reference			Reference		
No evidence	1.102	0.710–1.711	0.664	1.209	0.833–1.755	0.371
Tumor size						
< 2.9	Reference			Reference		
2.9–10.0	7.719	2.802–21.266	< 0.001	7.742	3.474–17.252	< 0.001
> 10.0	4.359	1.748–10.872	0.002	3.635	1.755–7.529	0.001
Chemotherapy						
Yes	Reference			Reference		
No evidence	0.404	0.185–0.880	0.022	0.591	0.274–1.273	0.179

There were six variables involving patient age, primary site, histology, tumor stage, use of surgery and tumor size which were related to OS ($P < 0.05$), and the other variables lost significance. And six variables involving patient age, histology, tumor stage, tumor size, use of surgery and chemotherapy were related to CSS ($P < 0.05$), and the other variables lost significance.

CI, confidence interval; HR, hazard ratio.

base chordomas, whereas chemotherapy has limited efficacy on most chordomas [5,7–9].

Identifying prognostic factors for patients with chordoma is a significant part of treatment planning. Previous studies have proved that metastasis and surgical margin are independent prognostic factors for patients with chordoma [10–12]. In addition, patient age, recurrence, and tumor size have also been shown to influence patient survival [10–14]. However, single prognostic factors exert limited influence on a precise individualized prediction of prognosis. The prognostic nomogram is an efficient statistical tool that has been suggested as a new standard to predict an individual patient's survival. And, this graphic calculating scales method has been proved to be a useful method in the management of several types of cancer [15–17]. The obvious advantages of prognostic nomograms are robustness and better predictive accuracy, which enhance its potential for the predictive accuracy of individual prognosis [17]. However, a prognostic nomogram that can be applied to predict the overall survival (OS) and cancer-specific survival (CSS) of patients with chordoma has not been reported, and this might be ascribed to the limited number of chordoma cases in a single institution [2].

In the present study, the clinical information of patients with chordoma of the skull base, vertebral column, and pelvis between 1973 and 2013 were collected from the Surveillance, Epidemiology and End Results (SEER) dataset and analyzed. SEER is a US population-based cancer database that contains approximately 28% of the overall US population [17] and collects clinical information of tumor patients in 18 registries in the US. The current study aimed to develop validated

prognostic nomograms to predict OS and CSS of patients with chordoma.

2. Materials and methods

2.1. Patient eligibility and variables

The patient information was collected from the SEER database. The SEER*Stat software (Version 8.3.5; NCI, Bethesda, USA) was applied to the patient information acquired from the SEER database.

The inclusion criteria in the present study were as follows:

- (1) diagnosed with chordoma (International Classification of Diseases for Oncology: 9370, 9371, and 9372) as primary malignancy between 1973 and 2014;
- (2) Positive histological confirmation of chordoma;
- (3) site limited to the skull base, vertebral column, and pelvis;
- (4) confirmation of histologic type of chordoma;
- (5) known cause of death and survival months after diagnosis.

The exclusion criteria in the present study were as follows:

- (1) unknown use of radiotherapy, chemotherapy or surgery;
- (2) unknown surgical stage;
- (3) unknown tumor size

The clinicopathological features including patient age, gender,

Table 3
Multivariate cox regression analysis of cancer-specific survival and Overall survival in the training cohort.

Covariates	Cancer-specific survival			Overall survival		
	HR	95%CI	P	HR	95%CI	P
Sex						
Male	Reference			Reference		
Female	1.511	0.940–2.428	0.088	1.060	0.706–1.591	0.778
Age						
< 38	Reference			Reference		
38–54	5.820	2.543–13.320	< 0.001	7.032	3.482–14.204	< 0.001
55–66	1.960	0.891–4.313	0.094	1.345	0.654–2.765	0.420
> 66	3.274	1.403–7.642	0.006	3.159	1.521–6.559	0.002
Primary site						
Bones of skull and face and associated joints	Reference			Reference		
Vertebral column	0.995	0.524–1.891	0.989	1.065	0.607–1.866	0.827
Pelvic bones, sacrum, coccyx and associated joints	0.302	0.153–0.596	0.001	0.419	0.237–0.739	0.003
Histology						
Conventional Chordoma	Reference			Reference		
Chondroid chordoma	1.601	0.641–3.997	0.314	1.438	0.579–3.572	0.435
Dedifferentiated chordoma	7.946	1.569–40.240	0.012	6.407	1.354–30.326	0.019
Surgical stage						
Localized	Reference			Reference		
Regional	1.984	1.149–3.428	0.014	2.048	1.283–3.267	0.003
Distant	1.498	0.638–3.518	0.353	1.549	0.742–3.234	0.244
Surgery						
Yes	Reference			Reference		
No	2.095	1.145–3.835	0.016	2.425	1.484–3.963	< 0.001
Radiation						
Yes	Reference			Reference		
No evidence	1.401	0.875–2.244	0.160	1.468	0.984–2.190	0.060
Tumor size						
< 2.9	Reference			Reference		
2.9–10.0	8.331	2.564–27.072	< 0.001	6.435	2.513–16.478	< 0.001
> 10.0	4.693	1.832–12.021	0.001	3.420	1.609–7.269	0.001
Chemotherapy						
Yes	Reference			Reference		
No evidence	0.624	0.252–1.545	0.308	1.276	0.543–2.998	0.576

Age, primary site, histology, surgical stage, use of surgery and tumor size were identified as independent prognostic factors for both OS and CSS ($P < 0.05$), and the other variables lost significance.

CI, confidence interval; HR, hazard ratio.

histology, surgical stage, tumor size, use of surgery, use of radiation, use of chemotherapy, and survival time were incorporated in the present study. The cutoff value of tumor size and age at diagnosis were calculated via X-tile software (Yale University, New Haven, Connecticut, USA). X-tile software was initially developed to determine the best cutoff values for variables in breast malignancy [18]. The optimal cutoff values of chordoma tumor size in the current study were identified as 2.9 and 10.0 cm (Fig. 1). The optimal age cutoff values of patients with chordoma were 38.54 and 66 years. The surgical stage in patients with chordoma was further categorized as localized, regional, and distant according to the American Joint Committee on Cancer (AJCC) staging system for bone sarcomas. Tumors confined to the periosteum were defined as localized tumors. And, a tumor that extended beyond the periosteum but without distant metastasis was defined as a regional tumor. Surgical resection was assigned to those who underwent surgical resection. However, the type of surgical resection such as wide, marginal, and intralesional resection could not be obtained from the SEER database. Radiation was divided into those treated with radiation and those who did not undergo radiation. Nuances such as radiation type and fractionation could not be acquired from the SEER database. Chemotherapy was dichotomized into those who received it and those who did not.

2.2. Statistical analysis

All the chordoma patients identified according to aforementioned inclusion and exclusion criteria ($n = 558$) were randomly divided into the training cohort ($n = 372$) and the validation cohort ($n = 186$) to

construct and validate the prognostic nomograms. A chi-square test was applied to compare the clinical characteristics between the training and validation cohorts.

Continuous variables and categorical variables were presented as the number of patients with the respective percentages. The cutoff value of tumor size and age at diagnosis were calculated via X-tile software (Yale University, New Haven, Connecticut, USA) based on OS (Fig. 1). The prognostic factors (age, gender, primary site, tumor size, histology, surgical stage, use of surgery, use of chemotherapy and use of radiation) were further evaluated via univariate and multivariate Cox proportional hazards regression analyses. Furthermore, hazard ratios and corresponding 95% confidence intervals (CIs) of variables were calculated. The two primary endpoints of the study were OS and CSS. Survival time was calculated from the date of disease diagnosis to the date of death from any disease cause (OS) and death from chordoma (CSS). Missing data were excluded from the present study. Nomograms for 3- and 5-year OS and 3- and 5-year CSS were constructed according to the analysis results of univariate and multivariate Cox proportional hazards regression analyses. And, both internal and external validations of the prognostic nomogram based on the training cohort and validation cohort were performed in the present study. Harrell's concordance index (C-index), a useful evaluation value similar to area under curve of receiver operating characteristic curve [19], was applied to evaluate the performances of the prognostic nomograms. The C-index ranges from 0.5 to 1.0, with 0.5 indicating the total chance and 1.0 indicating a perfect match [20]. Consistency between the predicted survival and the observed survival were assessed via calibration curves of the nomograms. The chi-square test and univariate and multivariate Cox analyses

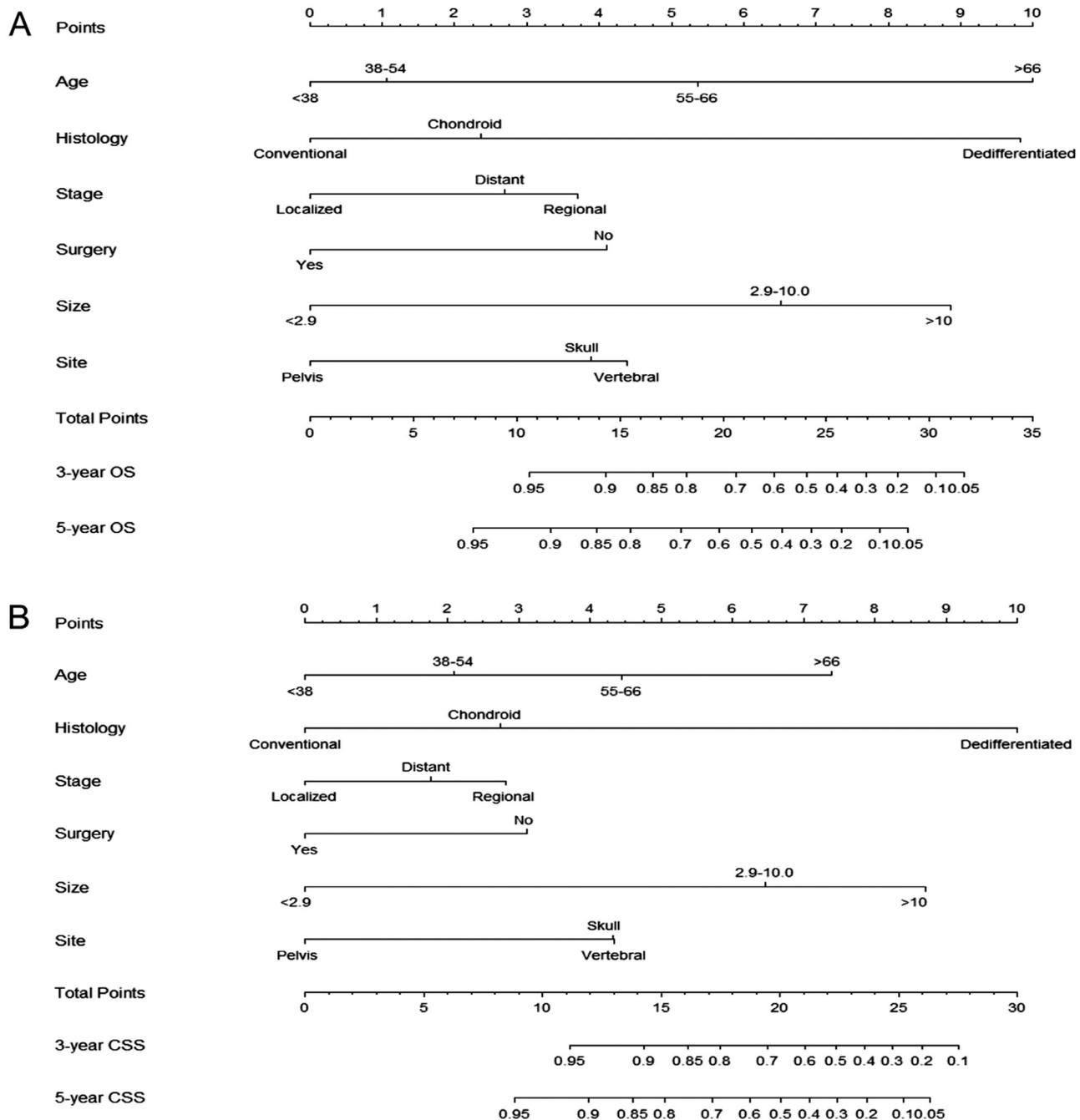


Fig. 2. Nomograms to predict 3- and 5-year (A) overall survival (B) cancer-specific survival for patients with chordoma. A vertical line can be drawn between each variable and the points scale to acquire the points of each variable. Predicted survival rate was calculated according to the total points by drawing a vertical line from the Total Points scale to the overall survival or cancer-specific survival scale.

were performed via SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Rms package in R (version 3.3.1) was applied to construct and validate the nomograms. Statistical significance was defined as two-sided $P < 0.05$.

3. Results

3.1 Patient baseline characteristics

A total of 558 patients with chordoma of the skull base, vertebral column, and pelvis between 1973 and 2014 were identified from the SEER database according to inclusion and exclusion criteria. The patients were randomly divided into the training cohort ($n = 372$) and the validation cohort ($n = 186$). The training cohort was assigned for

construction and internal validation of the nomograms. And, the validation cohort was assigned for the external validation of the nomograms.

The patient characteristics are summarized in [Table 1](#). There were 327 (58.6%) male patients and 231 (41.4%) female patients in the current study. The primary site of 245 (43.9%) patients were the bones of the skull and face and associated joints; 90 (16.1%) patients' primary site was the vertebral column; and 261 (40.0%) patients' primary site was the pelvic bones, sacrum, coccyx, and associated joints. Among all the patients, 224 patients (40.1%) had localized disease, 283 patients (50.7%) had regional disease, and the remaining 51 patients (9.1%) had distant disease. In the entire cohort, 117 (20.9%) patients had death attributed to chordoma and 52 (9.3%) patients had death attributed to

Table 4
Detailed scores of prognostic factors in the OS and CSS nomograms.

Characteristic	OS nomogram	CSS nomogram
Age		
< 38	0	0
38–54	1.1	2.1
55–66	5.4	4.4
> 66	10.0	7.4
Primary site		
Bones of skull and face and associated joints	3.9	4.3
Vertebral column	4.4	4.3
Pelvic bones, sacrum, coccyx and associated joints	0	0
Histology		
Conventional Chordoma	0	0
Chondroid chordoma	2.4	2.7
Dedifferentiated chordoma	9.8	10.0
Surgical stage		
Localized	0	0
Regional	3.7	2.8
Distant	2.7	1.8
Surgery		
Yes	0	0
No	4.1	3.1
Tumor size		
< 2.9	0	0
2.9–10.0	6.5	6.5
> 10.0	8.9	8.7

other causes. No significant differences regarding patient age, gender, primary site, tumor size, histology, surgical stage, use of surgery, use of chemotherapy, and use of radiation were found between the training and validation cohorts.

Univariate and multivariate Cox proportional hazards regression analyses of the training cohort

The data of the training cohort, including patient age, gender, primary site, tumor size, histology, surgical stage, use of surgery, use of chemotherapy, and use of radiation, were selected to conduct the univariate Cox analysis. The results of the analysis (Table 2) showed that

there were six variables involving patient age, primary site, histology, tumor stage, use of surgery, and tumor size that were related to OS ($P < 0.05$), and the other variables lost significance. Further, six variables including patient age, histology, tumor stage, tumor size, use of surgery, and chemotherapy were related to CSS ($P < 0.05$), and the other variables lost significance (Table 3). Multivariate Cox analyses (Tables 2 and 3) were further performed to control for confounding variables. From multivariate analysis results, age, primary site, histology, surgical stage, use of surgery, and tumor size were identified as independent prognostic factors for both OS and CSS ($P < 0.05$), and the other variables lost significance.

3.2. Construction and validation of the nomograms for OS and CSS

After selection, patient age, primary site, histology, surgical stage, use of surgery, and tumor size were used to construct the prognostic nomograms that predict 3- and 5-year OS and CSS of patients with chordoma (Fig. 2 and Table 4). Internal and external validations of prognostic nomograms were performed. The predictive accuracy of the final prognostic nomogram models was evaluated by C-index. For the internal validation of the nomogram in the training cohort, the C-indices were 0.775 (95%CI, 0.770 to 0.779) and 0.756 (95%CI, 0.749 to 0.762) for internal validation of the OS and CSS nomograms, respectively. And, the external validation C-indices were 0.673 (95%CI, 0.660 to 0.685) and 0.603 (95%CI, 0.586 to 0.619) for the OS and CSS nomograms, respectively. A good agreement between nomogram prediction and actual survival was shown in calibration plots (Fig. 3). These prognostic nomograms can easily be used by surgeons to estimate the prognosis of patients with chordoma with the following data: age at diagnosis, primary site, histology, surgical stage, whether surgery was performed, and tumor size.

4. Discussion

Chordomas are specific tumors that originate from remnants of the embryonic notochord. The location of this bone tumor involves the

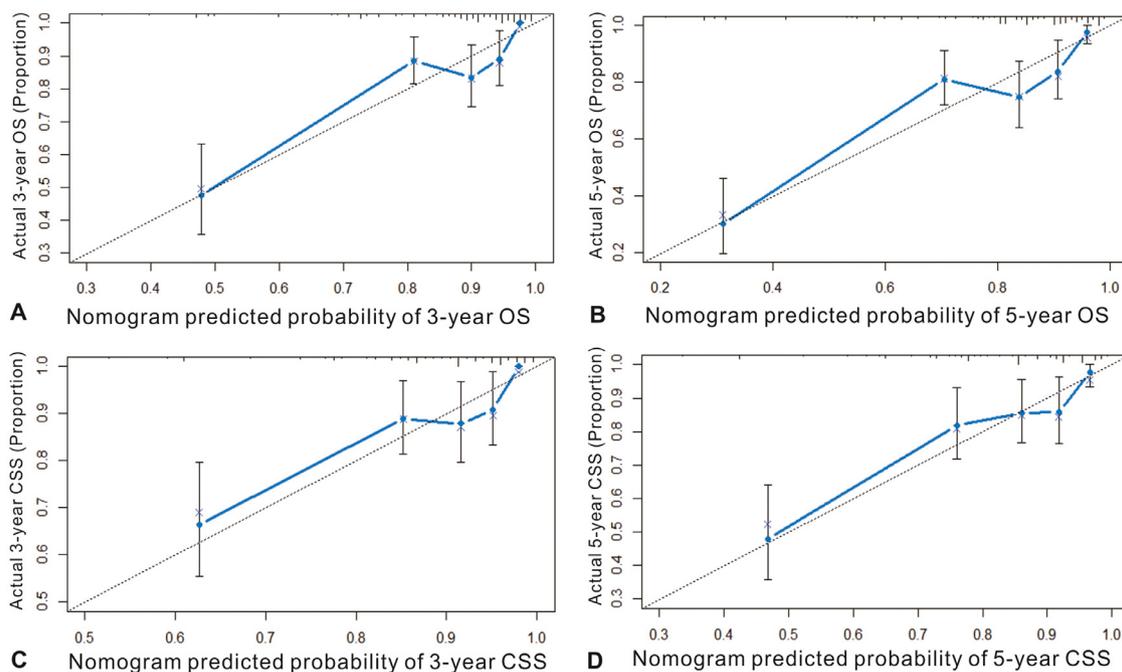


Fig. 3. Internal calibration plots of 3-year (A) and 5-year (B) overall survival nomogram calibration curves; 3-year (C) and 5-year (D) cancer-specific survival nomogram calibration curves.

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 indicate higher prediction accuracy.

sacral area in most (55%), followed by the skull base region (35%) and the vertebral column region (10%) [6]. Understanding the natural history of chordoma can help surgeons evaluate prognostic information. Various prognostic factors can influence patient survival; however, a single prognostic factor has only limited utility in predicting individual survival. The nomogram, a tool commonly used for estimating individual patient survival, is capable of calculating the accumulated effect by integrating all prognostic factors predict 3- and 5-year survival probabilities [20–22]. Nevertheless, no prognostic nomogram for patients with chordoma had been constructed. In the present study, we established comprehensive prognostic nomograms to predict 3- and 5-year OS and CSS rates for patients with chordoma of the skull base, mobile spine, and pelvis according to the SEER database, which covers approximately 28% of the US population. We hypothesized that these validated nomograms could be used in the clinical setting using specific clinical information of patients, which was likely to be available to the surgeon, to evaluate prognosis.

Via univariate and multivariate Cox analyses, which were used to identify independent prognostic factors for OS and CSS respectively, several clinical characteristics were proved to be independent prognostic factors for OS or CSS in the present study, including patient age, primary site, histology, tumor stage, use of surgery, and tumor size. Our study discovered that increased patient age is correlated with a worse survival for patients with chordoma. Tian et al. also indicated that patients older than 25 years had poorer neurologic status and survival outcomes [23]. In the present study, X tile software was applied in data stratification of age and tumor size according to survival time and status. X-tile software is an alternative method that was initially developed to determine best cutoff points of variables in breast malignancy [18]. The optimal age cutoff values of patients with chordoma in the current study were 38.54 and 66 years. With regard to tumor size, Bergh et al. had reported that patients with chordoma of the sacrum and mobile spine and with a large tumor size had the poorest survival [24]. In our study, X-tile software was also applied to determine the best cutoff points of chordoma tumor size. The optimal cutoff values of chordoma tumor size in the current study were identified as 2.9 and 10.0 cm. Our study showed that larger tumor size was an independent prognostic factor for survival in patients with chordoma. Larger tumor size was correlated with poorer survival.

Surgical stage and use of surgery were also identified as independent prognostic factors in the present study. Localized stage was correlated with better survival compared to regional and distant stage. With regard to surgical treatment, several previous literatures have reported that patients with chordoma who received surgical resection would have a better rate of survival compared with patients who did not receive surgery [25–27]. Surgical treatment is the most effective treatment for chordoma at present. The application of primary or adjuvant radiotherapy in these patients is controversial because of chordoma's radioresistance [28]. Chemotherapy including cisplatin, anthracyclines, and alkylating agents has been applied in patients with chordoma, and these treatments have not been shown to be effective [1,29].

There are three different histological subtypes in chordoma according to microscopic morphology: conventional, chondroid, and dedifferentiated. Among all the subtypes, dedifferentiated chordoma is the most aggressive subtype, which significantly affects overall survival [30]. Subtype has been shown in the present study to significantly affect survival outcomes [31].

Including independent prognostic factors identified from multivariate analysis, we constructed a nomogram that can estimate 3- and 5-year OS and CSS for patients with chordoma. Individual survival probability of these patients at certain time points can be evaluated precisely via these nomograms. To our knowledge, no such prognostic nomogram has been reported for patients with chordoma. A practicable nomogram can help surgeons to estimate the precise likelihood of survival at different time intervals. And, such a prognostic nomogram

can increase the surgeon's ability to identify patients who are at higher risk of early death.

Several potential limitations of this study should still be considered. First, we used only 3- and 5-year survival as the primary endpoints, but did not consider local recurrence, which is not available in the SEER database. Second, the information we applied to construct and validate the nomograms was from the same SEER database, which can reduce the reliability of the nomogram; it would be useful to validate the prognostic nomograms in the present study with another dataset.

5. Conclusions

Age at diagnosis, primary site, histology, tumor stage, use of surgery, and tumor size were identified as independent prognostic factors for both OS and CSS of patients with chordoma. We incorporated these prognostic factors to construct prognostic nomograms that can estimate 3- and 5-year OS and CSS for these patients. The nomogram constructed in present study can serve as an effective and convenient evaluation tool to help surgeons create personalized survival evaluations and mortality risk identification in patients with chordoma.

Declarations of interest

None

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