Development and Validation of Nomograms Predicting Overall and Cancer-specific Survival of Spinal and Pelvic Tumor Patients with Distant Metastasis

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Abstract

Background: Primary spinal bone tumors with distant metastasis are a sign of advanced stage and are usually accompanied by poor prognosis. This study is to identify the risk factors and establish prognostic nomograms to predict 1- and 3-year overall survival (OS) and cancer-specific survival (CSS) rates for spinal and pelvic bone tumor patients with distant metastasis.

Patients and methods: Spinal and pelvic bone tumor patients with distant metastasis between 1998 and 2016 were selected for this study from the Surveillance, Epidemiology, and End Results (SEER) database. Nomograms to predict 1- and 3-year OS and CCS rates were constructed based on independent risk factors identified by univariate and multivariate Cox analyses. Concordance indexes (C-indexes), receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA) were used to assess the nomograms.

Results: All patients (n=343) were randomly divided into a training cohort (n=243) and validation cohort (n=100). No significant differences were found in the

demographic data of all patients in the training and validation cohorts. Ultimately, only four independent risk factors (patient age, histology, grade and surgery) were identified as significantly associated with OS and CCS. The C-indices were 0.722 (95% CI, 0.685 to 0.759) and 0.686 (95% CI, 0.61 to 0.760) for the internal validation and external validation of the OS nomogram, respectively. Similarly, the C-indices based on the CCS nomogram were 0.717 (95% CI, 0.678 to 0.757) and 0.695 (95% CI, 0.619 to 0.771) for the internal validation and external validation, respectively. The calibration curves revealed that the predicted survival and actual survival were in concordance. DCA showed the clinical utility and benefits of the nomograms.

Conclusion: The nomograms we constructed based on the SEER database can accurately predict individual patient survival.

Introduction

Primary bone tumors of the spine are an uncommon disease, accounting for approximately 2.8–13% of all bone cancers.(1) Primary osseous spine tumors have been the research focus of many studies in the last three decades. (1, 2) The most common histologies of these tumors include chordomas, chondrosarcomas, Ewing sarcomas, and osteosarcomas.(3)

Primary spinal bone tumors with distant metastasis are a sign of advanced stage and are usually accompanied by poor prognosis. However, physicians lack experience in choosing a treatment plan and predicting prognosis because the understanding of the condition and relevant data are limited to rare cases. A well-developed model is essential for clinical decision-making and would benefit both clinicians and patients.(4) Clinically, several risk factors are considered to affect the survival of patients with spinal and pelvic bone tumors, including patient age, race, tumor size, grade, histology, surgery, marital status,

etc. Therefore, multiple indicators should be considered when predicting the survival outcome of tumors. Nomograms based on clinical modeling have been one of the most widely used statistical methods to precisely predict individual patient survival by incorporating all prognostic factors and the probability calculations of risk factors.(4–8) The combination of visual and mathematical approaches and the accuracy of the predictions of individual prognosis are the advantages of nomograms.(9) The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute covers 18 registries and approximately 30% of the U.S. population

The purpose of the current study was to establish prognostic nomograms based on the SEER database to predict 1- and 3-year overall survival (OS) and cancer-specific survival (CSS) rates for spinal and pelvic bone tumor patients with distant metastasis.

Material And Methods

Patients and data source

Patient data were obtained and filtered using SEER*Stat software (version 8.3.6; NCI, Bethesda, MD, USA) from SEER web site (https://seer.cancer.gov/data/). Ethics approval was not required for the study because the data were publicly available and without identifying information.(10)

The inclusion criteria for data screening were as follows:

1.Patients were diagnosed with a histologically confirmed primary osseous tumor (Ewing sarcoma, chordoma, chondrosarcoma, or osteosarcoma) and distant metastasis.

2.The primary site was limited to the osseous spine and pelvis.

The exclusion criteria for data screening were as follows:

1.Unknown survival months after diagnosis and unknown cause of death.

2.Unknown general information (age, race, sex, year of diagnosis and marital status).

3.Unknown tumor size.

4.Unknown use of surgery.

Clinicopathological features

The patients were described based on the following clinicopathological features of interest: patient age (<23 years, 23-68 years, or >68 years), tumor size (<9 cm, 9-11 cm, or >11 cm), sex (female or male), race (white, black, or other), year of diagnosis (1998-2007 or 2008-2016), marital status (married or unmarried), grade (grade I/II, grade III/IV, or unknown), lung metastasis (yes or no), histology (Ewing sarcoma, chordoma, chondrosarcoma, or osteosarcoma), surgery (yes or no), chemotherapy (yes or

no/unknown), radiotherapy (yes or no/unknown), primary site (vertebral column or pelvic bones, sacrum, coccyx or associated joints), survival time (months), and survival status (alive, cancer-specific death or all-cause death). The optimal cutoff values of age and tumor size were determined by X-tile software (version 3.6.1, Yale University, New Haven, USA) (Figure 1).(11)

The primary endpoints of our study included OS and CSS. OS was defined as the duration from the date of diagnosis to the date of the last follow-up or date of all-cause death. CCS was defined as the duration from the date of diagnosis to the date of the last follow-up or date of cancer-specific death.

Statistical analysis and nomogram construction

All patients were randomly divided into a training cohort and a validation cohort by using R software version 3.6.2 (www.r-project.org). The chi-square test was applied to compare the clinical categorical variables between the cohorts. Univariate Cox proportional hazards regression analysis was used to evaluate prognostic factors related to OS and CCS in the training cohort.

The factors with P values < 0.2 selected in univariable analysis were further incorporated into the multivariable Cox proportional hazards regression analyses.(7) Multivariate Cox proportional hazards regression analysis was performed to determine the independent risk factors (P<0.05) and removal factors (P >0.05) from the associated models. The hazard ratios and corresponding 95% CIs of the variables were also calculated. All statistical analyses were performed using SPSS 22.0 (IBM Corp, Armonk, NY, USA) and R software version 3.6.2 (www.r-project.org). However, based on multivariate analysis, only patient age, grade, histology and surgery were identified as significant independent risk factors associated with both OS and CCS.

Therefore, the prognostic nomograms for 1- and 3-year OS and 1- and 3-year CSS were constructed based on these four independent risk factors.

Nomogram validation

The OS and CSS nomograms were validated both internally and externally by the concordance indexes (C-indexes), receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

The C-index was used to measure the performance and predicted results of the nomograms. The C-index is also a useful evaluation value similar to calculating the area under the ROC curve (AUC).(12) ROC curves were used to assess the sensitivity and specificity of the nomograms. The calibration curves were used to determine whether the predicted survival and actual survival were in concordance based on an optimal model constituted by a 45-degree line. DCA was used to further investigate the clinical utility and benefits of the nomograms. (13)

Results

Patient Characteristics

Ultimately, 343 patients were enrolled in the study between 1998 and 2016 according to the screening criteria. The training cohort and validation cohort consisted of 243 and 100 patients, respectively. In the study, there were 138 (40.23%) females, 134 (39.07%) patients diagnosed between 1998 and 2007, and 209 (60.93%) patients unmarried. The primary site of 53 (15.46%) patients was the vertebral column. Based on the optimal cutoff value determined by X-tile software for age and tumor size, 153 (44.61%) patients were between 23 and 68 years old, and 69 (20.12%) patients had a tumor size between 9 and 11 cm. Ewing sarcoma was the most common histopathological type, and grades I/II and III/IV of tumor differentiation accounted for 11.08% and 34.11% of the cases, respectively. Only 119 (34.69%) patients underwent surgery, and 92 (26.82%) patients had metastasis to the lung. It should be noted that 233 patients died, of which 220 patients died from cancer. The clinicopathological features in the training and validation cohorts are shown in Table 1. No significant differences were found in the demographic data of all patients in the training and validation cohorts.

Table 1

Baseline demographics and clinical characteristics of patients in training cohort and validation cohort

Variables	Training cohort (n = 233)		Validation cohort n=(100)		Total cohort (n = 343)		P-Value
Age (years), n, %							0.676
< 23	112	46.1%	41	41.0%	153	44.6%	
23–68	105	43.2%	48	48.0%	153	44.6%	
> 68	26	10.7%	11	11.0%	37	10.8%	
Gender, n, %							0.853
Female	97	39.9%	41	41.0%	138	40.2%	
Male	146	60.1%	59	59.0%	205	59.8%	
race, n, %							0.287
Black	20	8.2%	4	4.0%	24	7.0%	
Other	22	9.1%	7	7.0%	29	8.5%	
White	201	82.7%	89	89.0%	290	84.5%	
Year of diagnosis, n, %							0.455
1998–2007	98	40.3%	36	36.0%	134	39.1%	
2008–2016	145	59.7%	64	64.0%	209	60.9%	
Marital, n, %							0.987
Married	95	39.1%	39	39.0%	134	39.1%	
unmarried	148	60.9%	61	61.0%	209	60.9%	
Primary Site, n, %							0.611
Vertebral column	36	14.8%	17	17.0%	53	15.5%	
Pelvic bones, sacrum, coccyx and associated joints	207	85.2%	83	83.0%	290	84.5%	
Size, n, %							0.467
< 9	86	35.4%	29	29.0%	115	33.5%	
9–11	49	20.2%	20	20.0%	69	20.1%	
> 11	108	44.4%	51	51.0%	159	46.4%	

$p < 0.05$ considered statistically significant

Variables	Training cohort (n = 233)		Validation cohort n=(100)		Total cohort (n = 343)		P-Value
Histology, n, %							0.268
Ewing sarcoma	112	46.1%	46	46.0%	158	46.1%	
Chordoma	21	8.6%	11	11.0%	32	9.3%	
Chondrosarcoma	43	17.7%	24	24.0%	67	19.5%	
Osteosarcoma	67	27.6%	19	19.0%	86	25.1%	
Grade, n, %							0.764
Unknown	134	55.1%	54	54.0%	188	54.8%	
Grade I/II	25	10.3%	13	13.0%	38	11.1%	
Grade III/IV	84	34.6%	33	33.0%	117	34.1%	
Metastasis, n, %							0.559
Others	180	74.1%	71	71.0%	251	73.2%	
Lung	63	25.9%	29	29.0%	92	26.8%	
Surgery, n, %							0.939
Yes	84	34.6%	35	35.0%	119	34.7%	
No	159	65.4%	65	65.0%	224	65.3%	
Radiation, n, %							0.87
Yes	124	51.0%	52	52.0%	176	51.3%	
No/Unknown	119	49.0%	48	48.0%	167	48.7%	
Chemotherapy, n, %							0.332
Yes	187	77.0%	72	72.0%	259	75.5%	
No/Unknown	56	23.0%	28	28.0%	84	24.5%	
$p < 0.05$ considered statistically significant							

Nomogram Construction and Validation

Based on the univariate Cox proportional hazards regression analysis, patient age, year of diagnosis, marital status, primary site, tumor size, histology, grade and surgery were selected from the training cohort for inclusion in the multivariable Cox analysis. (Table 2, Table 3). The 1- and 3-year OS and CCS

nomograms were constructed based on the four independent risk factors (patient age, histology, grade and surgery) that were identified in the multivariate analysis (Fig. 2).

Table 2

Univariate and Multivariate analysis of overall survival in the training cohort

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Age (years), n, %						
< 23	Ref			Ref		
23–68	1.834	1.327–2.535	< 0.001	1.804	1.137–2.862	0.012
> 68	3.498	2.201–5.560	< 0.001	3.003	1.508–5.980	0.002
Gender, n, %						
Female	Ref					
Male	1.038	0.763–1.413	0.812			
race, n, %						
Black	Ref			Ref		
Other	0.843	0.422–1.686	0.629	1.042	0.480–2.260	0.917
White	0.649	0.386–1.090	0.102	1.136	0.628–2.057	0.673
Year of diagnosis, n, %						
1998–2007	Ref			Ref		
2008–2016	0.741	0.550–0.999	0.049	0.827	0.602–1.137	0.243
Marital, n, %						
Married	Ref			Ref		
unmarried	0.502	0.371–0.678	< 0.001	0.652	0.410–1.038	0.071
Primary Site, n, %						
Vertebral column	Ref					
Pelvic bones, sacrum, coccyx and associated joints	0.964	0.635–1.463	0.863			

$p < 0.2$ considered statistically significant in Univariate analysis; $p < 0.05$ considered statistically significant in Multivariate analysis;

Variables	Univariate analysis			Multivariate analysis		
Size, n, %						
< 9	Ref			Ref		
9–11	1.455	0.956–2.214	0.080	1.347	0.855–2.120	0.199
> 11	1.642	1.167–2.312	0.004	1.352	0.938–1.950	0.106
Histology, n, %						
Ewing sarcoma	Ref			Ref		
Chordoma	1.238	0.695–2.205	0.469	0.736	0.367–1.479	0.389
Chondrosarcoma	1.676	1.108–2.536	0.015	1.292	0.700-2.385	0.413
Osteosarcoma	2.837	1.987–4.051	< 0.001	2.122	1.337–3.369	0.001
Grade, n, %						
Grade I/II	Ref			Ref		
Grade III/IV	1.918	1.119–3.290	0.018	2.221	1.120–4.403	0.022
Unknown	1.430	0.851–2.402	0.177	2.169	1.119–4.205	0.022
Metastasis, n, %						
Others	Ref					
Lung	1.034	0.720–1.487	0.855			
Surgery, n, %						
Yes	Ref			Ref		
no	1.696	1.229–2.34	0.001	1.771	1.221–2.569	0.003
Radiation, n, %						
Yes	Ref					

$p < 0.2$ considered statistically significant in Univariate analysis; $p < 0.05$ considered statistically significant in Multivariate analysis;

Variables	Univariate analysis			Multivariate analysis
No/Unknown	1.132	0.840–1.524	0.415	
Chemotherapy, n, %				
Yes	Ref			
No/Unknown	1.236	0.877–1.741	0.226	
$p < 0.2$ considered statistically significant in Univariate analysis; $p < 0.05$ considered statistically significant in Multivariate analysis;				

Table 3

Univariate and Multivariate analysis of cancer-specific survival in the training cohort

Variables	Univariate analysis			Multivariate analysis		
	HR	95%	P	HR	95%	P
Age (years), n, %						
< 23	Ref			Ref		
23–68	1.783	1.281–2.480	0.001	1.771	1.103–2.841	0.018
> 68	3.115	1.914–5.071	0.000	2.672	1.333–5.357	0.006
Gender, n, %						
Female	Ref					
Male	1.087	0.790–1.495	0.608			
race, n, %						
Black	Ref					
Other	0.965	0.470–1.978	0.922			
White	0.710	0.409–1.233	0.224			
Year of diagnosis, n, %						
1998–2007	Ref			Ref		
2008–2016	0.729	0.536–0.990	0.043	0.798	0.581–1.098	0.166
Marital, n, %						
Married	Ref			Ref		
unmarried	0.517	0.380–0.704	0.000	0.669	0.415–1.080	0.100
Primary Site, n, %						
Vertebral column	Ref					
Pelvic bones, sacrum, coccyx and associated joints	0.904	0.594–1.374	0.635			

$p < 0.2$ considered statistically significant in Univariate analysis; $p < 0.05$ considered statistically significant in Multivariate analysis;

Variables	Univariate analysis			Multivariate analysis		
Size, n, %						
< 9	Ref			Ref		
9–11	1.445	0.944–2.209	0.090	1.318	0.837–2.076	0.234
> 11	1.521	1.072–2.158	0.019	1.252	0.862–1.818	0.237
Histology, n, %						
Ewing sarcoma	Ref			Ref		
Chordoma	0.998	0.526–1.893	0.994	0.615	0.290–1.303	0.204
Chondrosarcoma	1.678	1.102–2.555	0.016	1.275	0.709–2.292	0.418
Osteosarcoma	2.751	1.912–3.957	0.000	2.060	1.308–3.245	0.002
Grade, n, %						
Grade I/II	Ref			Ref		
Grade III/IV	1.801	1.047–3.099	0.034	2.060	1.040–4.081	0.038
Unknown	0.289	0.787–2.233	0.289	2.011	1.044–3.873	0.037
Metastasis, n, %						
Others	Ref					
Lung	1.027	0.707–1.490	0.890			
Surgery, n, %						
yes	Ref			Ref		
no	1.692	1.216–2.356	0.002	1.743	1.195–2.541	0.004
Radiation, n, %						
yes	Ref					

$p < 0.2$ considered statistically significant in Univariate analysis; $p < 0.05$ considered statistically significant in Multivariate analysis;

Variables	Univariate analysis			Multivariate analysis
No/Unknown	1.124	0.829–1.527	0.450	
Chemotherapy, n, %				
yes	Ref			
No/Unknown	1.168	0.817–1.669	0.394	
p < 0.2 considered statistically significant in Univariate analysis; p < 0.05 considered statistically significant in Multivariate analysis;				

The C-indices were 0.722 (95% CI, 0.685 to 0.759) and 0.686 (95% CI, 0.61 to 0.760) for the internal validation and external validation of the OS nomogram, respectively. Similarly, the C-indices based on the CCS nomogram were 0.717 (95% CI, 0.678 to 0.757) and 0.695 (95% CI, 0.619 to 0.771) for the internal validation and external validation, respectively.

The AUCs for the 1- and 3-year OS and CCS nomograms in the training cohort (1-year OS AUC = 0.758, 3-year OS AUC = 0.757, 1-year CCS AUC = 0.756, 3-year CCS AUC = 0.741) and the validation cohort (1-year OS AUC = 0.717, 3-year OS AUC = 0.713, 1-year CCS AUC = 0.698, 3-year CCS AUC = 0.702) were all higher than those of each independent risk factor, which demonstrated that the nomograms had better discriminative ability (Fig. 3, Fig. 4).

As shown in the figure, the calibration plots of the OS and CCS nomograms showed excellent agreement between the actual survival and nomogram prediction for 1- and 3-year survival (Fig. 3, Fig. 4). Moreover, the DCA curves showed ideal net clinical benefits of the 1- and 3-year OS and CCS nomograms in the training and validation cohorts (Fig. 5).

Discussion

Primary spinal bone tumors with distant metastasis are considered to have a worse prognosis. With the development of surgery and medicine, we found that many factors are now part of the model that predicts OS and CCS.(2) However, no prognostic model has been constructed for spinal and pelvic bone tumor patients with distant metastasis. Therefore, it is necessary to determine prognostic risk factors that impact the 1- and 3-year OS and CCS and establish a model to predict the survival risk for these patients.

Multiple prognostic factors can affect the survival outcomes of cancer, and neglecting some significant risk factors may limit the ability to estimate patient survival prognosis.(5) Wong et al. reported that the range of variables considered is usually determined based on data availability and clinical evidence rather than on statistical significance.(14) Therefore, to predict prognosis precisely, we constructed nomograms based on a combination of four independent risk factors (patient age, histology, grade and

surgery) that were identified as significant independent risk factors associated with both OS and CCS in univariate and multivariate Cox proportional hazards regression analyses from 13 variables.

Most studies have demonstrated that tumor size is also a risk factor for the overall and cancer-specific survival prognosis of patients with spinal tumors. (4, 5, 15, 16) In our study, the size of the tumor was not associated with a statistically significant decrease in OS and CCS prognosis in the multivariate Cox analysis. Consistent with the findings of previous reports, we found that surgery was significantly associated with patient OS and CCS. In other words, patients who underwent surgery may have a better survival prognosis. Tumor histology was also an independent risk factor for patients diagnosed with spinal and pelvic tumors with distant metastases. Based on the nomograms, we observed that osteosarcoma patients with metastases may have a poor survival prognosis, especially cancer-specific survival. Patent age was an important independent risk factor to predict OS and CCS in our nomogram model. The optimal cutoff values of age (23 years and 68 years) were identified by X-tile software. Based on the cutoff value of age, we divided patients into 3 groups (< 23 years, 23–68 years and > 68 years) and further identified significant survival differences among the three age groups.

Nomograms for different histologies of spinal tumors have been constructed. Zheng et al constructed a nomogram to predict overall and cancer-specific survival in osteosarcoma patients.(15) In 2018, Song et al constructed a nomogram to predict the overall and cancer-specific survival of spinal chondrosarcoma patients.(5)

Zhou et al. reported that increasing age, distant metastasis, osteosarcoma, and non-surgery may be heightened risk factors for the CSS of patients initially diagnosed with osseous spinal and pelvic tumors. (17) In addition to patient age, histology, and surgery, grade has also been demonstrated to influence the survival of spinal and pelvic tumor patients with distant metastases in our study. Grade III/IV patients had high risk scores in the OS nomogram, similar to the CCS nomogram, which indicates that a higher grade of tumors was associated with poor prognosis.

The good C-indexes, calibration curves and DCA results in the training and validation cohorts indicate that the nomograms can predict the 1- and 3-year OS and CCS for patients with spinal and pelvic bone tumors with distant metastasis.

Some limitations of the study must be noted, which may reduce the predictive power of the nomograms. First, some inherent biases may be present in the retrospective study design and data from the SEER database. Second, the number of patients enrolled in the study was relatively small because some data were inevitably missing. Third, some potential risk factors may have been neglected in the study. Finally, the use of an independent large-scale database for external validation would improve the reliability of the prognostic models.

Conclusion

Our nomograms can accurately predict the 1- and 3-year OS and CSS of patients who are diagnosed with spinal and pelvic bone tumors with distant metastasis. We hope that our study can provide a reference for individual treatment and survival predictions.

Abbreviations

OS:Overall survival; CSS:Cancer specific survival; AUC:Area under curve; SEER:Surveillance, Epidemiology, and End Results; C-indexes:Concordance indexes; ROC:Receiver operating characteristic; DCA:Decision curve analysis

Declarations

Acknowledgments

Not applicable

Authors' contributions

HZ and XXM designed the study. HZ, CH, ZZZ, and QHT collected the data. HZ, CLZ, CZ, MK, and KZ conducted the analyses and interpreted the data. HZ and CW drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data supporting the findings of the current study are available within the article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author reports no conflicts of interest in this work.

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Figures

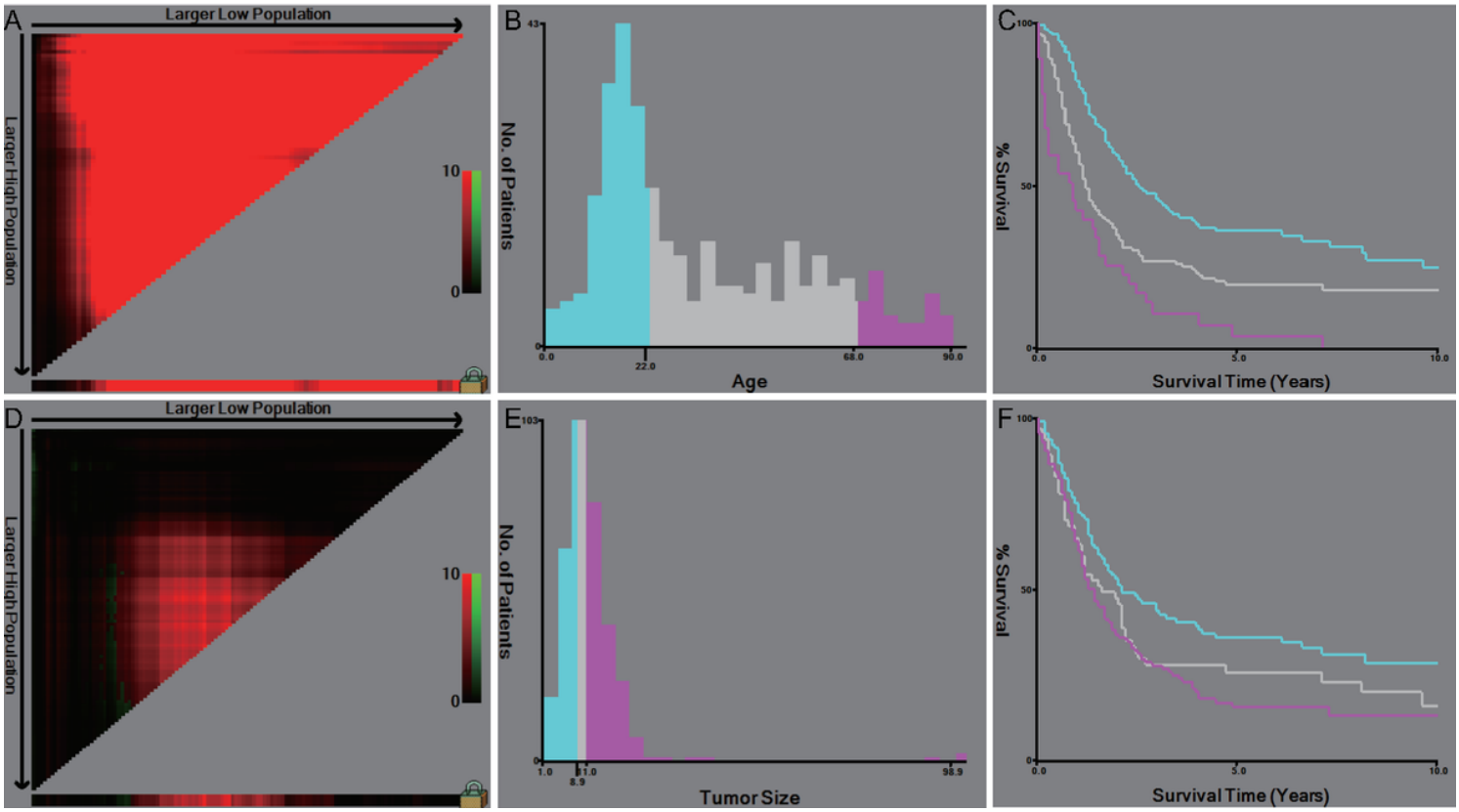

Figure 1

Defining the optimal cutoff values of age(A-C) and tumor size(D-F) via X-tile software. Notes: The optimal cutoff values of age and tumor size were identified as 23 years and 68 years, 9cm and 11cm based on overall survival, respectively. Histogram and Kaplan–Meier analysis were constructed based on the optimal cutoff values.

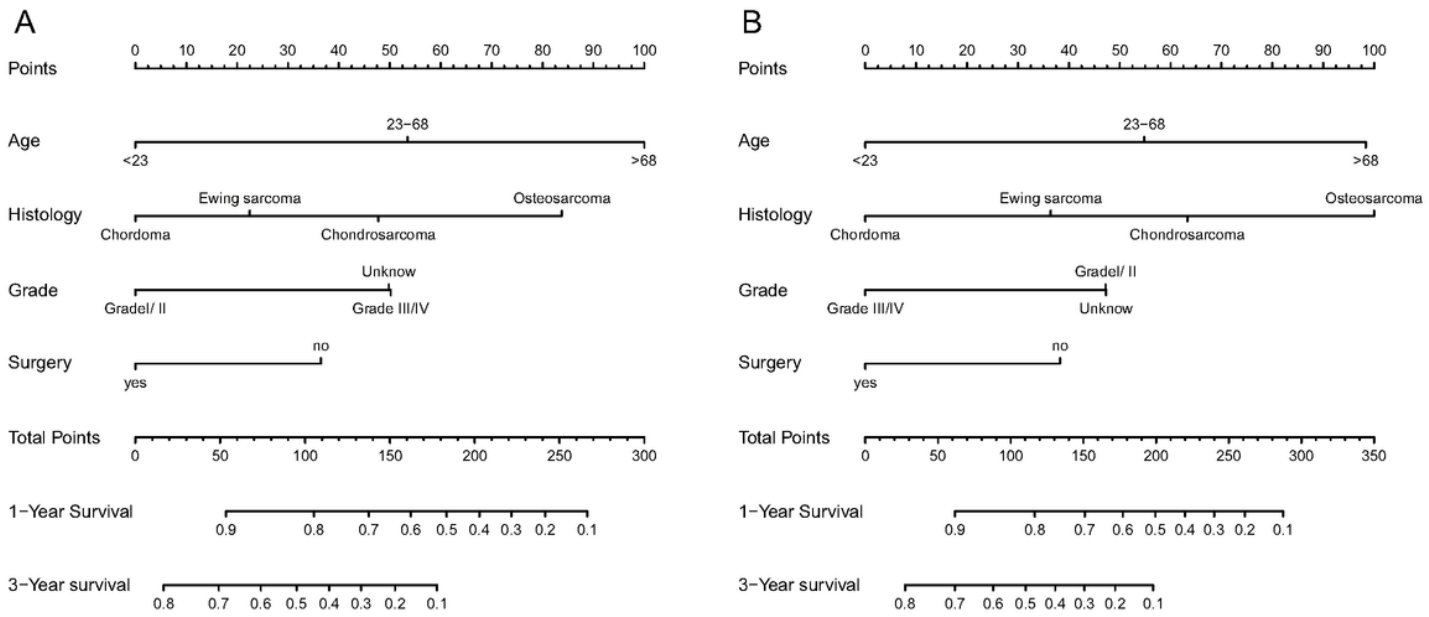

Figure 2

Nomograms for predicting the 1-, and 3-year overall survival (A) and cancer-specific (B) survival of spinal and pelvic tumor patients with distant metastasis. Notes: Sum the scores of each variable and draw a vertical line form the total score scale to obtain the survival probability.

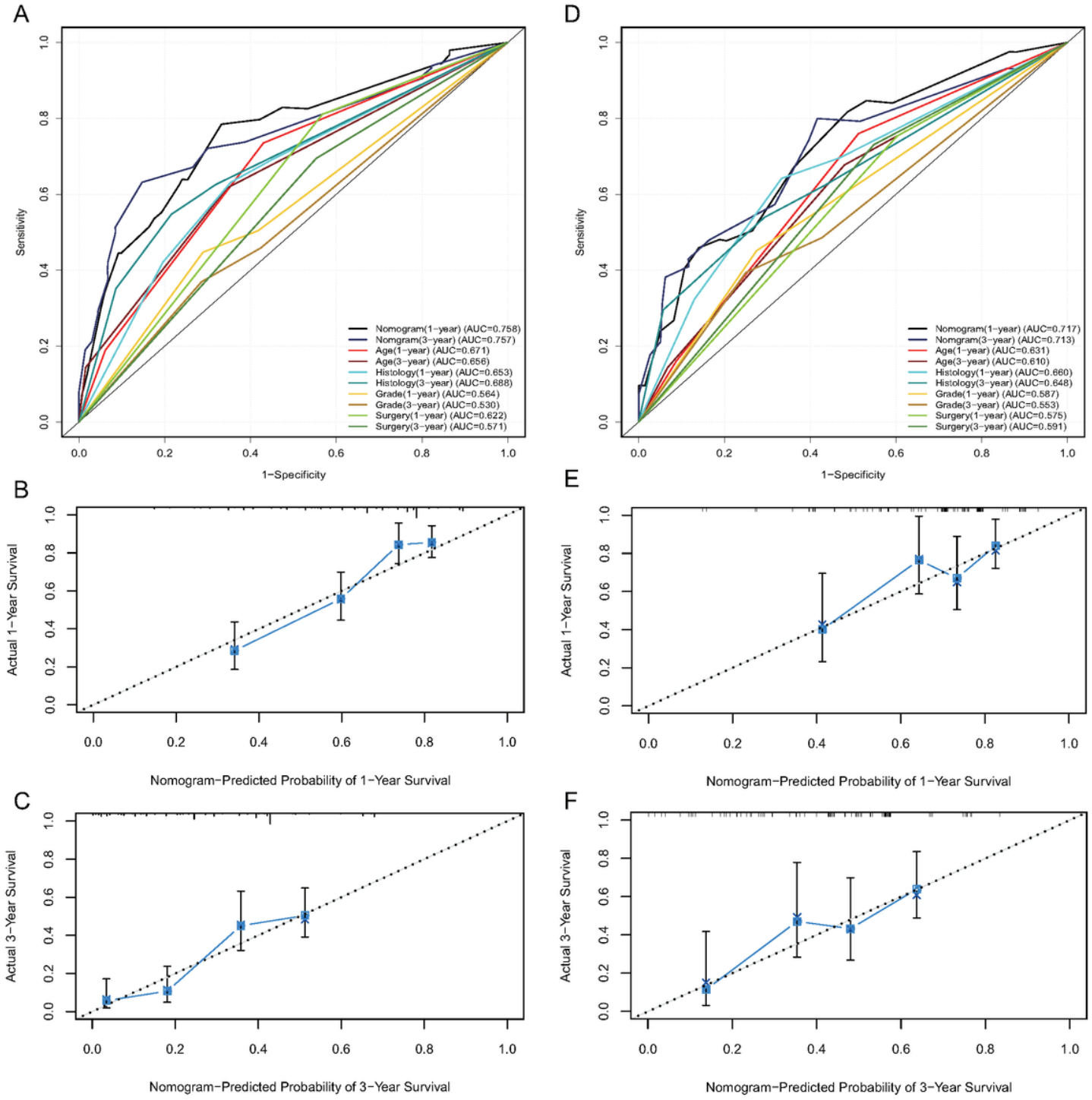

Figure 3

ROC curves of 1- and 3-year overall survival prognostic nomogram and each variable in the training cohorts (A) and validation cohort (D). Calibration plots of 1- and 3-year overall survival nomograms in the training cohorts (B-C) and validation cohort (E-F). Notes: ROC curves and Calibration curves were used to measure predicted results of the nomograms.

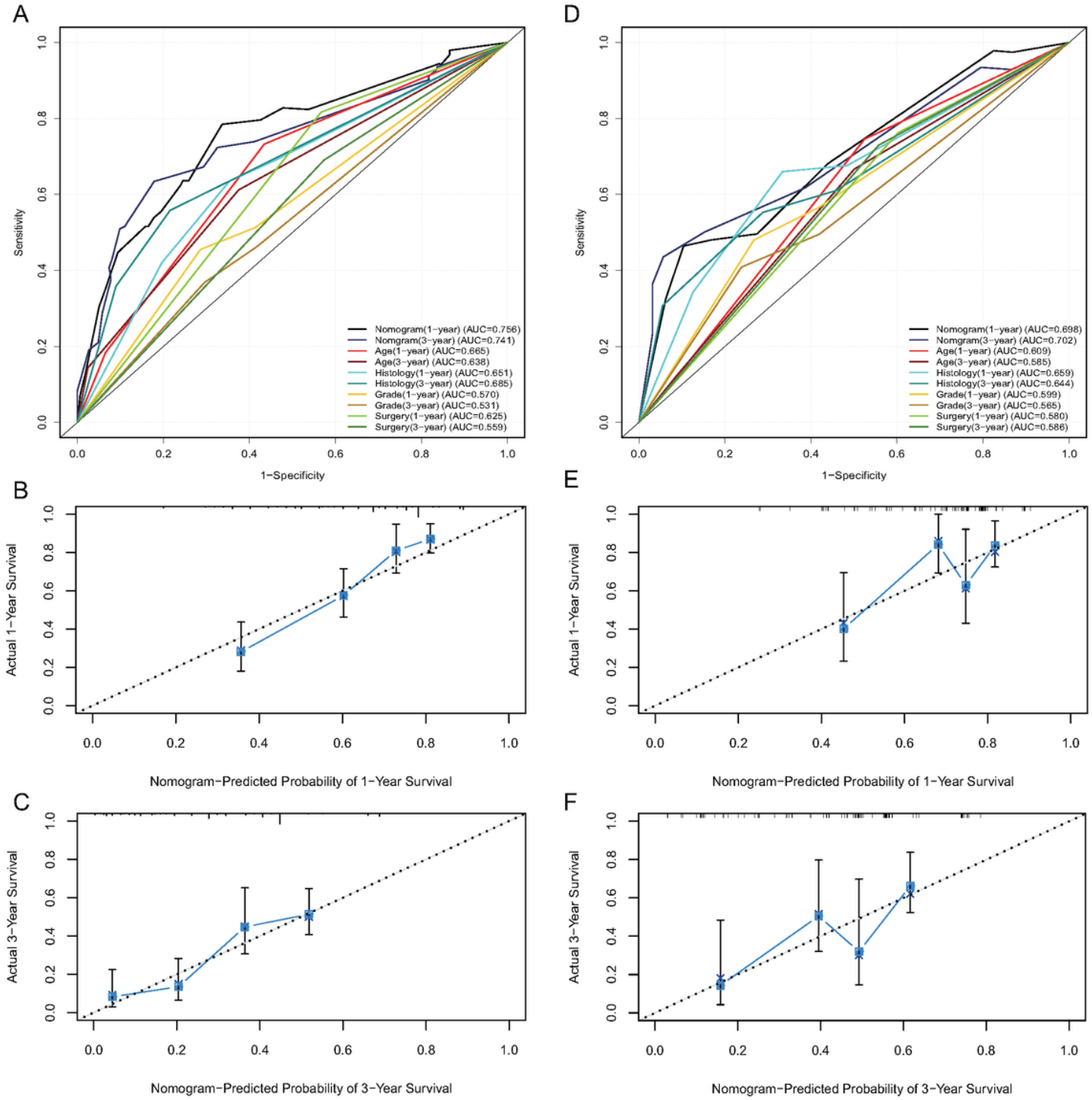

Figure 4

ROC curves of 1- and 3-year cancer-specific survival prognostic nomogram and each variable in the training cohorts (A) and validation cohort (D). Calibration plots of 1- and 3-year cancer-specific survival nomograms in the training cohorts (B-C) and validation cohort (E-F). Notes: ROC curves and Calibration curves were used to measure predicted results of the nomograms.

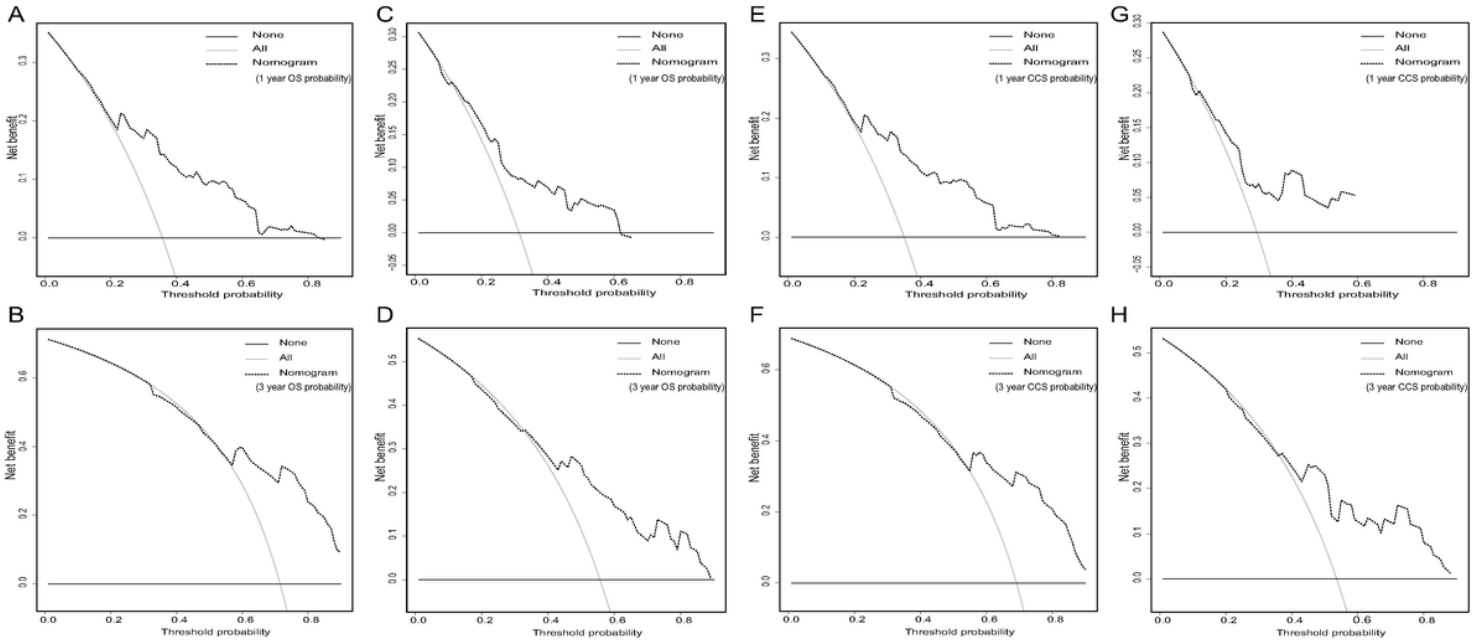

Figure 5

Decision curve analysis of the training cohort (A-B) and validation cohort (C-D) for 1- and 3-year overall survival. Decision curve analysis of the training cohort (E-F) and validation cohort (G-H) for 1- and 3-year cancer-specific survival. Notes: The horizontal axis is the threshold value and the vertical axis is the net benefit rate. The larger net benefit implies more benefit of the nomogram.