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Establishing a novel prognostic tool for Ewing sarcoma patients

Surveillance, Epidemiology, and End Results database analysis

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Abstract

Patients diagnosed with Ewing sarcoma (ES) usually experience poor outcomes. Accurate prediction of ES patients' prognosis is essential to improve their survival. Given that ES is a relatively rare tumor with a low incidence, we aim at developing a prognostic nomogram of ES patients based on a large sample analysis.

We used the Surveillance, Epidemiology, and End Results (SEER) database to screen eligible patients diagnosed ES of bone. This retrospective study presented the clinicopathological characteristics and prognosis of ES. We randomly assigned all ES patients to 2 sets (training set and validation set) with an equal number of patients. In order to identify independent factors of survival, we performed univariate and multivariate Cox analysis in the training set. Then, we constructed novel nomograms to predict survival of ES patients by integrating significant independent variables from the training set. The prognostic performance of constructed nomograms was examined using concordance index (C-index) and calibration curves in both training and validation set.

We included a total of 988 eligible cases diagnosed ES of bone between 2000 and 2015. Age >18 years, distant metastasis, tumor size >10 cm, and no surgery were independent risk factors for poorer survival. Our survival prediction nomograms were established based on those 4 independent risk factors. Good calibration plots were achieved in internal and external validation. The internal validation C-indexes of the nomogram for overall survival (OS) and cancer-specific survival (CSS) were 0.733 and 0.737, respectively. Similar good results were also achieved in external validation setting.

The established nomograms show good performance and allow for better evaluating the prognosis of ES patients and recommending appropriate instructions.

Abbreviations: C-index = concordance index, CSS = cancer-specific survival, ES = Ewing sarcoma, ICD-O-3 = 3rd edition of International Classification of Diseases for Oncology, OS = overall survival, SEER = surveillance, epidemiology, and end results.

Keywords: clinical tool, Ewing sarcoma, nomogram, prediction, prognosis

1. Introduction

Ewing sarcoma (ES) is the second most common primary malignancy of the bone and often occurs in children and adolescents.[1] Conventional therapies against ES consist of surgery, chemotherapy, and radiotherapy. With multidisciplinary treatment modalities, the 5-year survival rate for local ES has been reported to approach 65% to 80%.[2,3] However, the survival of ES patients presenting with metastasis usually have a poor prognosis. Approximately one-third of ES patients present clinically with metastatic disease.[4,5] ES patients with metastasis at diagnosis have a 5-year event-free survival rate between 20% and 30%.[2,6] Although many variables have been determined to have impact on the survival of ES patients, including age at diagnosis, tumor location, tumor size, tumor stage, surgery, chemotherapy, and radiotherapy,[4,7–12] survival prediction for ES is still difficult for clinicians. Therefore, it is necessary to establish a prognostic model that is easily accessible and technically feasible for survival prediction of ES patients.

Nomograms are recognized as a novel predictive tool to predict the clinical outcomes in various cancers by incorporating numerous predictors.[13–15] They are easy to determine the survival and very useful for decision-making. The present study was performed in order to establish a prognostic nomogram for ES based on a large population, which could guide individualized survival prediction and medical treatment.

2. Methods

2.1. Study design

All cases were obtained from the publicly available Surveillance, Epidemiology, and End Results (SEER) database (http://www.

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The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are publicly available.

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Table 1

Baseline demographics and clinical characteristics of 988 patients with Ewing sarcoma.

Category	All patients (n = 988)	Training cohort (n = 494)	Validation cohort (n = 494)
Mean age, yr	18.7	18.9	18.5
Age, yr			
≤18	616 (62.3%)	283 (57.3%)	291 (58.9%)
>18	372 (37.7%)	211 (42.7%)	203 (41.1%)
Gender			
Female	370 (37.4%)	168 (34.0%)	202 (40.9%)
Male	618 (62.6%)	326 (66.0%)	292 (59.1%)
Location			
Appendicular	435 (44.0%)	216 (43.7%)	219 (44.3%)
Axial	338 (34.2%)	170 (34.4%)	168 (34.0%)
Other locations	215 (21.8%)	108 (21.9%)	107 (21.7%)
Tumor size, cm			
<5	190 (19.2%)	89 (18.0%)	101 (20.4%)
5–10	499 (50.5%)	254 (51.4%)	245 (49.6%)
>10	299 (30.3%)	151 (30.6%)	148 (30.0%)
Extent of disease			
Localized	264 (26.7%)	129 (26.1%)	135 (27.3%)
Regional	418 (42.3%)	211 (42.7%)	207 (41.9%)
Distant	306 (31.0%)	154 (31.2%)	152 (30.8%)
Surgical treatment			
Yes	633 (64.1%)	312 (63.2%)	321 (65.0%)
No	355 (35.9%)	182 (36.8%)	173 (35.0%)
Radiation treatment			
Yes	498 (50.4%)	254 (51.4%)	244 (49.4%)
No	490 (49.6%)	240 (48.6%)	250 (50.6%)
Dead			
Yes	326 (33.0%)	172 (34.8%)	154 (31.2%)
No	662 (67.0%)	322 (65.5%)	340 (68.8%)

seer.cancer.gov/). Following the 3rd edition of International Classification of Diseases - Oncology (ICD-O-3), this retrospective study included ES cases (ICD-O-3 histologic type: 9260; ICD-O-3 musculoskeletal site code: C40.0–40.3, C40.8–41.4, C41.8–41.9) from 2000 to 2015.

The criteria for inclusion were listed below: diagnosis acquired from histology; diagnosis after 2000; primary ES of bone; and patients receiving chemotherapy. The criteria for exclusion were listed below: diagnosis acquired from clinical manifestation, imaging; site limited to soft tissues; and cases with missing tumor size, tumor stage, surgery, radiotherapy, or survival time. Finally, we randomly divided 988 ES patients into 2 sets (training set, n = 494 and validation set, n = 494). Patient identification information was absent in this cancer database. The present study used retrospective and anonymized data from the SEER database, and was exempt from ethics committee approval.

2.2. Clinical and outcome variables

Age at diagnosis, gender, tumor site, tumor stage, tumor size, surgery, radiotherapy, chemotherapy, death cause, and survival time were extracted from the cancer database. We chose 18 years old as a cutoff point for ES patients because it was a negative factor of survival among ES patients.[11] Outcome variables included overall survival (OS) and cancer-specific survival (CSS). We calculated OS as the interval from diagnosis to death from any cause, and CSS as the interval from diagnosis to death from EW.[16] The follow-up period was from the date of diagnosis with ES to December 2015.

2.3. Construction and validation of survival nomogram

Both univariate and multivariate analyses were performed to obtain independent variables via the Cox proportional hazards model in the training set. We then integrated those independent risk factors to develop nomograms. The prognostic performance of constructed nomograms was examined using concordance index (C-index) and calibration curves[17] in both training and validation sets. We performed statistical analyses with the help of IBM SPSS Statistics 22 software and the R 3.5.0 software (http://www.r-project.org/).

3. Results

3.1. Basic characteristics

The sociodemographic and clinical characteristics of 988 ES patients from 2000 to 2015 are presented in Table 1. There were 618 (62.6%) males and 370 (37.4%) females, and their mean age at diagnosis was 18.7 years (training set, 18.9 years old and validation set 18.5 years old). Tumors in 435 (44.0%) patients were located in the limbs. Approximately one-third of ES patients (31.0%) present with metastatic disease at diagnosis. Over half of the ES patients received radiotherapy (50.4%) or surgery (64.1%). Of these 988 patients, 326 (33.0%) patients died and the 5-year OS rate was 64.7%.

3.2. Independent predictors for ES

Table 2 summarize the results of univariate Cox regression analysis of survival in the training set. Age, tumor site, extent of

Table 2

Univariate analysis of OS and CSS in the training cohort (n = 494).

Category	OS (Log-rank *P*)	CSS (Log-rank *P*)
Age at diagnosis (≤18 vs >18)	<.001	<.001
Gender (female vs male)	.556	.341
Location	.002	.001
appendicular vs axial	.001	<.001
appendicular vs other location	.135	.175
axial vs other location	.124	.078
Extent of disease	<.001	<.001
Distant vs localized	<.001	<.001
Distant vs regional	<.001	<.001
Regional vs localized	.208	.245
Tumor size	<.001	<.001
>10 cm vs <5 cm	<.001	<.001
>10 cm vs 5–10 cm	.051	.049
5–10 cm vs <5 cm	.004	.005
Surgical treatment (yes vs no)	<.001	<.001
Radiation treatment (yes vs no)	.053	.076

CSS = cancer-specific survival, OS = overall survival.

disease, tumor size, and surgery were significant variables of predicting OS and CSS. The results of multivariate Cox analyses in the training set are summarized in Table 3. Age >18 years, distant metastasis, tumor size >10 cm, and no surgery were independent risk factors for poorer OS and CSS.

3.3. Nomogram construction and validation

We incorporated significant independent risk factors of survival from the ES training set into developing survival prediction nomograms (Figs. 1 and 2). Extent of disease contributed most to both OS and CSS based on survival prediction nomograms. The prognosis of each patient can be easily predicted by summing up the scores assigned to each predictor and correlating the total points with the survival (Table 4).

Internal and external validation of the newly established survival prediction nomograms was required and performed. The C-indexes of the nomogram for OS and CSS in internal validation (training set) were 0.733 [95% confidence interval (95% CI), 0.696–0.770] and 0.737 (95% CI, 0.699–0.775), respectively. The C-indexes of the nomogram for OS and CSS in external validation (validation set) were 0.702 (95% CI, 0.658–0.746) and 0.711 (95% CI, 0.667–0.755), respectively. Good calibration plots were achieved in internal and external validation (Figs. 3 and 4).

4. Discussion

4.1. Main findings of the present study

We first identified 4 independent risk factors of survival from the training set and then integrated them to develop survival prediction nomograms for ES patients. These proposed nomograms exhibited wonderful discrimination both internally and externally. In addition, the calibration curves revealed good survival prediction of the proposed nomograms.

4.2. Comparison with other studies

Our data showed that age, extent of disease, tumor size, and surgical resection were significant independent risk factors of OS and CSS. Age less than 18 years was significantly associated with improved survival, which was also confirmed by other

Table 3

Multivariate analysis for OS and CSS in the training cohort (n = 494).

	OS		CSS	
Variable	**Hazard ratio (95% CI)**	***P***	**Hazard ratio (95% CI)**	***P***
Age, yr				
≤18	1		1	
>18	1.961 (1.438–2.674)	<.001	1.863 (1.353–2.566)	<.001
Gender				
Female	1	.857	1	.825
Male	0.971 (0.703–1.341)		1.039 (0.740–1.458)	
Location				
Appendicular	1	.193	1	.115
Axial	1.279 (0.883–1.855)	.053	1.360 (0.928–1.992)	.102
Other locations	1.528 (0.995–2.347)	.309	1.455 (0.929–2.281)	.360
Extent of disease				
Localized	1	<.001	1	<.001
Regional	1.285 (0.793–2.080)	.050	1.266 (0.764–2.100)	.072
Distant	3.194 (1.981–5.149)	.004	3.413 (2.078–5.604)	.007
Tumor size, cm				
<5	1	.004	1	.014
5–10	1.696 (1.000–2.878)		1.648 (0.956–2.843)	
>10	2.239 (1.287–3.894)	.362	2.202 (1.247–3.888)	.337
Surgical treatment				
Yes	1		1	
No	1.690 (1.179–2.422)		1.588 (1.098–2.297)	
Radiation treatment				
Yes	1		1	
No	1.164 (0.840–1.612)		1.178 (0.843–1.645)	

CSS = cancer-specific survival, OS = overall survival.

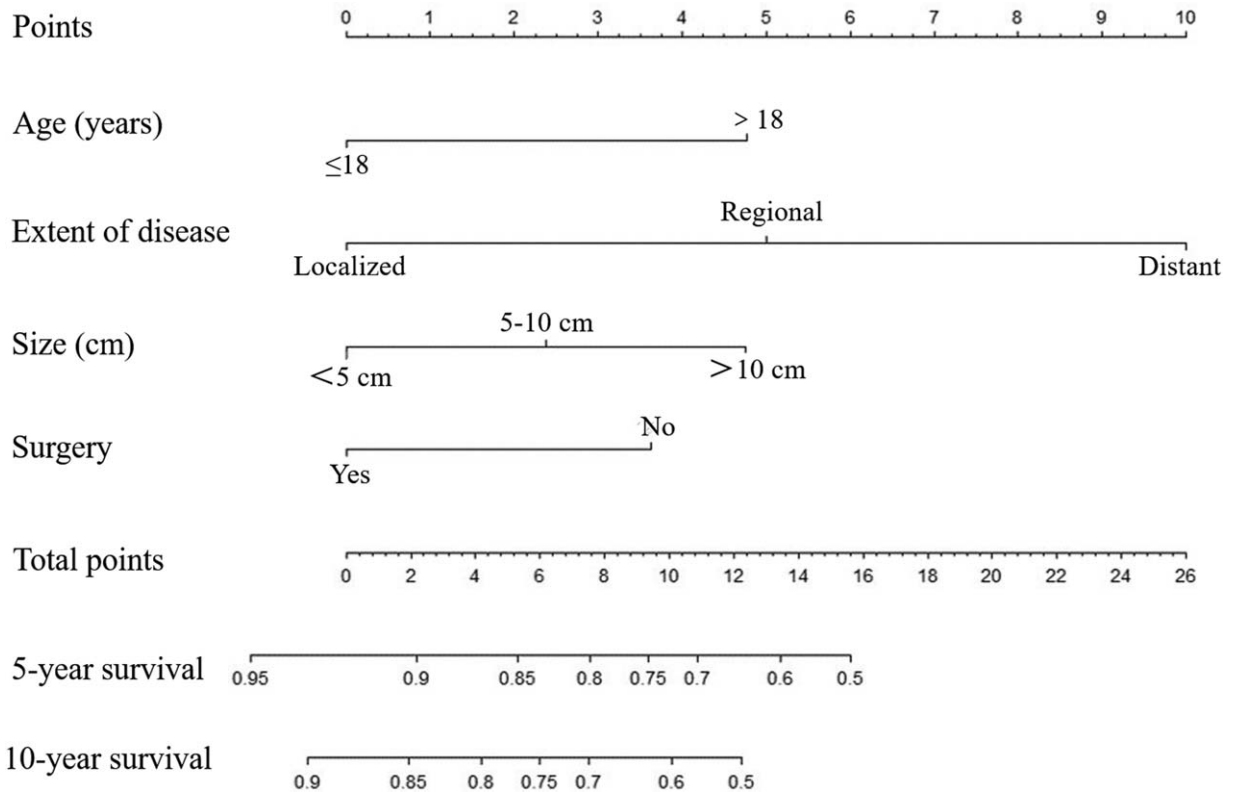

Figure 1. Nomogram for predicting 5- and 10-year OS of ES patients.

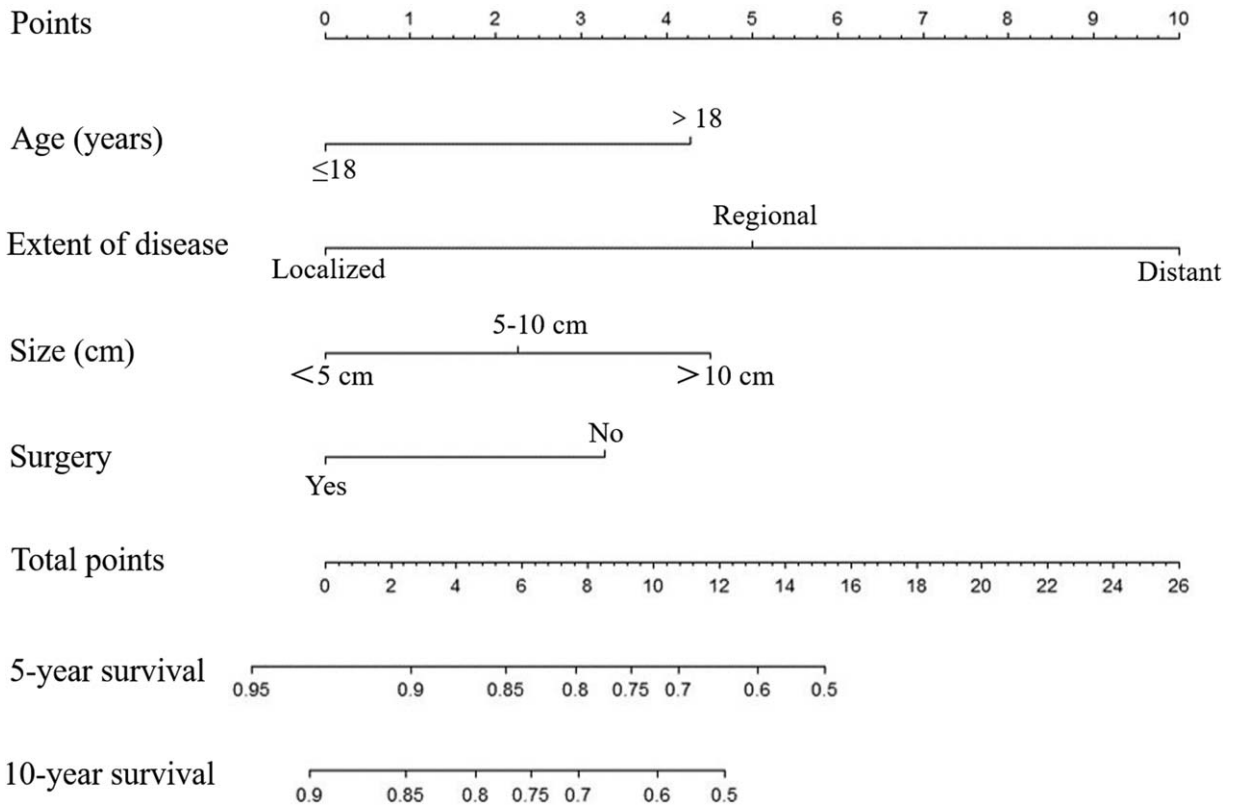

Figure 2. Nomogram for predicting 5- and 10-year CSS of ES patients.

Table 4

Point assignment and prognostic score.

Variable	OS nomogram	CSS nomogram
Age, yr		
≤18	0.0	0.0
>18	4.8	4.3
Extent of disease		
Localized	0.0	0.0
Regional	5.0	5.0
Distant	10.0	10.0
Tumor size, cm		
<5	0.0	0.0
5–10	2.4	2.3
>10	4.8	4.5
Surgical treatment		
Yes	0.0	0.0
No	3.6	3.3

studies.[4,18,19] However, the precise mechanism remains unknown. This study found axial tumor location had no independent effect on survival in ES patients. Bacci et al[19] achieved the same result and supported our conclusion. However, Cotterill et al[21] performed multivariate analysis and found that ES patients with axial tumors experienced poorer survival. The prognostic significance of axial tumor location for ES patients needs to be investigated further. ES patients with distant metastasis usually experienced poor prognosis,[4,20] which was consistent with our results. Our data showed tumor size less than 10 cm was an independent variable of improved survival, which was consistent with previous research results.[4,21,22] Surgery remains the major therapy for ES and is associated with increased survival.[11] Our multivariate analysis identified surgery as a significant and independent variable of prolonged survival. ES patients who performed radiotherapy could obtain better local control and present with lower local recurrence rates.[23] However, our study showed that radiotherapy was not associated with survival.

4.3. Implication and explanation of findings

We constructed the survival prediction nomograms based on four easily accessible and independent variables (Figs. 1 and 2). Furthermore, we validated nomograms with high discriminatory power (C-index, 0.733 for OS and 0.737 for CSS) and good calibration plots. Patients with high nomogram scores should be followed closely. Taken together, our proposed nomograms can clearly reflect the influence of each predictor and accurately predict the prognosis of ES patients.

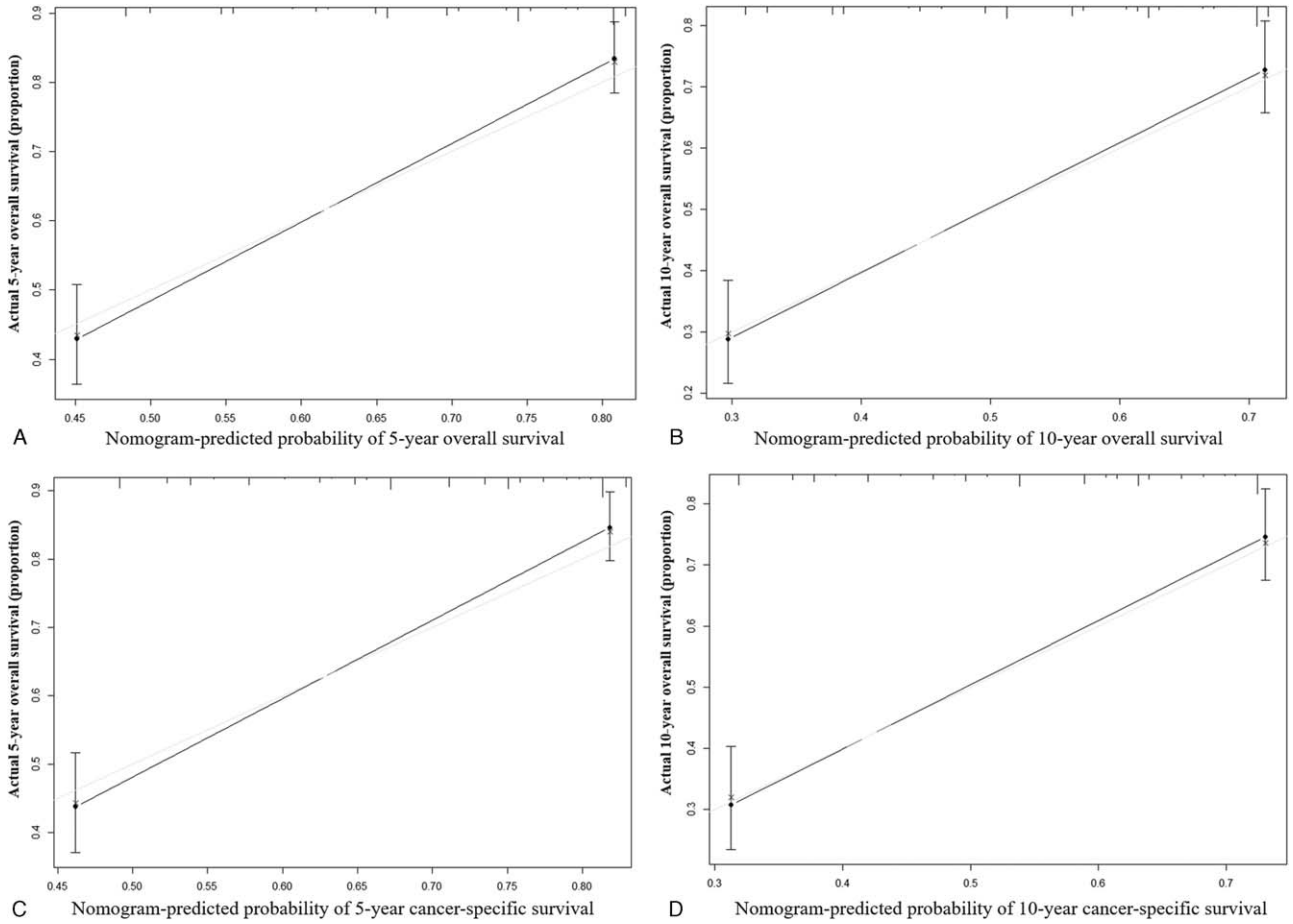

Figure 3. Calibration curves compare predicted and actual OS at 5-year (A), 10-year (B), and CSS at 5-year (C), 10-year (D) in the training set.

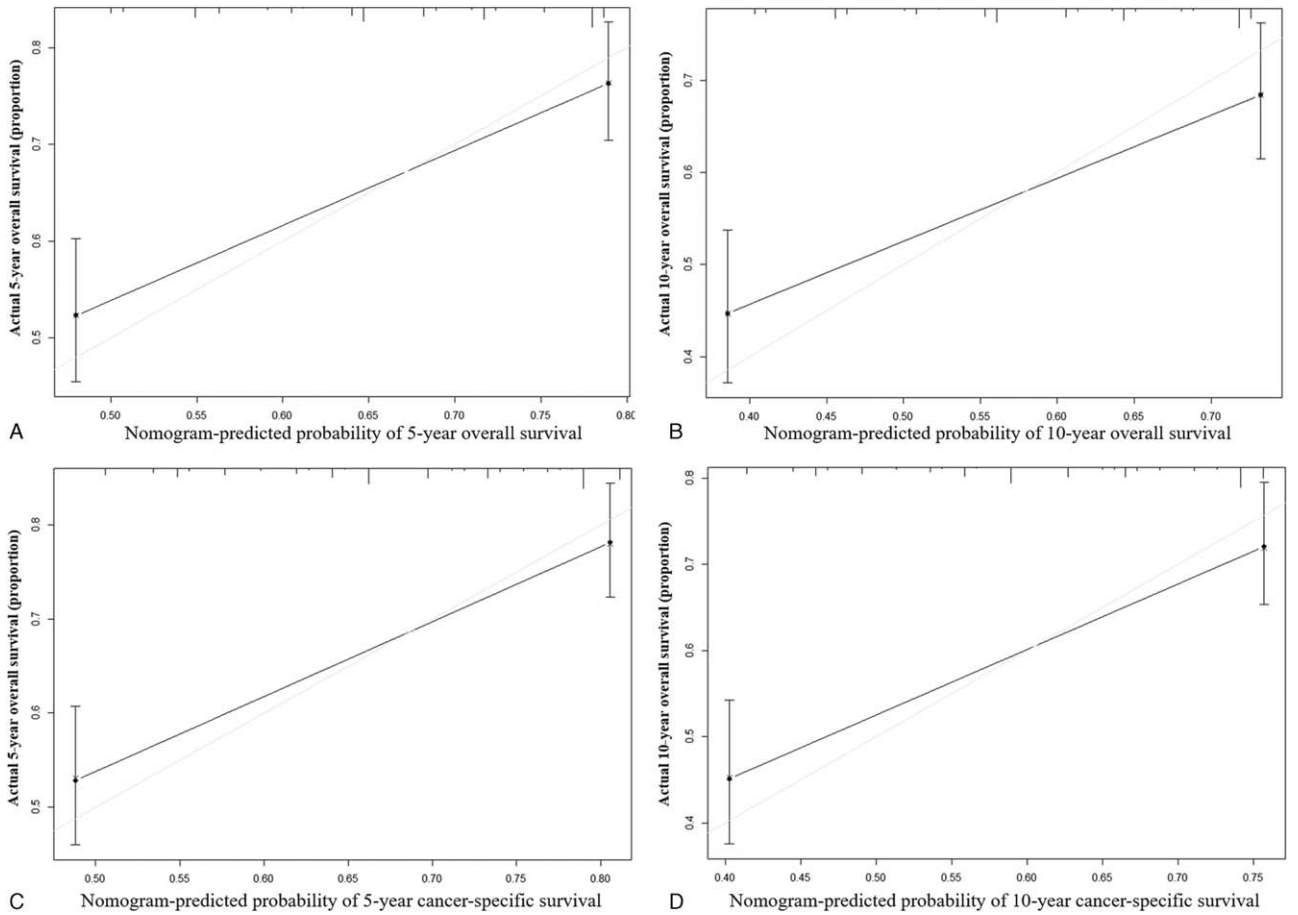

Figure 4. Calibration curves for 5-year (A), 10-year (B) OS, and 5-year (C), 10-year (D) CSS in the validation set.

4.4. Strengths and limitations

There are some limitations that need to be pointed out. We only included those patients who had complete information for survival analysis, which might generate potential selection bias. Second, this cancer database lacks severable important variables such as treatment procedure and gene or protein expression differences, which might affect the prognosis. Nevertheless, the SEER database provides an opportunity to study rare tumors such as ES of bone. In addition, this cancer database is updated annually to facilitate clinical research.

4.5. Recommendation and future directions

The novel nomograms provided an insightful and applicable tool to evaluate the prognosis of ES patients. In the future, more clinical variables should be analyzed and included to further improve the accuracy of the nomogram models. More databases from different countries should be applied for external validation.

5. Conclusion

The established nomograms show good performance and allow for better evaluating the prognosis of ES patients and recommending appropriate instructions. Nevertheless, further research is required for validation.

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Methodology: Feng Gao, Yuanxi Zhou, Renbo Zhao.
Project administration: Feng Gao.
Supervision: Yingqing Ren.
Writing – original draft: Feng Gao.
Writing – review & editing: Yingqing Ren.

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