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The development and external validation of a web-based nomogram for predicting overall survival with Ewing sarcoma in children

Yi Chen[1,2*], Zirui Liu[1,2*], Yaobin Wang[1,2], Hongwei Zhan[1,2], Jinmin Liu[1,2], Yongkang Niu[1,2], Ao Yang[1,2], Fei Teng[1,2], Jinfeng Li[3], Bin Geng[1,2], and Yayi Xia[1,2]

Abstract

Background: Ewing sarcoma remains the second most prevalent primary aggressive bone tumor in teens and young adults. The aim of our study was to develop and validate a web-based nomogram to predict the overall survival for Ewing sarcoma in children.

Methods: A total of 698 patients, with 640 cases from the Surveillance, Epidemiology, and End Results (the training set) and 58 cases (the external validation set), were included in this study. Cox analyses were carried out to determine the independent prognostic indicators, which were further included to establish a web-based nomogram. The predictive abilities were tested through the concordance index, calibration curve, decision curve analysis, and area under the receiver operating characteristic curve.

Results: As suggested by univariate and multivariate Cox analyses, age, primary site, tumor size, metastasis stage (M stage), and chemotherapy were included as the independent predictive variables. The area under the receiver operating characteristic curve values, calibration curves, concordance index, and decision curve analysis from training and validation groups suggested the model has great clinical applications.

Conclusion: We developed a convenient and precise web-based nomogram to evaluate overall survival for Ewing sarcoma in children. The application of this nomogram would assist physicians and patients in making decisions.

Keywords: Nomogram, Ewing sarcoma, prognosis, overall survival, children

Introduction

Ewing sarcoma (ES) is still the second most frequent primary aggressive bone tumor in teens and young adults, with a significant risk of metastasis.[1–3] During 1973 and 2004, the incidence of ES is 1 per 330,000 people in the United States, which indicates that data collected at one single research center cannot provide enough sample sizes.[4] With chemotherapy regimens of varying doses and schedules, the 5-year survival rate for patients with ES is approximately 70%, while the 5-year survival rate for patients with metastases is relatively low, ranging from 15% to 30%.[5,6] Metastases are most commonly found in the lungs (50%), bones (25%), and bone marrow (20%).[7] The prognosis for overall survival (OS) may differ from patient to patient. Individualized treatment is crucial since patients' survival times can vary, and the treatments should be tailored to each patient.[8] Clinically, ES patients' prognosis is influenced by a combination of

[1]Department of Orthopaedics, Lanzhou University Second Hospital, Lanzhou, China
[2]Orthopaedics Key Laboratory of Gansu Province, Lanzhou, China
[3]Department of Orthopaedics, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

*These authors have contributed equally to this work and share first authorship.

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Corresponding Author:
Yayi Xia, Department of Orthopaedics, Lanzhou University Second Hospital, Lanzhou, Gansu, 730030, China.
Email: xyylzu@126.com

factors, with the final conclusions varying due to the different study methods used and influencing factors analyzed by different researchers and the low incidence of ES. ES patients exhibit unique clinical characteristics, making the development of prognostic tools urgently essential. Therefore, a comprehensive set of prediction methods of ES is crucial to impede the advancement of disease and predict the OS.

As a tool for predicting future events, the nomogram is visualized as a way to represent a model of prediction that can be used to calculate the probability of outcomes for every individual in the future.[9–11] Using this graph, the probability of various events is calculated for each individual based on multiple factors. In addition, the nomogram has been proven to be a reliable indicator of tumor prognosis in numerous studies.[12–14] Risk estimation can be readily individualized and visualized through the nomogram, facilitating physicians in the decision-making process.[15,16] However, prediction models for ES in children are still not well established. In addition, the inconvenient risk calculation methods of ordinary graphical nomograms may confine their clinical applicability.[17,18] In children, ES poses a serious threat to their health. Hence, we used the Surveillance, Epidemiology, and End Results (SEER) database to extract data from ES patients in children, aiming to develop and validate a web-based nomogram that predicts OS of childhood ES.

Materials and methods

We conducted a retrospective analysis of the SEER database from 2004 to 2015 and also collected data on patients admitted to our hospital. All children under 18 years of age diagnosed with bone ES were included. The SEER data include clinically relevant information on patients with a variety of tumor types in the United States from 1973 to 2016, covering more than 30% of the total population, and are the most detailed and authoritative clinical database providing evidence-based medical evidence.[19] Data from the SEER cancer registries can be used without the need for informed patient consent, and none of the information used is identifiable.

The inclusion criteria comprises (1) age less than 18 years; (2) diagnosed as ES of the bones with International Classification of Diseases for Oncology, 3rd Edition/ World Health Organization (ICD-O-3/WHO) 2008 morphology codes 9260 from the SEER database and the only tumor and primary tumor diagnosed; (3) complete clinical information; and (4) complete survival time records.

The exclusion criteria comprises (1) unknown tumor size; (2) non-primary tumor; (3) incomplete information on survival status; and (4) treament information were unknown.

Patients were categorized according to their clinicopathological features: (1) age (0–6 years, 6–12 years, 12–18 years); (2) race (white, black, or other); (3) sex (male or female); (4) primary site[20,21] (axial (skull, pelvis, spine, or ribs), extremity (long or short bones of the upper or lower extremities), or other locations); (5) tumor size (<5 cm, 5–10 cm, >10 cm); (6) Tumor, Lymph Node, Metastasis (TNM) staging (T-stage, N-stage, M-stage); (7) surgery (yes or no); (8) radiotherapy (yes, no/unknown); (9) chemotherapy (yes, no/unknown).

Nomogram construction

The cohort from the SEER database was included in the training group, and the cohort from our hospital was included in the validation group. This nomogram was built using data gathered from the training group. Using univariate and multivariate Cox regression analyses, we determined the survival-related variables. The nomogram was further developed in light of the multivariate Cox regression results.

Nomogram validation

The nomogram was validated by using both the training and validation groups. The concordance index (C-index), calibration curve, and area under the receiver operating characteristic curve (AUC) were used as measures of the nomogram's discrimination. An evaluation of the fit of a nomogram between the predicted and observed values is performed by calibrating curves. In addition, we assessed the clinical usefulness and net benefits of the nomogram using decision curve analysis (DCA).

Development of web-based nomogram

To facilitate running dynamic nomogram on the network, we registered a cloud account at https://www.shinyapps.io/ and finally obtained the network version of the development of web-based nomogram.

Statistical analysis

We used SPSS statistics software (26.0) to perform chi-square tests. The rest of the statistical analyses were conducted by R software (4.1.1). P values < 0.05 (both sides) were considered statistically significant.

Results

Baseline information

According to the inclusion and exclusion criteria, 698 patients with ES have been identified. The ES patients included the training (640) and validation (58) sets. In Table 1, there were significant differences between the two groups in terms of race, and the two groups were similar in other aspects such as demographics and clinical information.

Table 1. Demographic and clinical information.

Variables	Total cohort, n = 698		Training cohort, n = 640		Validation cohort, n = 58		*P* value
	n	%	n	%	n	%	
Age (years)							0.299
0–6	84	12.0	79	12.3	5	8.6	
6–12	268	38.4	247	38.6	21	36.2	
12–18	346	49.6	314	49.1	32	55.2	
Sex							0.519
Female	285	40.8	259	40.5	26	44.8	
Male	413	59.2	381	59.5	32	55.2	
Race							<0.001
Black	20	2.9	20	3.1	0	0	
White	566	81.1	566	88.4	0	0	
Other	112	16.0	54	8.5	58	100	
Primary site							0.863
Axial	291	41.7	269	42.0	22	37.9	
Extremity	260	37.2	235	36.7	25	43.1	
Other	147	21.1	136	21.3	11	19.0	
Radiotherapy							0.422
Yes	324	46.4	300	46.9	24	41.4	
No/Unknown	374	53.6	340	53.1	34	58.6	
Chemotherapy							0.232
Yes	679	97.3	624	97.5	55	94.8	
No/Unknown	19	2.7	16	2.5	3	5.2	
Surgery							0.322
Yes	221	31.7	206	32.2	15	25.9	
No	477	68.3	434	67.8	43	74.1	
Tumor size(cm)							0.296
<5	165	23.6	149	23.3	16	27.6	
5–10	325	46.6	297	46.4	28	48.3	
>10	208	29.8	194	30.3	14	24.1	
T stage							0.295
T1	343	49.1	310	48.4	33	56.9	
T2	328	47.0	305	47.7	23	39.7	
T3	14	2.0	13	2.0	1	1.7	
Tx	13	1.9	12	1.9	1	1.7	
N stage							0.609
N0	619	88.7	568	88.7	51	87.9	
N1	47	6.7	44	6.9	3	5.2	
Nx	32	4.6	28	4.4	4	6.9	
M stage							0.227
M0	889	72.3	477	74.5	39	67.2	
M1	341	27.7	163	25.5	19	32.8	

Prognostic factors in the training cohort

The preliminary analyses are summarized in Table 2. Univariate Cox analysis indicated that age, primary site, radiotherapy, chemotherapy, surgery, tumor size, and T/N/M stage were risk factors in children with ES. The results of the multivariate Cox analysis suggested that age, primary site, chemotherapy, tumor size, and M Stage were independent prognostic factors for childhood OS.

Construction of the nomogram

Five independent variables of age, primary site, chemotherapy, tumor size, and stage M were integrated into the model, and then the nomogram of 1-year, 3-year, and 5-year survival rates for childhood ES was constructed (Figure 1). According to the patient's corresponding prognostic factors, a vertical line is drawn to the score scale to obtain a specific score, and then the scores of all variables

Table 2. Cox analyses in the training cohort.

	Univariate Cox analysis (n = 640)		Multivariate Cox analysis (n = 640)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
<6	Reference		Reference	
6–12	1.842 (0.939–3.614)	0.076	1.589 (0.801–3.151)	0.186
12–18	2.680 (1.398–5.137)	0.003	2.006 (1.027–3.918)	0.042
Sex				
Female	Reference			
Male	1.026 (0.750–1.404)	0.872		
Race				
Black	Reference			
White	1.385 (0.513–3.741)	0.520		
Other	1.464 (0.482–4.449)	0.502		
Primary site				
Axial	Reference		Reference	
Extremity	0.530 (0.366–0.766)	<0.001	0.673 (0.457–0.991)	0.045
Other	0.771 (0.522–1.138)	0.190	0.959 (0.628–1.464)	0.845
Radiotherapy				
Yes	Reference		Reference	
No/Unknown	0.498 (0.363–0.683)	<0.001	0.814 (0.573–1.155)	0.248
Chemotherapy				
Yes	Reference		Reference	
No/Unknown	3.075 (1.510–6.265)	0.002	3.669 (1.708–7.882)	<0.001
Surgery				
Yes	Reference		Reference	
No	0.529 (0.388–0.722)	<0.001	0.887 (0.629–1.250)	0.492
Tumor size (cm)				
<5	Reference		Reference	
5–10	1.767 (1.108–2.817)	0.017	1.596 (0.957–2.661)	0.073
>10	2.559 (1.589–4.121)	0.001	2.171 (1.154–4.086)	0.016
T stage				
T1	Reference		Reference	
T2	1.545 (1.119–2.132)	0.008	0.802 (0.509–1.265)	0.342
T3	3.029 (1.308–7.014)	0.010	1.469 (0.601–3.591)	0.399
Tx	2.794 (1.123–6.951)	0.027	1.558 (0.581–4.173)	0.378
N stage				
N0	Reference		Reference	
N1	2.136 (1.321–3.456)	0.002	1.420 (0.851–2.369)	0.180
Nx	1.709 (0.924–3.161)	0.088	1.021 (0.533–1.959)	0.949
M stage				
M0	Reference		Reference	
M1	3.958 (2.904–5.395)	<0.001	2.931 (2.052–4.187)	<0.001

HR: hazard ratio; CI: confidence interval.

are summed to calculate the overall score, which is matched with the outcome scale to obtain the predicted survival probability.

Validation of the nomogram

The AUC values for the 1-, 3-, and 5-year prognosis in the training set were 0.754, 0.739, and 0.740, respectively. While they were 0.733, 0.741, and 0.745, respectively, in the validation group, suggesting that the nomogram is good at discriminating events and reliable predictive efficacy (Figure 2). The C-index can be used to assess how well a prediction model corresponds to actual results. The C-index for the training and validation set were 0.73 and 0.71, respectively. In general, a high C-index is a measurement of the ability to differentiate distinctive patients' survival outcomes. According to Figure 3, the calibration curves reflect the agreement between predicted probability

and observed endings for 1-, 3-, and 5-year survival in children. We utilize DCA to evaluate the nomogram's clinical value and net benefits (Figure 4).

Web-based nomogram

With the help of "DynNom" software, a network-based nomogram was constructed to compute the OS for childhood ES (https://chenlzu.shinyapps.io/DynNomapp/). By entering the patient's demographic and clinical information, we can calculate the score for this patient and obtain the survival curve and OS according to the corresponding scores. For example, in a 3-year-old white female ES patient, the primary site was at central axis bone, the tumor size was 4 cm, and it had not metastasized. In addition, the patient accepted the treatment of chemotherapy. After entering the aforementioned information in the web-based nomogram, we can obtain the evaluatation of the patient's OS at 12, 36, and 60 months to be 97%, 79%, and 62%, respectively (Figure 5).

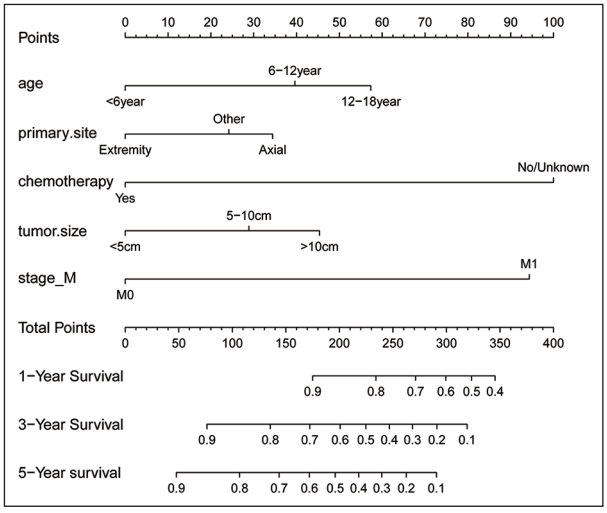

Figure 1. Nomogram for predicting 1-, 3-, and 5-year survival of children with Ewing sarcoma.

Discussion

ES is an aggressive tumor and constitutes less than 5% of all soft-tissue sarcomas.[3] Most cases involve 10- to 15-year-olds, but about 30% of cases are among children under the age of 10 years, and another 30% affect adults over 20 years of age.[4] Hence, our study used a large sample size from the SEER database. To make our findings more credible, we included a total of 698 patients, with 640 cases from the SEER program from 2004 to 2015 (the training set) and 58 cases from the first Affiliated Hospital of Zhengzhou University (the external validation set). In our study, multivariate Cox regression analyses showed that age is an independent prognostic risk element for ES patients. The results of the nomogram model showed that patients aged 12–18 years with ES have significantly higher scores than other age groups. Patients aged 12–18 years with ES might have more complications and have poorer physical tolerance, which makes early detection, prognostic monitoring, and follow-up of ES particularly

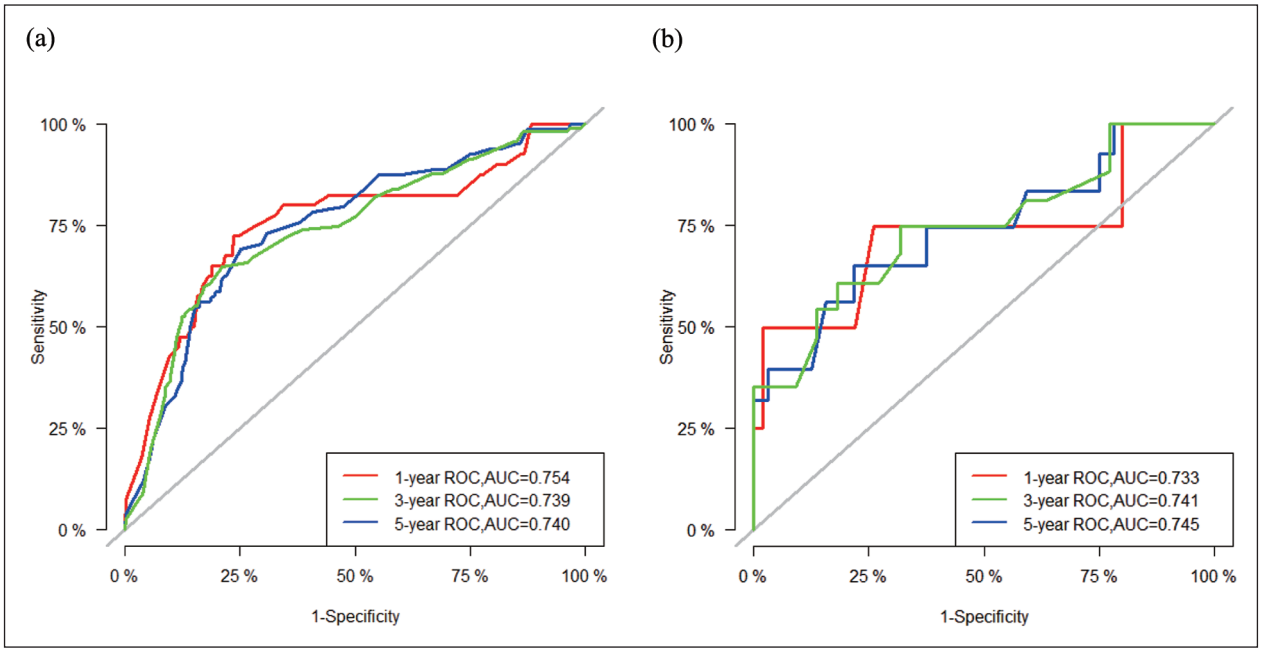

Figure 2. The AUC ROC values at 1, 3, and 5 years of the training (a) and validation (b) sets.
AUC ROC: area under the receiver operating characteristic curve.

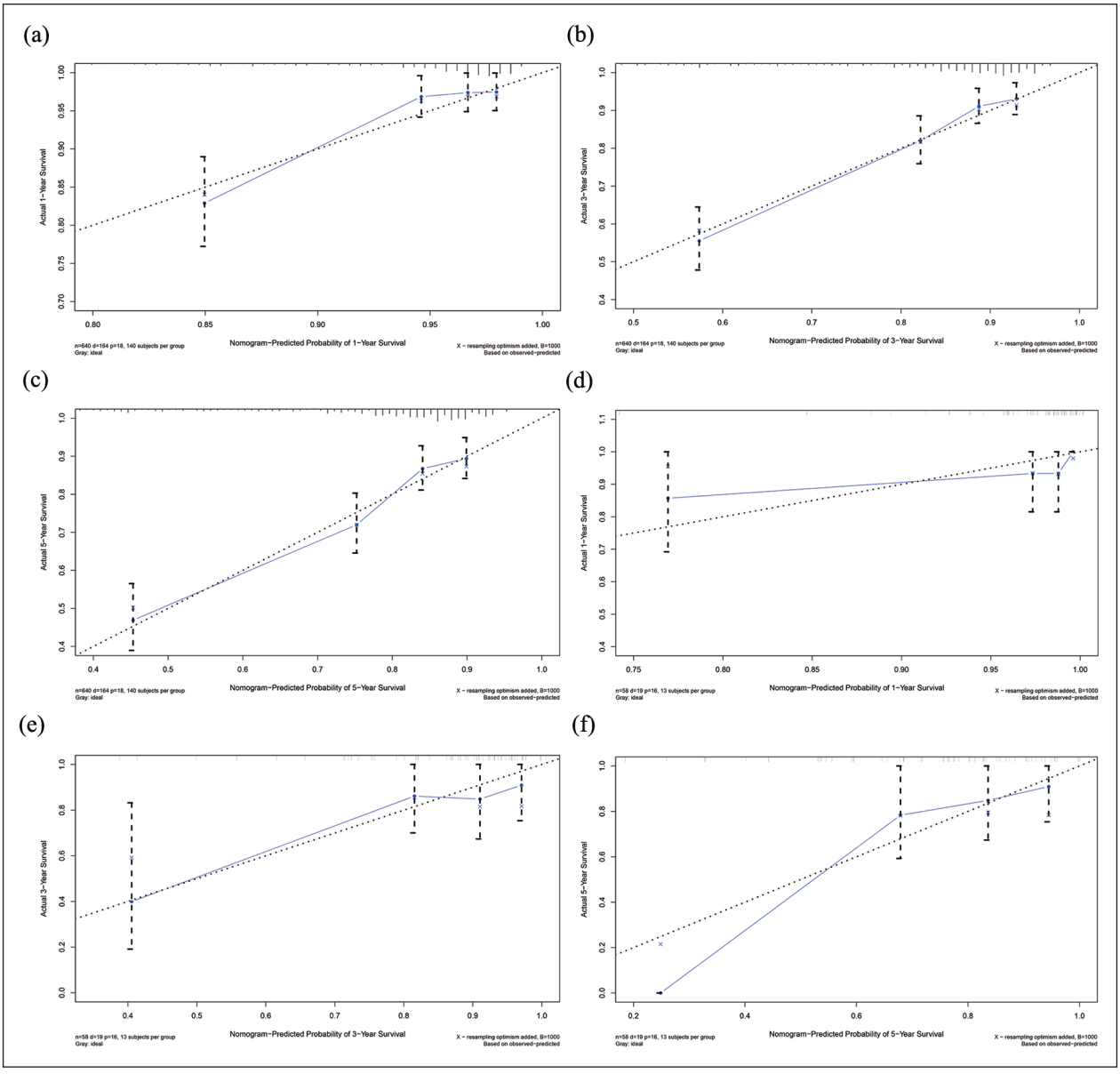

Figure 3. Calibration curves in the training set (a–c) and validation set (d–f).

important. In addition, our multivariate analysis indicated that stage M, larger size (>10 cm), and the axial leads to a poor prognosis. Earlier studies have found that tumors with a primary site in the axial bone are worse than tumors with other primary sites, which is consistent with the results obtained from our study.[22] Tumors arising in the axial region are usually located in a central area of the body, such as the thoracic or pelvic cavities, which makes them more likely to come into direct contact with surrounding internal organs. In addition, tumors located in the central region usually have a relatively rich blood supply, further increasing the likelihood of spread. The larger tumor sizes and the site of axial origin may be correlated with the occurrence of metastatic pathology, both of which have been substantiated as contributory factors linked to diminished rates of survival.[23] Brunetto et al.[24] analyzed that OS was directly affected by the presence of metastases at diagnosis. In fact, ES is one of the most aggressive tumors, characterized by a high rate of recurrence and metastasis, and about 30% of patients have metastases when diagnosed.[25,26]

Clinically, common treatments for ES include chemotherapy, surgery, and radiation therapy.[27–29] Currently, the efficacy of chemotherapy for ES has gained acceptance among physicians, but surgery and radiation therapy still have some different views among different physicians as well as different clinical indications.[30] In the context of radiotherapy, divergent

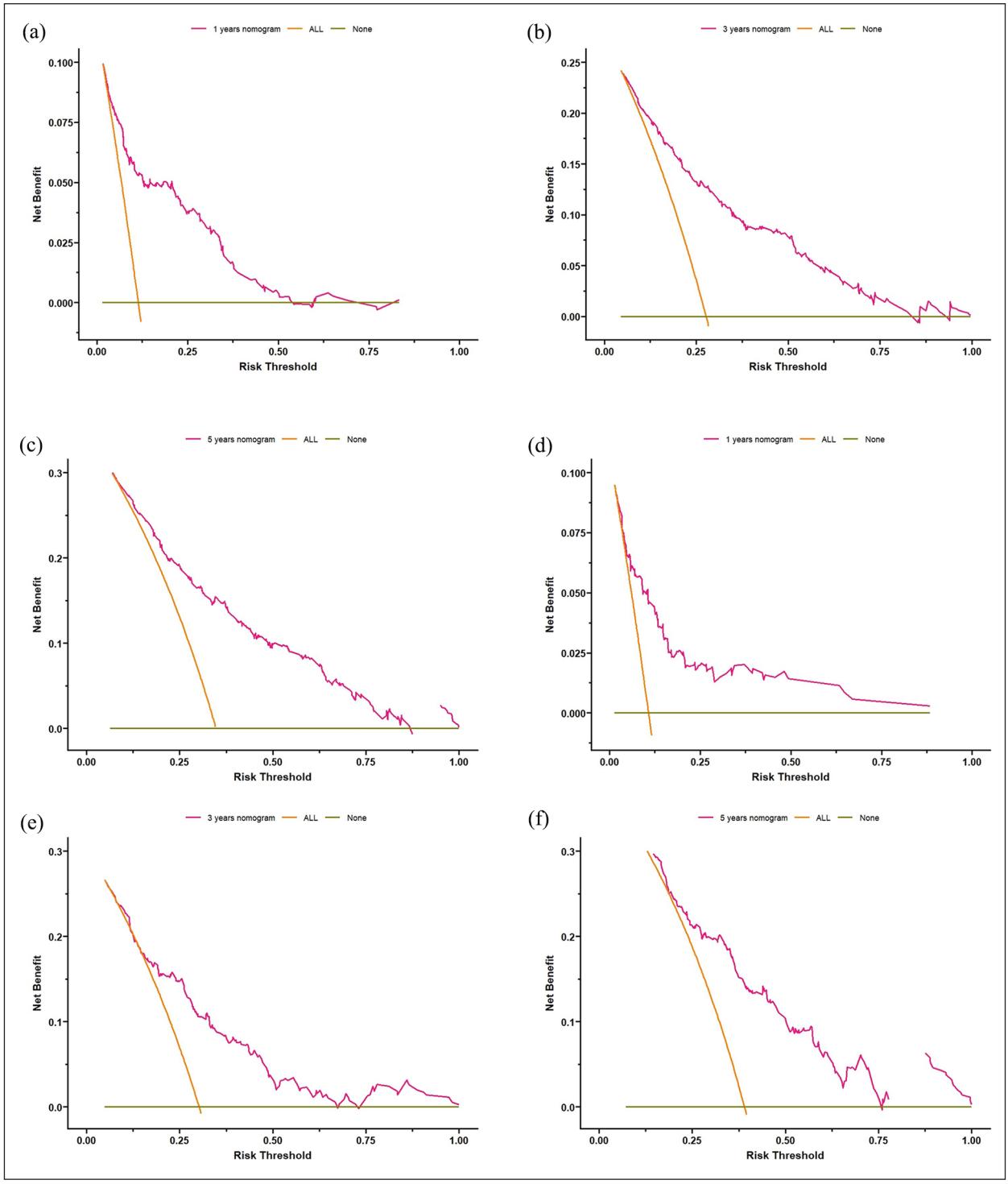

Figure 4. Decision curve analysis of the training set (a–c) and validation set (d–f).

perspectives exist. While amalgamated local therapy for non-sacral tumors demonstrates enhanced efficacy in mitigating both local recurrence and OS in comparison to solitary surgical interventions, certain retrospective studies suggest that patients subjected to induction chemotherapy exhibit superior surgical outcomes, with adjunctive radiotherapy failing to yield discernible improvements in survival outcomes.[31–33] Similarly, we could not conclude that radiotherapy was related to OS independently in our study. Moreover, whether those who had surgery for local treatment experienced a longer survival rate than those who were not operated on remains

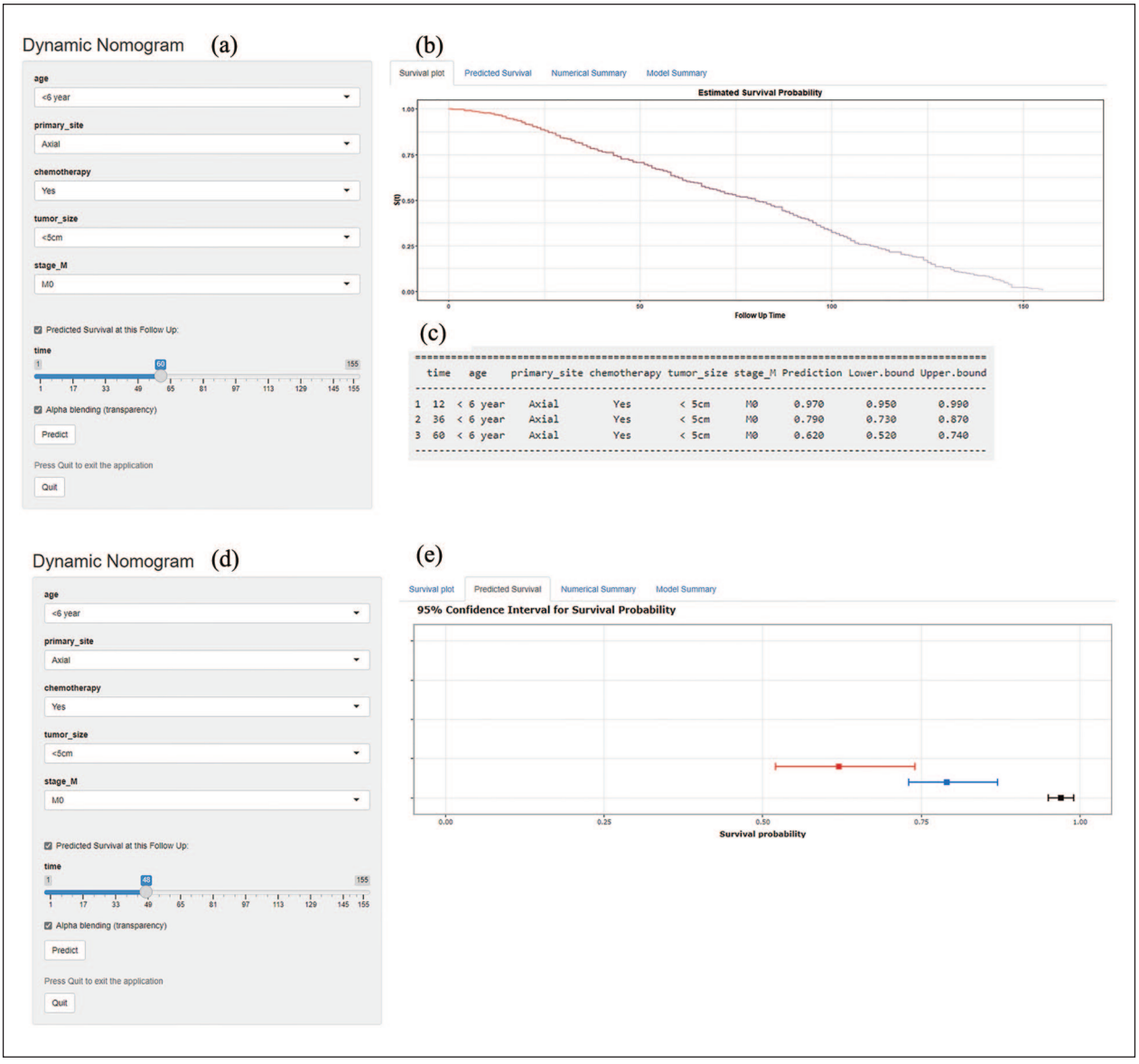

Figure 5. A web-based nomogram for predicting children's OS. The web-based nomogram (a, d). The survival curves of OS (b). The numerical summary showed the OS at 12, 36, and 60 months (c). The line segments showed the approximate range of OS rates (e). OS: overall survival.

controversial.[34,35] Similarly, our study could not conclude that surgery was related to OS independently. Although with or without surgery did not affect the OS of patients in our and a few other studies, to the best of current knowledge, combining chemotherapy with surgical local control achieves the greatest survival benefit and is the standard treatment for ES.[31–33] In the previous studies, chemotherapy groups had a 6-month increase in OS over non-chemotherapy groups.[36] According to our multivariate Cox regression analyses, the prognostic value of chemotherapy within ES in children was observed to be independent. However, the SEER database lacks detailed information on chemotherapy regimens, providing only details on whether patients received chemotherapy or not. A great deal of further research is needed to predict the efficacy of specific drugs in improving ES survival and the efficacy of surgical interventions.

The analyses of multivariate Cox regressions allowed us to develop a nomogram to determine the survival likelihood of children with ES. In addition to being concise, nomograms can be customized to fit the specific characteristics of each patient. The independent factors we included were age, primary site, stage M, tumor size, and chemotherapy. The AUC values at 1, 3, and 5 years for training group were 0.754, 0.739, and 0.740, while for the validation group, they were 0.733, 0.741, and 0.745, respectively.

The AUC values showed that the nomogram model we constructed had better ability to distinguish survival time and high predictive efficacy. The C-index 0.73 in the training group and 0.71 in the internal validation set suggested a good stability of the model. The fitted prediction curves in the two groups were close to the standard curves, and the fit was high, which suggested good calibration. In addition, the prediction model had high prediction compliance, and the prediction probability was close to the actual survival rate. Moreover, we evaluated the clinical utility of the developed model by plotting a DCA curve. It is generally believed that the more the model fitting curve is away from the X and Y axis, the stronger the clinical utility of the model is. The nomogram model we developed showed great clinical utility. In our study, we established a web-based nomogram, and by entering the patient's demographic and clinical information, the clinicians can calculate the score for this patient and obtain the survival curve and OS according to the corresponding scores. In contrast to traditional nomograms, the web-based nomograms can predict prognosis more accurately and conveniently since they do not require multiple summations of variable scores.[37,38] Due to these factors, we established a web-based nomogram. Medical workers could approach the website in a direct way on the cellphone or computer anytime and anywhere and input matching variables to get the ES chilhood's OS probability with 95% confidence interval. As a result, the application process would be simplified, and the decision-making process made easier. With the combination of a prediction model to an information and communication system, clinical applications can be substantially optimized.

Limitations

Nevertheless, this study has some limitations. First, because it is retrospective in nature, some bias was inevitable. Second, some information that determine prognosis is not included in the SEER database, such as disease markers and causative genes. In addition, despite the fact that our prediction model has a high predictive power, there is no doubt that it can be inaccurate for certain populations. Finally, while our multivariate Cox analysis did not yield results related to surgery, this does not negate the benefits of surgery for patients with ES. Further extensive multicentre studies are needed to clarify the efficacy of surgical interventions. In spite of the limitations, we exploited a convenient, intelligent, and forecasted tool to predict OS in children with ES. The web-based nomogram we established does not mean to replace medical workers' judgments, but it should assist and enhance their judgments.

Conclusion

We developed a convenient and precise web-based nomogram to evaluate OS for ES in children. The application of this nomogram would assist physicians and patients in making decisions.

Author contributions

Y.C. and Z.R.L. performed the research, interpreted data, and drafted and wrote the manuscript. Y.B.W., H.W.Z., J.M.L., and J.F.L. collected and analyzed the date. Y.K.N., A.Y., and F.T. supervised the data collection. B.G. and Y.Y.X. critically reviewed the paper and revised the manuscript. B.G. and Y.Y.X. designed the research. All authors read and approved the final manuscript.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://seer.cancer.gov/

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the The First Affiliated Hospital of Zhengzhou University Of Ethics Committee (approval number: ZDYFY-202204012) on 04, 2022. The study was conducted according to the guidelines of the Helsinki Declaration.

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