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Research article

Development and verification of prognostic nomogram for extraskeletal Ewing's sarcoma based on the SEER database

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ABSTRACT

Background: Extraskeletal Ewing's sarcoma (EES) is a rare tumor, and there is currently no predictive model for overall survival of EES patients. This study sought to use data from the Surveillance, Epidemiology, and End Results (SEER) database to develop a clinical predictive model that could be used to assess the prognosis of EES patients.

Methods: We selected and downloaded prognostic data on 356 patients diagnosed with extraskeletal Ewing's sarcoma based on screening criteria, These patients were distributed between 2004 and 2015. 356 patients were randomly divided into a training cohort (70 %) and an internal validation cohort (30 %). After univariate or multifactor Cox regression analysis, the relevant variables were screened and a nomogram was constructed. The consistency index (C-index), calibration chart and receiver operating characteristic (ROC) curve were used to evaluate the established nomogram. The clinical utility of the model was verified by clinical decision curve. Study conducted and outcomes reported according to STROBE statement.

Results: After multifactor regression analysis, we identified five factors that were significantly associated with EES prognosis, and subsequently established a nomogram. Verification data showed that the C-index of this nomogram was 0.829 (95 % CI 0.774–0.884). the AUCs of the nomogram for predicting the 3- and 5-year OS were 0.91 and 0.863. the calibration curves and Decision curve analysis showed that nomogram could predict the prognosis of EES patients.

Conclusion: Stage, age, tumour size, chemotherapy, and surgery may be independent prognostic factors for EES. our study produced a survival nomogram that can be used to predict the prognosis of patients with EES and validated its performance, which may help clinicians evaluate the condition of patients with EES and choose personalised treatment.

1. Introduction

Extraskeletal Ewing's sarcoma (EES) belongs to the neoplastic Ewing sarcoma family of tumours (ESFT). Akin to Ewing's sarcoma, it occurs in 0.6 per 100,000 people, according to the Surveillance, Epidemiology, and End Results (SEER) program [1]. Currently, research on Ewing's sarcoma is abundant, but studies on EES are less extensive and lack depth. EES accounts for about a quarter of Ewing sarcomas and urgently requires more attention and research. The limited research may be partly owing to the fact that Ewing

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osteosarcoma (ESB) is primarily observed in children, while more than half of adult ESFT cases occur in exoskeletal sites. Additionally, the small number of patients with EES contributes to the lack of sufficient research [2]. We found that these patients were mostly younger, with a median age of 20 years, which is 5–10 years older than that of patients with ESB; moreover, these patients have a wider age range.

Studies on EES often have several shortcomings, including small sample sizes, single-centre settings, age restrictions, and a lack of essential prognostic data [3,4]. Therefore, research with a larger sample size and more detailed data is required to better understand the prognosis of patients with EES.

Jiang et al. [5]. studied 3178 Ewing sarcoma cases from the SEER database in 2018 and reported differences in clinicopathological features, prognosis, and prognostic factors between patients with EES and those with extraosseous Ewing sarcoma; extraosseous origin was found to be an adverse prognostic factor. therefore, it is necessary to study the prognosis of EES patients.the study of disease prognosis can help clinicians make appropriate diagnoses and treatment choices based on the patient's condition. At present, a graphical assessment system based on a statistical prediction model to quantify risk is a more commonly used method in prognostic research [6,7]. Furthermore, the SEER database provides the advantages of large sample sizes and complete data from multicentre settings. Previous studies have revealed controversies and uncertainties regarding the prognostic factors for patients with EES. Therefore, establishing a prognosis model based on a large sample of patients with EES is necessary. Thus, we constructed a survival nomogram for patients with EES based on the SEER database and fully validated it to ensure feasibility and validity.

2. Methods

2.1. Data source and participants

Patient data were acquired from SEER*Stat (version 8.4.2),and the database name is Incidence - SEER Research Limited-Field Data, 22 Registries, Nov 2023 Sub(2000–2021). The third edition of the International Clfication of Oncological Diseases (ICD-O-3) code for Ewing sarcoma is 9260. EES patients diagnosed from 2004 to 2015 were searched in the SEER database, and clinicopathologic data were collected. the selection process was as follows. (1) Ewing sarcoma("Histologic Type ICD-O-3″, 9260); (2)site code: except C40.0-C41.9(primary site-labelled ! = 'C40.0-C41.9′).(3)positive pathology ("Diagnostic Confirmation", positive histology). (4) The following clinical information and tumour characteristics were selected from the table: age(Age recode with single ages and 85+), sex (Sex), race(Race recode (White, Black, Other)), primary site(Primary Site), tumor volume(CS tumor size,2004–2015), TNM stage (Derived AJCC TNM, 6th ed,2004–2015), stage(Combined Summary Stage,2004+),distant metastasis(SEER Combined Mets,2010+), surgery(RX Summ–Surg Prim Site,1998+), radiotherapy(Radiation recode,2003+),chemotherapy(Chemotherapy recode,2004+), survival months(Survival months), and survival status(Vital status recode). All three treatments were classified as either 'No' or 'Yes'. Exclusion criteria were as follows: (1) patients with incomplete or unavailable clinical and follow-up data (absence, not available, or unknown); (2) patients with a follow-up period of less than 5 years, except in cases of death; (3) patients with other types of tumours; and (4) autopsy was the pathological examination. Owing to the lack of cancer-specific survival data, overall survival (OS) was the primary endpoint. Patients who met the SEER database criteria were randomly divided into training (70 %) and validation (30 %) cohorts. This retrospective study was based on clinical data obtained from SEER * Stat (version 8.4.2) and was approved without patient informed consent. The study conducted and outcomes reported according to STROBE statement.

2.2. Study variables

Common clinical features included age(Age recode with single ages and 85+), sex(Sex), race(Race recode (White, Black, Other)), primary site(Primary Site), tumor volume(CS tumor size,2004–2015), TNM stage(Derived AJCC TNM, 6th ed,2004–2015), stage (Combined Summary Stage,2004+),distant metastasis(SEER Combined Mets,2010+),surgery(RX Summ–Surg Prim Site,1998+), radiotherapy(Radiation recode,2003+),chemotherapy(Chemotherapy recode,2004+),survival months(Survival months), and survival status(Vital status recode). For further analysis, we categorised the quantitative data. Fig. S1 shows the age and tumour size obtained with X-tile(a common bioinformatics tool for biomarker evaluation and outcome-based pointcut optimization) for optimal cut-off values [8]. These cut-off values were obtained for continuous variables (age, tumour size) (Fig. S1), and these variables were converted to categorical variables for analysis. Based on previous literatures, we divided the primary location variable into three categories: limbs, head, and trunk [9]. The description of tumour size variable in the database is the largest diameter(code 001–400 means that the tumor diameter ranges from 0.1 cm to 40.0 cm,code999 means unknown or size unreasonable (including any tumor sizes 401–989)).Racial variables were mainly divided into Black, White, and Other races (American Indian/AK Native, and Asian/Pacific Islander). The T stage was divided into T0, T1, T2, and Tx (T3 patients were not included in the data). The N stages were described as N0, N1, and Nx. The M stage was divided into the M0 and M1 stages. The 'combined summary stage (2004+)' variables were mainly divided into localized(cancer is limited to find parts, no sign of diffusion), regional(cancer has spread to surrounding lymph nodes or tissues), and distant(cancer spreads to distant parts of the body) groups. survival months Survival months refers to the survival time by month from the time of pathological diagnosis until death,The endpoints of this study were 3 - and 5-year OS.

2.3. Statistical analysis

We used r4.3.1 version for statistical analysis and considered $P < 0.05$ to be statistically significant. Independent sample *t*-test and Chi-square test were employed to analyse differences in survival time and clinical variables, respectively. Variables related to survival

time and outcomes were further screened by conducting univariate and multivariate Cox regression analysis. The screened variables were used to construct nomogram prognostic models to predict the 3-year and 5-year survival of patients with EES. The model's performance was evaluated based on its discriminative ability and precision. The consistency index and subject area under the working characteristic curve (AUC) were utilised to evaluate the ability of the prognostic model. The closer the area ratio under the ROC curve was to 100 %, the closer the prediction of the model was to the real data. A calibration curve was used to evaluate the similarity between the actual data and the nomogram prediction data. Finally, the clinical application value of the model was evaluated with clinical decision curve. Decision curve analysis (DCA) is commonly used to how much a model-based decision improves disease outcomes.The flow chart for patient screening and study design is shown in Fig. S2.

3. Results

3.1. The clinicopathological features of EES patients

The flow chart for patient screening and study design is shown in Fig. S2 a total of 356 eligible patients with EES were screened from

Table 1
Univariate and multivariate cox regression analysis of EES patients.

Characteristic	Univariate analysis			Multivariable analysis		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age(years)						
< 17	Reference			Reference		
18-41	3.03	1.96–4.67	<0.001	2.55	1.63–3.99	<0.001
> 41	5.11	3.15–8.3	<0.001	4.93	2.94–8.29	<0.001
Sex						
Female	Reference		0.256	Not included		
Male	0.83	0.6–1.14				
Race						
White	Reference			Not included		
Black	0.69	0.28–1.67	0.407			
Other	1.52	0.92–2.52	0.104			
T stage						
T1	Reference			Reference		
T2	4.08	2.41–6.9	<0.001	1.24	0.6–2.57	0.5583
T4	0	0-Inf	0.993	0	0 - Inf	0.9945
N stage						
N0	Reference			Reference		
N1	2.34	1.52–3.62	<0.001	1.17	0.74–1.87	0.4995
NX	1.81	1.07–3.06	0.026	0.95	0.53–1.71	0.8749
M stage						
M0	Reference			Reference		
M1	4.23	09–5.81	<0.001	1.38	0.56–3.38	0.4854
Stage						
Localized	Reference			Reference		
Regional	2.56	1.61–4.06	<0.001	2.09	1.27–3.44	0.0036
Distant	7.39	4.78–11.42	<0.001	3.9	1.51–10.09	0.005
Tumor size						
8-65	Reference			Reference		
66-114	2.32	1.45–3.7	<0.001	1.61	0.86–2.99	0.1354
> 114	3.76	2.49–5.68	<0.001	2.11	1.17–3.8	0.0128
Primary Site						
Limb	Reference			Reference		
Head	0.85	0.4–1.8	0.663	0.82	0.36–1.87	0.6412
Trunk	1.57	1.11–2.24	0.012	1.23	0.84–1.8	0.2818
Radiation						
No	Reference			Not included		
Yes	1.21	0.89–1.66	0.224			
Chemotherapy						
No	Reference			Reference		
Yes	0.51	0.33–0.79	0.003	0.55	0.34–0.91	0.0189
surgery						
No	Reference			Reference		
Yes	0.39	0.28–0.54	<0.001	0.65	0.45–0.94	0.0209
Bone metastasis						
No	Reference			Reference		
Yes	3.35	2.14–5.25	<0.001	1.18	0.68–2.03	0.5573
Lung metastasis						
No	Reference			Reference		
Yes	2.53	1.56–4.09	<0.001	0.89	0.51–1.54	0.6667

the SEER database and randomly divided into training (n = 252) and validation (n = 104) cohorts. The patients' average age was 26.19 years old, and the majority were White. The study included 198 male (55.62 %) and 158 female (44.38 %) patients.Patients with non-metastatic EES had a mean survival of 93.2 months, with a 5-year survival rate of 69 %, and patients with metastatic EES had a mean survival of 44.5 months, with a 5-year survival rate of 32 %.The clinicopathological features of all patients are shown in Table S1. There was no significant difference between the two groups.

3.2. Univariate and multivariate cox regression analysis of EES patients

Based on the training cohort data, we first conducted a univariate Cox regression analysis. As shown in Table 1, the univariate Cox regression analysis results showed that age, T stage, N stage, M stage, tumour stage, tumour size, tumour site, chemotherapy, surgery, bone metastasis, and lung metastasis were statistically significant with survival time and survival status. Next, the significant variables in the single factor were included in the multivariate analysis, with $P < 0.05$ set as the cut-off value. In subsequent multivariate Cox regression analysis, significant independent prognostic variables for OS were age, stage, tumour size, chemotherapy, and surgery (Table 1).

3.3. nomogram predicting the 3- and 5-year OS in patients with EES

Fig. 1 illustrates a nomogram predicting the 3- and 5-year OS in patients with EES. These nomogram was established based on five variables screened from the training cohort data (Fig. 1). The model showed that factors affecting prognosis were stage with the highest proportion, followed by age, tumour size, and chemotherapy, while surgery had the least effect on prognosis. Table 2 shows the 95 % CI accuracy of nomogram and TNM staging in predicting patient prognosis. In the validation cohort, the C-index of OS predicted by nomogram was 0.829 (95 % CI 0.774–0.884) (Table 2). Furthermore, the nomogram showed a higher C-index in the validation cohort than in the TNM phase. In the validation cohort, TNM staging predicted OS with a C-index of 0.72 (95 % CI 0.65–0.79) (Table 2). Thus, the nomogram was more effective than TNM staging in predicting patient prognosis.

3.4. Validation of the nomogram for predicting the prognosis of EES patients

Fig. 2 shows the ROC curves of nomogram and 6th TNM prognosis in the training and validation groups. As shown in Fig. 2, the AUC for 3-year and 5-year OS prediction by nomogram in the training cohort was 0.83, while the AUC for TNM stage prediction was 0.786 and 0.772, respectively. In the validation cohort, the nomogram AUC for 3-year and 5-year OS prediction was 0.91 and 0.863, respectively, and the TNM staging AUC for OS prediction was 0.794 and 0.732, respectively. This indicated that the model had good predictive power in predicting the 3-year and 5-year survival times and OS of patients with EES and performed better than the classical TNM staging (Fig. 2).

Fig. 3 shows the difference between the actual OS curves and the monogram-predicted OS probabilities in the training and verification cohorts at 3- and 5-year survival points. The calibration curves of both cohorts showed that the difference between the predicted values of the nomogram and the actual data was very small, and the long-term prediction data were more accurate.

Fig. 4 depicts DCA for the training and validation cohorts. Under the same threshold probability (x), the red line represents significantly higher net benefits than the brown and orange lines. This prognostic model has good clinical efficacy in assisting decision-making and improving the 3-year and 5-year survival of patients with EES, and the 5-year benefit degree was slightly higher than that at 3-year.

4. Discussion

EES is a rare aggressive malignancy that occurs most frequently in children and adolescents [10]. Studies on EES are more commonly case reports than comprehensive studies [11–13]. In addition, studies on prognostic factors have been limited and often yield conflicting results, with a predominance of single-centre research [14]. Personalised cancer treatment is crucial [15]. The establishment of a prognostic model through the analysis of large-sample data and the promotion of personalised treatment can prevent over- or under-treatment. Nomogram prognostic models can be used to predict individual survival by combining various prognostic factors. In this study, we selected relevant data from the SEER database and identified five independent factors of prognostic

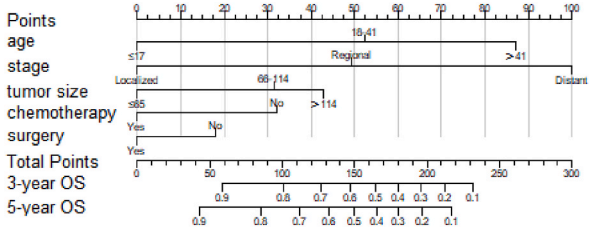

Fig. 1. Nomograms for predicting the 3-year and 5-year overall survival of EES patients.

Table 2
Accuracy of the prediction score of the nomogram and TNM stage for estimating prognosis of patients. OS, Overall Survival; CI, Confidence Interval.

Variables	training set	validation set
	OS(95%CI)	OS(95%CI)
nomogram	0.786(0.747–0.825)	0.829(0.774–0.884)
tnm stage	0.747(0.706–0.788)	0.72(0.65–0.79)

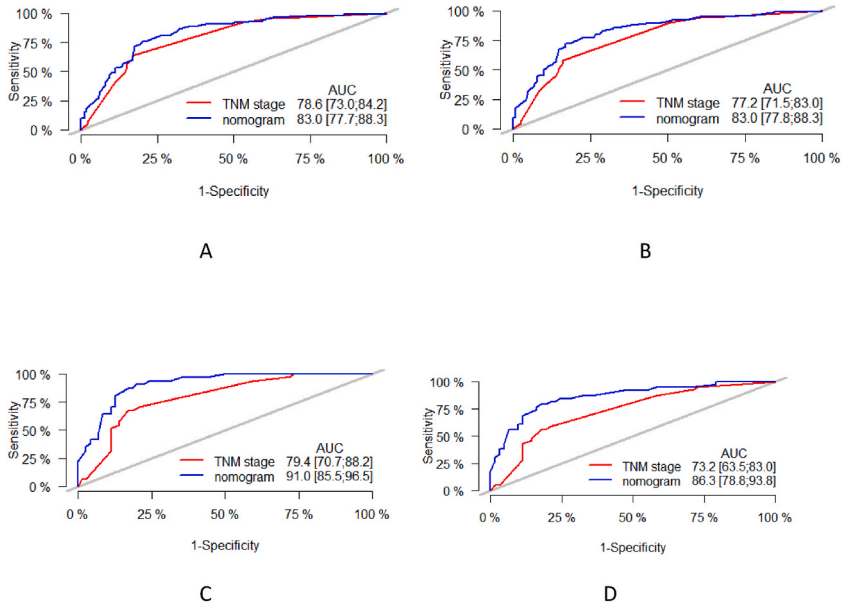

Fig. 2. ROC curve of the nomogram and 6th TNM stage in predicting the prognosis of training cohort and validation cohort patients. (A, B) ROC curve for the 3-year and 5-year points in the training cohort. (C, D) ROC curve for the 3-year and 5-year points in the validation cohort.

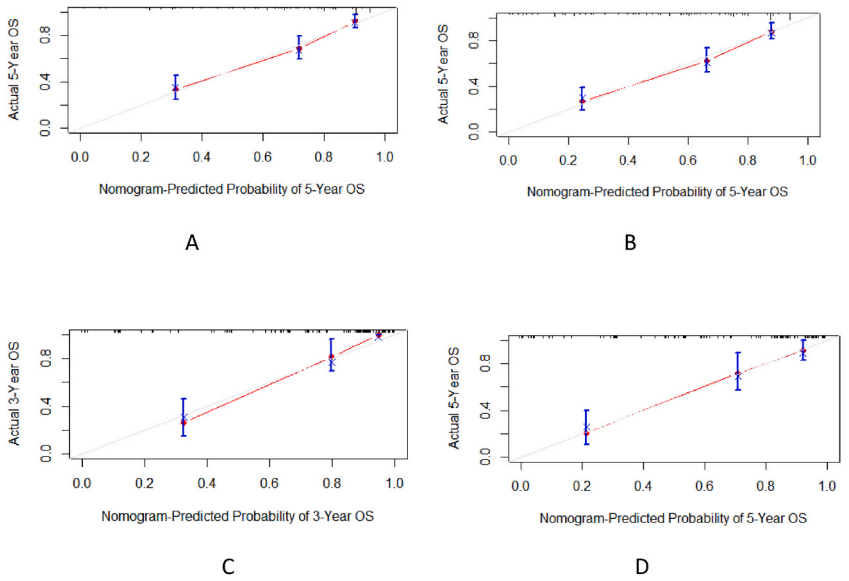

Fig. 3. The calibration curves for predicting OS at (A) 3-year and (B) 5-yearin the training cohort, and at (C) 3-year (D) 5-year in thel validation cohort.

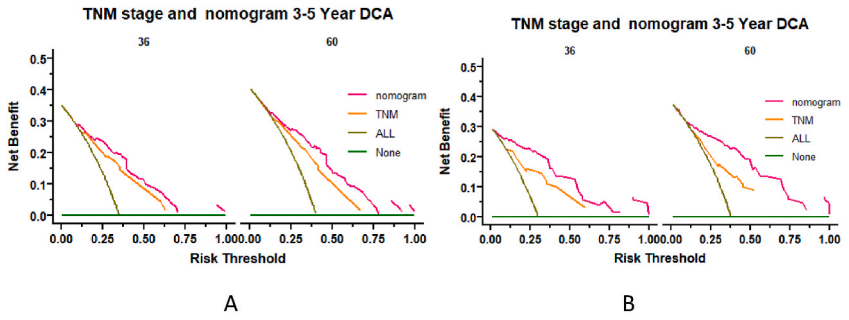

Fig. 4. Decision curves analysis (DCA) at3-year and 5-yearin the training cohort(A), and at 3-year and5-year in thel validation cohort(B).The green horizontal line (none) indicates patients who did not participate in the intervention; brown line (all), patients who were prompted to undergo intervention; red line, nomogram assisted decision-making; and orange line, decision analysis based on TNM staging.

outcomes in patients with EES through data analysis. Based on these five outcome prognostic factors, a nomogram prognostic model with good prediction of 3-year and 5-year OS rates was established. Numerous studies have revealed that older age, larger tumour diameter, and distant tumour metastasis are prognostic factors affecting the survival of these patients; hence, these factors can be used to predict the survival and prognosis [16].

In our study, patient demographics and clinical characteristics included a higher percentage of White patients, with an average age of 26 years, less lymph node involvement, and more tumour sites in the trunk [17]. The current estimated 5 year survival in non metastatic Ewings is 65 %–75 % and under 30 % in patients with metastatic disease. The 5-year survival rate in our study was 69 % for patients with non-metastatic EES and 32 % for patients with metastatic EES, indicating that our study population was qualified [18]. Jawad et al. [1]. conducted a study of prognostic factors in 1631 cases of Ewing sarcoma, which revealed a clear racial difference in the incidence of ES, with Caucasians having a significantly higher incidence than Asians and Africans. However, our univariate and multifactorial regression analyses showed that sex, race, and tumour site were not significantly associated with OS, indicating that prognostic factors differed between patients with EES and ES, which is consistent with the results of the study by Cash et al. [19]. This may be attributable to differences in the microenvironment and angiogenesis between extraskeletal and skeletal origins.

Our nomogram model revealed that the stage accounts for the highest proportion of the total score and is the most significant factor affecting prognosis. Patients with distant-stage disease face a higher risk and shorter survival time. This finding aligns with those of previous studies [20]. Staging had the highest weight coefficient for predicting prognosis, indicating that it is both scientifically robust and effective. Multivariate analysis showed that patients with EES with distant stages at the time of diagnosis had significantly lower survival rates than those with local or regional stages. In addition, the proportion of distant metastases in these patients was not very high, accounting for 28.93 %, which may also be one of the factors for better prognosis.

The prognosis of malignant tumours is closely associated with age. According to our research and clinical experience, younger patients generally have a better prognosis and longer survival time. This may be because older patients with EES are more susceptible to distant metastasis and often develop resistance to chemotherapy and other treatments. In addition, older patients often have diabetes, high blood pressure, and heart disease, which can worsen their prognosis.

As a malignant aggressive tumour, EES is prone to recurrence, and after metastasis, it significantly affects patient prognosis. Currently, surgery, chemotherapy, and radiotherapy are the primary therapeutic methods for tumours; however, previous studies on EES have only included surgery as a prognostic factor, failing to consider chemotherapy and radiotherapy [21]. In this study, although radiotherapy is one of the routine methods for clinical treatment of EES, our univariate and multivariate analyses showed that radiotherapy did not significantly affect the overall survival of EES patients.We speculated that EES tumours are primarily located deep within the trunk, where the effectiveness of radiotherapy may be limited. Another reason could be that very few patients receive radiotherapy as part of their EES treatment. The rates of surgery and chemotherapy were 70.22 % and 89.61, respectively. Both univariate and multivariate analyses confirmed that these treatments were crucial for patient prognosis. However, owing to the lack of specific information on chemotherapy protocols, it is difficult to determine whether patients benefit more from preoperative or postoperative chemotherapy.

Lee et al. [22]. found that metastases at presentation, tumour size, and surgery were significantly associated with OS. Our study found that tumour diameter was an important factor affecting the prognosis and survival of patients with EES. Multivariate analysis showed that patients with larger tumours had a significantly lower OS.

The patients with EES in our study were diagnosed between 2004 and 2015, ensuring adequate follow-up time. In addition to surgery-related information, we collected data on chemotherapy and radiotherapy, which were not available in previous studies. After screening and verification analysis, five common and clinically convenient prognostic factors of age, stage, chemotherapy, tumour size, and surgery were established, and a nomogram was constructed. In the training cohort, OS had a C-index of 0.786. In the verification queue, the corresponding value was 0.829, indicating good reliability of the nomogram. The ROC curve showed that our nomogram could predict OS with higher accuracy than that of the 6th TNM staging system. The final correction curve also revealed that the predicted value obtained from the nomogram was very close to the actual value. Taken together, these findings suggest that nomograms can help assess patient outcomes and are useful and convenient for predicting the OS of patients with EES. When using our nomogram to predict OS, Clinicians and patients can predict OS through relatively simple clinical indicators, which takes a few

minutes to learn the interpretation of nomogram.

This study had certain limitations. Firstly, the SEER database contains some common risk factors related to prognosis, but there are still some commonly used and interesting factors such as detailed information on chemotherapy drug therapy, blood markers (such as anemia, hypoalbuminemia, and high lactate dehydrogenase levels) that were not included in the prognostic factors. Unfortunately, these prognostic factors are not available in the SEER database, which limits their inclusion in our current model. In order to improve the accuracy of prognostic models, further research is needed in the future based on incorporating more prognostic factors of interest [23]. Secondly, the inclusion time of this study was long, which led to changes in surgical and pathological methods over time, thus affecting the prognostic significance of some parameters. In addition, data were extracted from 2004 to 2015, and newer chemotherapy agents and regimens may have improved outcomes in these patients. Thirdly, because the SEER database does not include genetic sequencing of patients, we used pathological results and tumor location to include EES patients, which may not fully distinguish EES patients in our inclusion, and ESFT patients may also be included. Finally, our screening and exclusion criteria limited the applicability of our nomogram; hence, it cannot be used for all patients with EES. Owing to the lack of tumour-specific survival study data, OS was used as the primary endpoint in this study, which may not fully account for the impact of non-cancer-related deaths. Despite these limitations, this study provides a new perspective on the study of patients with EES.

5. Conclusions

To the best of our knowledge, this is the first study to construct a nomogram model that can predict the prognosis of patients with EES with good reliability and validity. Compared to the 6th edition TNM staging, this model can be used for accurate risk assessment and survival prediction in these patients. It provides clinicians and patients with a tool for personalised survival predictions.

CRediT authorship contribution statement

Feipeng Xiao: Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Weizhen Wang:** Visualization, Software.

Ethics statement

The data of our study were publicly available. Informed consent of patients was waived. No separate ethical approval was required for this study.

Data availability statement

The dataset supporting the conclusions of this article is available in the Surveillance, Epidemiology, and End Results (SEER) repository, and hyperlink to dataset in https://seer.cancer.gov/seerstat/, version number 8.4.2. The data included in this study will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial intesrsonalrelationships that could have appeared to influence the work reported in this paper.Artificial intelligence and AI-assisted technologies were not used in the writing of this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40854.

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