

Prognostic nomogram for overall survival in upper aerodigestive tract extranodal natural killer/T-cell lymphoma, nasal type, stages IE and IIE: A SEER-based study

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Abstract. The present study aimed to develop a widely accepted prognostic nomogram for stage IE and IIE extranodal natural killer/T-cell lymphoma (ENKTCL) of the upper aerodigestive tract by using the Surveillance, Epidemiology, and End Results program database. A total of 396 patients with ENKTCL were included in the present study and were divided into training (n=280) and validation (n=116) cohorts. The Kaplan-Meier method and Cox regression model were used to evaluate the prognostic value of multiple clinical parameters on overall survival. The C-index and calibration curves were both used to determine the predictive and discriminatory capacities of the nomogram. In the training cohort, multivariate analysis demonstrated that age, primary site, radiation therapy and stage were independent prognostic factors. Nomograms with a C-index of 0.717 in the training cohort and a C-index of 0.737 in the validation cohort were developed. The calibration curves reported excellent consistency between predicted and real survival in patients with ENKTCL. In addition, a subgroup analysis of 264 patients who were receiving chemotherapy revealed that based on chemotherapy, supplementation with radiation therapy was significantly beneficial to patients survival. In conclusion, the present study demonstrated that this prognostic model may serve as a novel tool for improving prediction of survival outcomes and may therefore be used in clinical applications.

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTCL) is a highly aggressive type of lymphoma strongly associated with Epstein-Barr virus infection that has a poor clinical outcome, and the incidence of ENKTCL is higher in Asian and Latin American countries compared with Western countries (1,2).

Most studies on ENKTCL are therefore based on the populations of eastern Asia, and Central and South America countries, and relatively little information about this disease in people from Western countries is available. Neoplastic cells express cytoplasmic-CD3 ϵ , CD56 and cytotoxic molecules. Most studies have reported a 5-year survival rate of <50% (3-7). The Ann Arbor staging system, which was originally used in Hodgkin lymphoma, is useful to assess prognosis (8). Most ENKTCL cases comprise local lesions and ~80% cases involve stage IE and IIE (7,9,10). The treatment options and clinical characteristics of this disease have always been an important issue (11-13). Previously, anthracycline-containing chemotherapy regimens, including the cyclophosphamide, doxorubicin, vincristine and prednisolone regimen, were commonly used in advanced ENKTCL treatment; however, they did not achieve satisfactory results (9). Currently, L-asparaginase-based regimens are the main treatment option (1). ENKTCL mainly originates from the upper aerodigestive tract (UADT), which usually involves the nasal cavity, hypopharynx, Waldeyer's ring, larynx and oral cavity (14-16). The involvement of extra-UADT sites is relatively rare in ENKTCL. Previous studies reported that UADT-ENKTCL and extra-UADT-ENKTCL have different clinical features and prognoses (17-19). The present study aimed therefore to investigate and analyze the characteristics and survival outcomes of patients from the United States (US) with stage IE and IIE primary UADT-ENKTCL of the nasal cavity by using the Surveillance, Epidemiology, and End Results (SEER) program database. In addition, by combining multiple independent factors, including age, stage, radiation and primary site, a nomogram based on patients overall survival (OS) was developed. This nomogram may be used to predict the OS and prognosis of patients with ENKTCL.

Materials and methods

Data source. Data were obtained from the SEER database (www.seer.cancer.gov), which includes 18 registries and comprises data from ~28% of the US population. The White, Black, Hispanic, American Indian and Alaskan, Asian and Hawaiian/Pacific Islander populations represented ~25, 26, 38, 44 and 50% of the total population, respectively, in the 18 registries (20-22).

Cases based on the third edition of the International Classification of Disease for Oncology (ICD-O-3) were selected (8). In this study, patients with ENKTCL were identified

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Key words: extranodal natural killer/T-cell lymphoma, prognostic nomogram, upper aerodigestive tract lymphoma, early-stage lymphoma

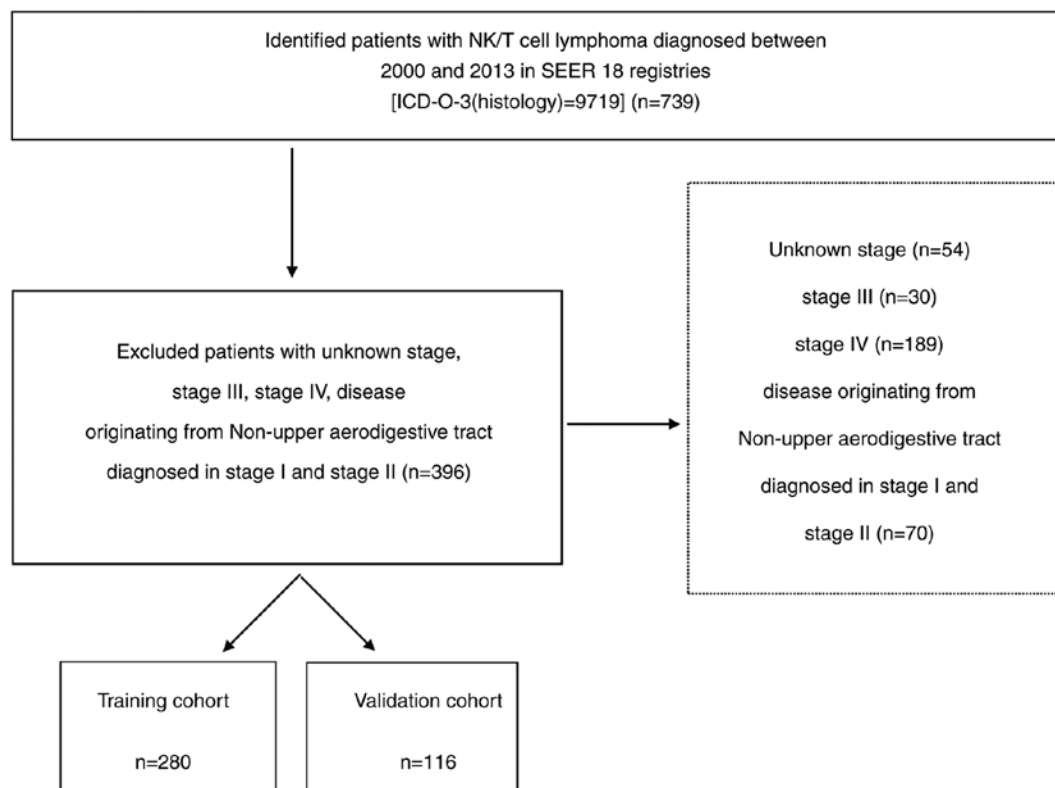


Figure 1. Flow diagram describing the evaluation and selection of patients with extranodal natural killer/T-cell lymphoma. ICD-O-3, International Classification of Disease for Oncology; NK/T, natural killer/T cell; SEER, Surveillance, Epidemiology, and End Results.

using the ICD-O-3 code for histology (9719, ENKTCL). In particular, patients with stage IE and IIE UADT-ENKTCL were selected; however, patients with unknown or higher stage UADT-ENKTCL and with stage I and II non-UADT-ENKTCL were excluded (Fig. 1). A total of 396 patients were eventually enrolled in the present study and were divided into training (n=280) and validation (n=116) cohorts.

Statistical analysis. Data were collected from the SEER database using the SEER stat 8.3.5 software (<https://seer.cancer.gov/data/>). Statistical analyses were performed using the statistical software packages SPSS 21.0 (IBM Corp.) and R-project version 3.5.1 (<http://www.r-project.org/>) for Windows. OS curves were analyzed using the Kaplan-Meier method and the differences between groups were compared using the log-rank test. Univariate and multivariate analyses and calculation of hazard ratio (HR) were performed using the Cox regression model. A nomogram based on multivariate analysis by the rms package (<https://cran.r-project.org/web/packages/rms/index.html>) in Rand Harrell's C statistic was built and calibration curves were used to estimate the accuracy of the prediction model (23,24). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 396 patients with UADT-ENKTCL identified in the SEER database were included in the present study. In the entire study cohort, median follow-up time was ~18 months (range, 0-152 months). Median

age at diagnosis was ~52 years (range, 8-93 years). There were 178 deaths among the 396 patients at 2-140 months, accounting for 44.9% of the cohort. The clinical characteristics of patients in the training and validation cohorts are listed in Table I.

Univariate and multivariate analyses of OS in the training cohort. In the training cohort, the variables in univariate Cox regression analysis were included as follows: Sex, ethnicity, stage, primary site, radiation therapy, surgery and age. Among these variables, stage, primary site, radiation therapy and age were significantly correlated with OS ($P < 0.05$; Table II). The survival curves are presented in Fig. 2. Due to the limited availability of chemotherapy data, this treatment variable was not included in the analysis. In the multivariate analyses, factors with $P < 0.1$, including age, stage, primary site, radiation therapy and stage primary site, which is defined as the interaction of two variables, were included for the Cox regression analysis. The results demonstrated that age, stage, primary site and radiation therapy were independently associated with unfavorable OS (Table II).

Nomogram development and validation. A nomogram was established based on the results of multivariate analyses. Age, stage, primary site and radiation therapy were included in the nomogram. A weighted total score was calculated for each factor and was then used to calculate and estimate the 3-year OS and the probability for 5-year OS (Fig. 3). Harrell's C statistic of the nomogram was calculated to be 0.717 in the training cohort and 0.737 in the validation cohort, which indicated that the discriminatory capacity of the nomogram

Table I. Clinical characteristics of patients with extranodal natural killer/T-cell lymphoma in the training and validation cohorts.

Variable	Training cohort, n (%)	Validation cohort, n (%)	Total, n	P-value
Age, years				
≤45	110 (39.3)	42 (36.2)	152	0.751
>45 and ≤65	107 (38.2)	49 (42.2)	156	
>65	63 (22.5)	25 (21.6)	88	
Sex				
Male	182 (65)	81 (69.8)	257	0.903
Female	98 (35)	35 (30.2)	139	
Ethnicity				
White	199 (72.1)	88 (75.9)	287	0.367
Other	77 (27.9)	27 (24.1)	104	
Stage				
IE	190 (67.9)	77 (66.4)	267	0.775
IIE	90 (32.1)	39 (33.6)	129	
B symptoms				
Yes	62 (30)	23 (27.6)	85	0.939
No	145 (70)	55 (72.4)	200	
Primary site				
Nasal cavity and sinus	216 (77.1)	93 (80.2)	309	0.520
Other	64 (22.9)	23 (19.8)	87	
Radiation				
Yes	183 (66.3)	83 (71.6)	266	0.508
No	93 (33.7)	33 (28.4)	126	
Surgery				
Yes	201 (71.8)	87 (75)	288	0.513
No	79 (28.2)	29 (25)	108	
Chemotherapy				
Yes			264	
No/unknown			132	

was relatively clear and accurate. In addition, the calibration curves revealed excellent consistency between predicted OS and actual OS (Fig. 4).

Further analysis of patients' outcomes associated with treatment methods. A subgroup analysis was performed involving 264 patients receiving chemotherapy. The subgroup analysis results are presented in Table III. Univariate analysis demonstrated that stage, primary site and radiation therapy were significant factors in the chemotherapy group. Variables with $P < 0.1$ on univariate analysis were included in multivariate analysis. Age, which is generally considered as a clinically important variable, was included in the Cox regression analysis. Stage and radiation therapy remained independent prognostic indicators. This result indicated that, based on chemotherapy, radiation therapy was beneficial for increasing OS.

Discussion

Stage IE and IIE UADT-ENKTCL account for the largest proportion of ENKTCL cases and have unique clinical

features, such as tumors usually infiltrating the nasopharynx or surrounding areas (15). Compared with other ENKTCL cases, stage IE and IIE UADT-ENKTCL cases usually exhibit lower lactate dehydrogenase levels and better performance status (25). In recent years, radiotherapy has been considered to be the most effective treatment (25). In the present study, a novel nomogram was built for this particular patient group based on the characteristics of the US population. This nomogram was validated in a validation cohort.

A nomogram is a simple and intuitive statistical tool used to calculate survival probability by incorporating relevant determinants of a disease. It may therefore be a useful tool for clinicians to make clinical decisions (26,27). In particular, in the field of oncology, nomograms can serve in designing various prediction models for survival, recurrence and metastasis (28-32).

The present study demonstrated that age, primary site, radiation therapy and stage were independent prognostic factors for OS. Previous studies reported that age is an important prognostic factor for OS (33,34). In order to further stratify the nomogram, two cut-off points for age (45 and

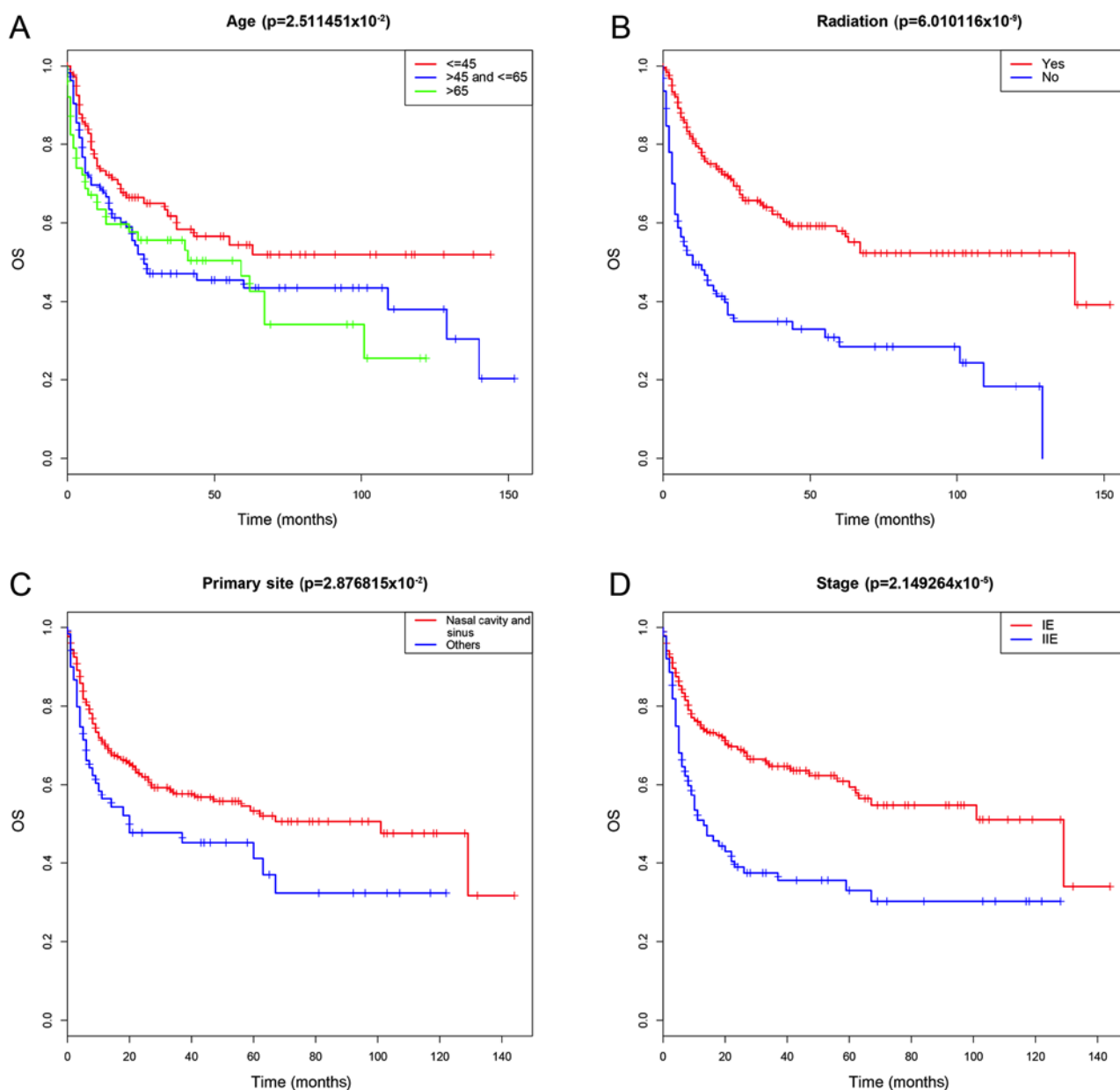


Figure 2. Kaplan-Meier curves of OS by (A) age, (B) radiation, (C) primary site and (D) stage. OS, overall survival.

65 years) were determined. The results demonstrated that HR of OS increased with age; however, older patients had worsened survival, notably patients >65 year old. The primary site was also an important prognostic variable for ENKTCL. It has been demonstrated that patients with extra-nasal UADT-ENKTCL are more likely to have worsened OS compared with those with ENKTCL (25,35,36). Data about chemotherapy treatment were divided into 'receiving chemotherapy' and 'No/Unknown' groups; however, due to the uncertainty of certain data, this information was unusable for univariate or multivariate analysis. Subsequently, the analysis focused on the efficacy of additional radiotherapy in patients who were receiving chemotherapy. Previous studies reported that initial treatment with radiation therapy and subsequent chemotherapy is superior to chemotherapy alone, and to chemotherapy followed by radiation (4,37). The present study also confirmed that radiation therapy was still an independent prognostic factor

in the chemotherapy subgroup, which was consistent with the results of previous studies (38,39). Avilés *et al* (38) and You *et al* (39) reported that radiation therapy, as complementary treatment for chemotherapy or as palliative treatment following chemotherapy, is superior to chemotherapy alone. With regards to the stage, numerous studies have compared the prognoses of stage IE and IIE ENKTCL with that of stage IIIIE and IVE ENKTCL (35,40,41), and these studies reported that stage IIIIE and IVE ENKTCL have worse prognostic results. However, only a few studies compared the prognoses of stage IE ENKTCL with that of stage IIE ENKTCL, including the studies by Wang *et al* (42) and Dai *et al* (43), which revealed that patients with stage IE ENKTCL have a longer OS, which was consistent with the results of the present study. In addition, the analysis of the subgroup of the chemotherapy group revealed that stage remained an important prognostic variable. Notably, studies from Wang *et al* (42) and Dai *et al* (43) reported that

Table II. Univariate and multivariate analysis for overall survival of patients with extranodal natural killer/T-cell lymphoma.

Variable	5-year OS (%)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years					
≤45	21.8				
>45 and ≤65	19.6	1.433 (0.957-2.146)		1.253 (0.832-1.889)	
>65	19.0	1.609 (1.017-2.547)	0.025	1.823 (1.147-2.896)	0.044
Sex					
Male	17.0				
Female	26.5	0.701 (0.483-1.018)	0.062		
Ethnicity					
White	19.1				
Other	22.1	0.923 (0.628-1.356)	0.682		
Stage					
IE	23.2				
IIE	14.4	2.065(1.458-2.923)	<0.001	2.143 (1.498-3.066)	<0.001
B symptoms					
No	19.3				
Yes	17.7	1.251 (0.797-1.962)	0.330		
Primary site					
Nasal cavity and sinus	22.7				
Other	12.5	2.030 (1.395-2.955)	0.029	1.686 (1.149-2.473)	0.008
Radiation					
Yes	24.6				
No	11.8	2.677 (1.888-3.795)	<0.001	2.752 (1.927-3.932)	<0.001
Surgery					
Yes	21.4				
No	17.7	0.730 (0.487-1.094)	0.127		

OS, overall survival; CI, confidence interval.

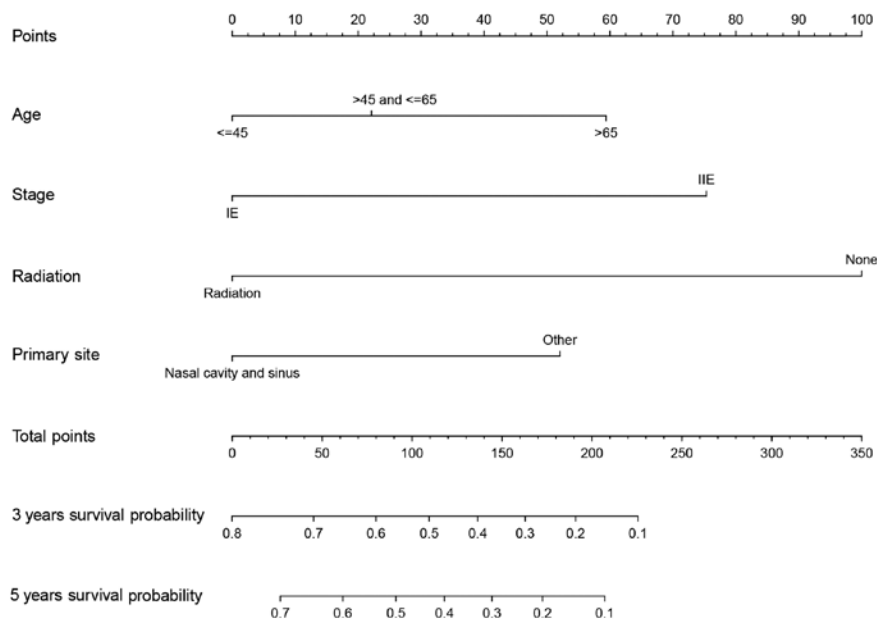


Figure 3. Nomograms for prediction of the 3-year and 5-year overall survival of patients with stages IE and IIE extranodal natural killer/T-cell lymphoma of the nasal cavity. OS, overall survival

Table III. Univariate and multivariate subgroup analysis for overall survival of patients with extranodal natural killer/T-cell lymphoma that received chemotherapy.

Variable	5-year OS (%)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years					
≤45	62.7				
>45 and ≤65	56.4	1.156 (0.776-1.722)			
>65	57.1	1.111 (0.599-2.061)	0.772		
Sex					
Male	57.9				
Female	62.4	0.785 (0.528-1.168)	0.232		
Race					
White	58				
Other	53.8	1.073 (0.709-1.622)	0.74		
Stage					
IE	69				
IIE	41.9	2.250 (1.548-3.270)	<0.001	2.316 (1.590-3.374)	<0.001
B symptoms					
No	63.8				
Yes	70.6	0.910 (0.529-1.568)	0.735		
Primary site					
Nasal cavity and sinus	62.1				
Other	48	1.840 (1.19-2.845)	0.006		
Radiation					
Yes	67.5				
No	37.1	2.621 (1.787-3.842)	<0.001	2.700 (1.841-3.962)	<0.001
Surgery					
Yes	58.5				
No	61.7	0.934 (0.621-1.404)	0.741		

OS, overall survival; CI, confidence interval.

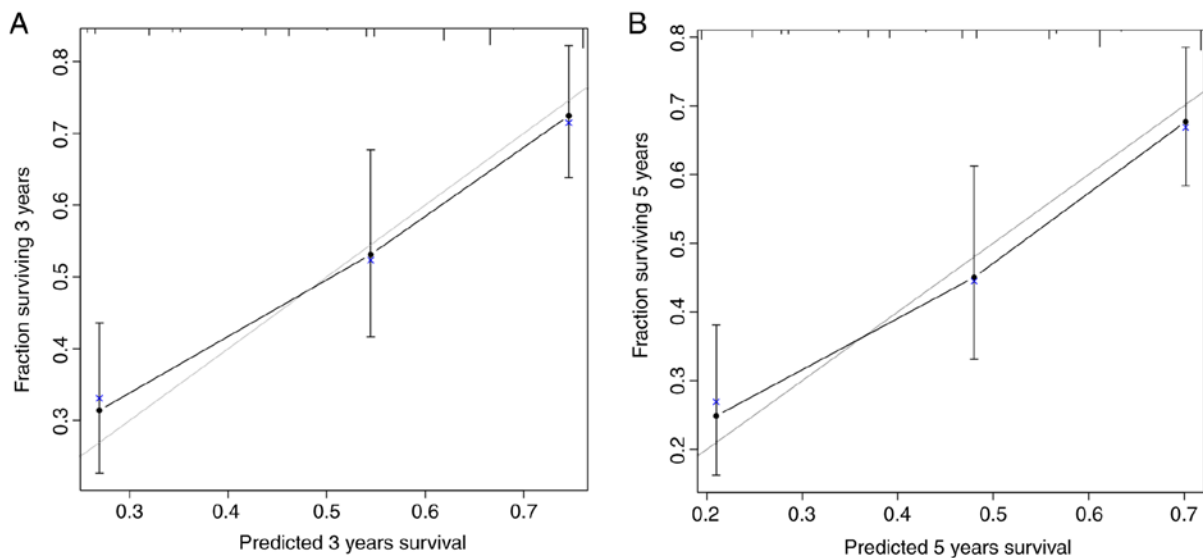


Figure 4. (A) Calibration curve of the nomogram for predicting 3-year OS of patients with stages IE and IIE extranodal natural killer/T-cell lymphoma of the nasal cavity. (B) Calibration curve of the nomogram for predicting 5-year OS of patients with stages IE and IIE extranodal natural killer/T-cell lymphoma of the nasal cavity. OS, overall survival.

in early-stage ENKTCL, B symptoms, including fever, weight loss and night sweats, are not associated with prognosis. The results from the present study were consistent with those from these previous studies (41,42), and were also similar to those from studies on some early-stage lymphomas (44,45).

The present study presented certain limitations. Firstly, data selection from the SEER database may potentially cause selection bias, since this is prevalent in all non-prospective, nonrandomized studies. Secondly, SEER database does not include clinically meaningful variables, including the expression levels of Ki-67, lactate dehydrogenase, β 2-microglobulin and local tumor invasiveness. Although the sample size was large, the present study is a retrospective study and needs to be validated in a cohort study. Thirdly, since information about patient treatment in the SEER database was incomplete, the present study did not include information on specific modalities and doses of radiotherapy and chemotherapy.

In conclusion, the present study analyzed prognostic data of stage IE and IIE UADT-ENKTCL from the SEER database and developed a prognostic nomogram. This nomogram may predict the OS of patients with ENKTCL by using some clinically common variables. This nomogram may guide clinicians in better decision-making and have crucial clinical applications.

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Availability of data and materials

The datasets generated and/or analyzed during the present study are available in SEER stat 8.3.5 software (<https://seer.cancer.gov/data/>).

Authors' contributions

MZ and GW designed the study, wrote the original draft and revised the manuscript. YC, XW, XL and LL contributed to the collection and analysis of the data and the preparation of figures and tables. All authors read and approved the final manuscript

Ethical approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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