Original Article

Construction and validation of a novel web-based nomogram for primary ocular adnexal lymphoma: a real-world analysis based on the Surveillance, Epidemiology, and End Results database

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Background: The occurrence rate of primary ocular adnexal lymphoma (POAL) is relatively low, and estimation of prognosis of these patients poses significant challenges. This study aims to investigate the independent prognostic factors of POAL patients and establish a predictive model to provide clinical data for the formulation of standardized treatment plans.

Methods: We conducted a retrospective analysis by extracting data of POAL patients diagnosed between 2000 and 2017 from the Surveillance, Epidemiology, and End Results (SEER) database. The enrolled patients were randomly divided into a training group and a testing group in a 7:3 ratio. To identify independent prognostic factors, we used both univariate and multivariate Cox regression analyses. Conditional survival (CS) pattern of these patients was analyzed. We formulated a nomogram model to forecast survival rates at intervals of 2, 5, 10, and 15 years. The reliability of the model's predictions was assessed through the concordance index (C-index) and the area under the receiver operating characteristic (ROC) curve (AUC). Moreover, we designed an online survival calculator using the nomogram model.

Results: The study ultimately analyzed 3,324 patients with POAL, of which 2,327 and 997 were respectively assigned to a training group and a testing group. Important prognostic factors including age, sex, tumor site, tumor histology, coexistence of other malignancy, surgery, radiotherapy (RT), and marital status were identified. Based on these predictors, a novel nomogram model was successfully developed with excellent predictive performance, which can also be accessed on the website: https://helloshinyweb.shinyapps.io/eye_dynamic_nomogram/. The calibration curves demonstrated good consistency between the predicted and actual survival rates. Additionally, the C-index and AUC demonstrated good discriminative ability.

Conclusions: This study has successfully developed and validated a prognostic nomogram model that accurately predicts the survival rate of patients with POAL. The model proves invaluable in enabling clinical doctors to assess patients' risk factors and formulate personalized treatment strategies, thereby enhancing survival assessment and clinical management for POAL patients.

Keywords: Primary ocular adnexal lymphoma (POAL); Surveillance, Epidemiology, and End Results (SEER); nomogram; prognosis factors; survival

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Introduction

Primary ocular adnexal lymphoma (POAL) encompasses both intraocular and ocular adnexal lymphomas, representing a subtype of extranodal non-Hodgkin's lymphoma (1-5). POAL typically manifests as a painless, slightly enlarged mass in the eye, which may lead to eye protrusion (4). However, it does not lead to diplopia (double vision) or any loss of vision. As there is no presence of lymphoid tissue, the incidence of POAL is low (3), only accounting for 5% to 10% of all extra-nodal lymphomas and 10% of all ocular tumors. Non-Hodgkin's lymphomas are the main pathological type (6-8). Early diagnosis and standardized treatment are important factors affecting the prognosis of POAL (9,10); and conventional treatments for this disease include surgical resection, radiotherapy (RT), and chemotherapy (CT) (11). Due to the low incidence of this type of tumor, there are fewer reports in the literature on POAL (12-15). Our present comprehension of POAL primarily derives from a collection of retrospective analyses and case studies (16-18). And the treatment strategies and survival patterns in POALs have not been adequately analyzed at a large population level (19-21).

The Surveillance, Epidemiology, and End Results (SEER) database is a valuable resource for studying rare malignancies in cases where clinical trials or prospective data are limited (22). Nomograms have been widely used in a variety of cancers for survival prediction with a comprehensive consideration of a range of prognostic factors (23,24). Therefore, the objective of this research is to examine the survival trends and determine the prognostic elements of patients diagnosed with POAL. Subsequently, a pioneering nomogram model based on the SEER database was designed and authenticated to assess long-term survival rates using accessible clinicopathological characteristics. In addition, an online survival calculator has also been constructed to facilitate the provision of therapy suggestions and assist clinical decision-making in clinical practice. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1556/rc).

Highlight box

Key findings

- We examined conditional survival (CS) pattern and possible prognostic factors in patients diagnosed with primary ocular adnexal lymphoma (POAL) and created a dependable nomogram for predicting their overall survival (OS).

What is known and what is new?

- Due to the low occurrence rate of POAL and the scarcity of relevant research data, there is limited analysis of CS and prognosis factors within the current literature.
- The OS of POAL patients can be predicted by the nomogram model.

What is the implication, and what should change now?

- The newly-established nomogram model proves invaluable in enabling clinical doctors to assess patients' risk factors and formulate personalized treatment strategies, thereby enhancing survival assessment and clinical management for POAL patients.

Methods

Data source

The SEER database contains demographic and clinical pathological information of American patients (25,26). We retrieved data from the SEER18 database and carefully screened suitable participants for inclusion. The eligibility criteria comprised: (I) patients diagnosed with POAL [International Classification of Disease for Oncology third edition (ICD-O-3) histology codes 9590–9599, 9650–9729]; (II) diagnosis year between 2000 and 2017; (III) primary site was restricted to ocular adnexa (site-specific code C69.0–69.9 and C44.1); and (IV) active follow-up. Patients without histological confirmation and those diagnosed only at autopsy were excluded from our study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection

We extracted the following clinicopathological features and treatment information from the SEER database: (I) age (≤50, 51–60, 61–70, 71–80 or >80 years); (II) sex (male or female); (III) race (white or nonwhite); (IV) coexistence with other malignancy; (V) tumor histology [mucosa-associated lymphoid tissue (MALT), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, or others]; (VI) tumor site [conjunctiva, eyelid, orbit, lacrimal gland or others/eye, not otherwise specified (NOS)]; (VII) laterality of tumor (bilateral or unilateral); (VIII) surgery (yes or no); (IX) RT (yes or no/unknown); (X) CT (yes or no); (XI) marriage status (single, married, or unknown); (XII) rural/urban status (metropolitan counties or non-metropolitan counties); (XIII) median household income (≥$70,000 or <$70,000); and (XIV) tumor stage (locoregional or

distant). The endpoints of our research were focused on the measurement of overall survival (OS), representing the duration from diagnosis to the event of passing away due to any cause.

Statistical analysis

The eligible POAL patients were randomly allocated to the training and testing groups in a 7:3 ratio. Descriptive statistics were utilized to present the characteristics of the patients, tumors, and treatments. The conditional survival (CS) trend of the POAL patients was analyzed. Univariate and multivariate Cox analyses were conducted on all predictive factors to screen for potential significant prognostic factors. Significant factors identified by the multivariate model were utilized to create a unique graphical nomogram and a dynamic online survival calculator. The nomogram model was validated in both the training and testing groups using the calibration curve, concordance index (C-index), receiver operating characteristic (ROC) curve, and time-dependent area under the ROC curve (AUC). The data were analyzed using R version 4.0.5 (The R Project for Statistical Computing, Vienna, Austria), with statistical significance defined as $P<0.05$. Finally, based on the significant prognosis factors, an online dynamic nomogram was created.

Results

Baseline characteristic

In accordance with the inclusion criteria set for this study, a total of 3,324 patients were included in the SEER database between 2000 and 2017. These patients were then randomly distributed into a training group (n=2,327) and a testing group (n=997), maintaining a ratio of 7:3. The baseline characteristics of the patients in both the training

Table 1 Baseline characteristics of the included patients

Variables	Training group (n=2,327)	Testing group (n=997)	Overall (n=3,324)
Age (years), mean ± SD	64.6±16.3	64.6±16.3	64.6±16.3
Age (years), n (%)			
≤50	444 (19.1)	184 (18.5)	628 (18.9)
51–60	415 (17.8)	194 (19.5)	609 (18.3)
61–70	532 (22.9)	225 (22.6)	757 (22.8)
71–80	534 (22.9)	222 (22.3)	756 (22.7)
>80	402 (17.3)	172 (17.3)	574 (17.3)
Sex, n (%)			
Male	1,065 (45.8)	425 (42.6)	1,490 (44.8)
Female	1,262 (54.2)	572 (57.4)	1,834 (55.2)
Race, n (%)			
White	1,881 (80.8)	823 (82.5)	2,704 (81.3)
Nonwhite	418 (18.0)	167 (16.8)	585 (17.6)
Unknown	28 (1.2)	7 (0.7)	35 (1.1)
Year of diagnosis, n (%)			
<2010	1,427 (61.3)	601 (60.3)	2,028 (61.0)
≥2010	900 (38.7)	396 (39.7)	1,296 (39.0)
Coexistence with other malignancy, n (%)			
Yes	749 (32.2)	340 (34.1)	1,089 (32.8)
No/unknown	1,578 (67.8)	657 (65.9)	2,235 (67.2)

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Training group (n=2,327)	Testing group (n=997)	Overall (n=3,324)
Tumor histology, n (%)			
MALT	1,265 (54.4)	541 (54.3)	1,806 (54.3)
Others	497 (21.4)	212 (21.3)	709 (21.3)
DLBCL	293 (12.6)	129 (12.9)	422 (12.7)
Follicular lymphoma	272 (11.7)	115 (11.5)	387 (11.6)
Tumor site, n (%)			
Conjunctiva	556 (23.9)	264 (26.5)	820 (24.7)
Eyelid	177 (7.6)	72 (7.2)	249 (7.5)
Orbit	1,168 (50.2)	458 (45.9)	1,626 (48.9)
Lacrimal gland	274 (11.8)	124 (12.4)	398 (12.0)
Others/eye, NOS	152 (6.5)	79 (7.9)	231 (6.9)
Laterality, n (%)			
Bilateral	190 (8.2)	92 (9.2)	282 (8.5)
Unilateral	2,137 (91.8)	905 (90.8)	3,042 (91.5)
Surgery, n (%)			
Yes	961 (41.3)	407 (40.8)	1,368 (41.2)
No/unknown	1,366 (58.7)	590 (59.2)	1,956 (58.8)
RT, n (%)			
Yes	1,388 (59.6)	580 (58.2)	1,968 (59.2)
No/unknown	939 (40.4)	417 (41.8)	1,356 (40.8)
CT, n (%)			
Yes	615 (26.4)	261 (26.2)	876 (26.4)
No	1,712 (73.6)	736 (73.8)	2,448 (73.6)
Marital status, n (%)			
Single	841 (36.1)	360 (36.1)	1,201 (36.1)
Unknown	191 (8.2)	89 (8.9)	280 (8.4)
Married	1,295 (55.7)	548 (55.0)	1,843 (55.4)
Rural/urban status, n (%)			
Metropolitan counties	2,088 (89.7)	892 (89.5)	2,980 (89.7)
Non-metropolitan counties	239 (10.3)	105 (10.5)	344 (10.3)
Median household income, n (%)			
≥$70,000	1,112 (47.8)	476 (47.7)	1,588 (47.8)
<$70,000	1,215 (52.2)	521 (52.3)	1,736 (52.2)
Tumor stage, n (%)			
Locoregional	1,966 (84.5)	849 (85.2)	2,815 (84.7)
Distant	361 (15.5)	148 (14.8)	509 (15.3)

SD, standard deviation; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; NOS, not otherwise specified; RT, radiotherapy; CT, chemotherapy.

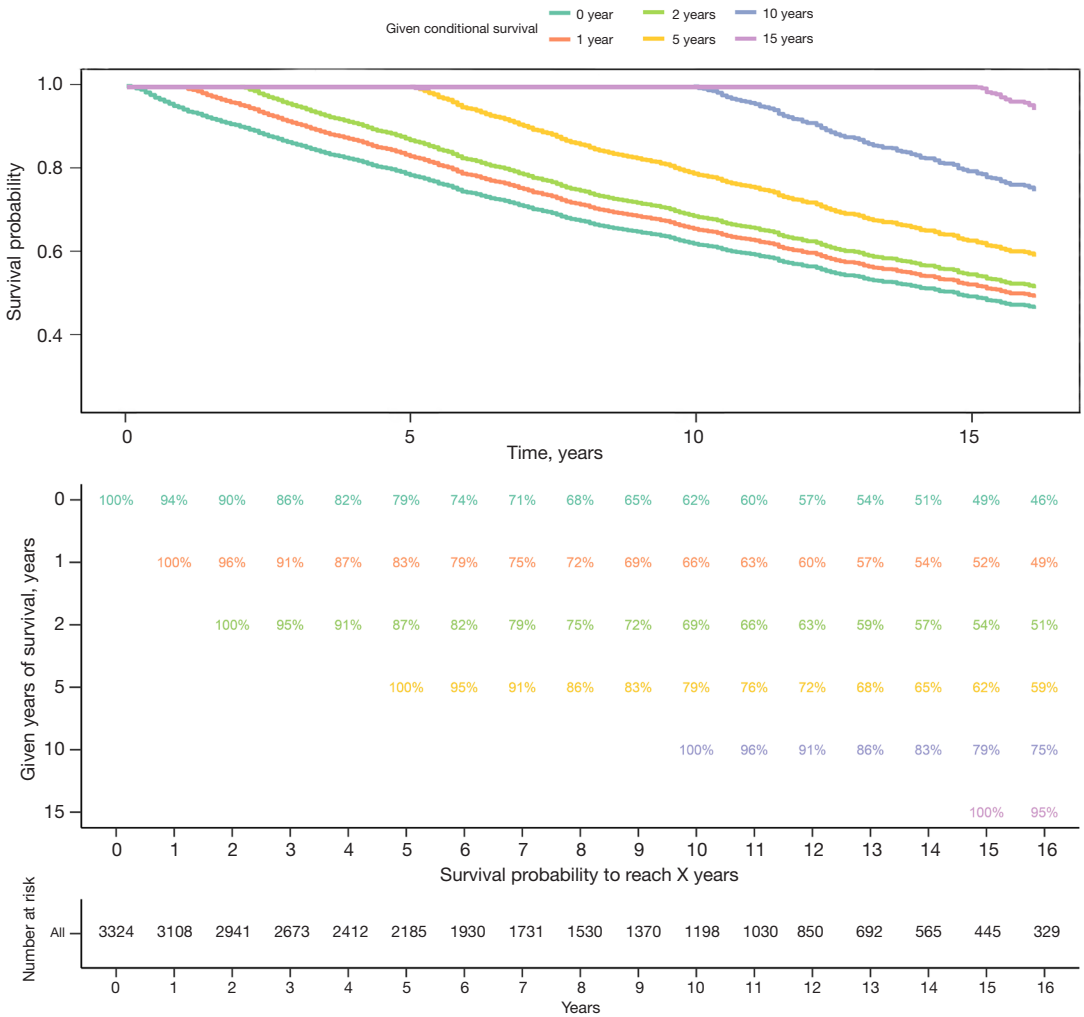

Figure 1 CS curves for patients with POAL at 0, 1, 2, 5, 10, and 15 years. POAL, primary ocular adnexal lymphoma; CS, conditional survival.

and validation cohorts have been summarized in *Table 1*. In the entire cohort, the mean age [standard deviation (SD)] was 64.6 (16.3) years and the majority of patients were over 50 years of age, with females and white patients being the predominant demographics. And the ratio of female to male was 1.23. Regarding tumor characteristics, the majority of patients were diagnosed with MALT situated in the orbit. In terms of tumor attributes, most patients were diagnosed with MALT located in the orbit. As for treatment, 41.2% of the included patients underwent surgical intervention, while 59.2% received RT and 26.4% were treated with CT.

We further described the CS pattern of these patients. The CS curves for all patients at 0, 1, 2, 5, 10, and 15 years are shown in *Figure 1*. Using CS analysis, we observed a noteworthy escalation in the survival rate among these patients for every additional year of survival.

Identify independent prognostic factors

The outcomes of the Cox analysis are displayed in *Table 2*. There were several factors that had a significant association with OS, including race [with a hazard ratio (HR) of 0.727 and a 95% confidence interval (CI): 0.612–0.863; P<*0.001*], tumor site (HR, 1.247; 95% CI: 1.182–1.315; P<0.001), tumor histology (HR, 1.255; 95% CI: 1.195–1.318; P<0.001), stage (HR, 1.563; 95% CI: 1.335–1.829; P<0.001), surgery (HR, 0.777; 95% CI: 0.680–0.889; P<0.001), RT (HR, 0.701; 95% CI: 0.615–0.798; P<0.001), CT (HR,

Table 2 Results of univariate Cox analysis

Variables	HR	Lower 95% CI	Upper 95% CI	P value
Race	0.727	0.612	0.863	<0.001***
Sex	0.889	0.781	1.013	0.077
Year of diagnosis	0.990	0.975	1.006	0.230
Tumor site	1.247	1.182	1.315	<0.001***
Laterality	0.940	0.739	1.196	0.616
Tumor histology	1.255	1.195	1.318	<0.001***
Surgery	0.777	0.680	0.889	<0.001***
RT	0.701	0.615	0.798	<0.001***
CT	1.258	1.092	1.450	0.002**
Coexistence of other malignancy	1.515	1.328	1.728	<0.001***
Age	2.146	2.020	2.280	<0.001***
Marital status	0.741	0.661	0.830	<0.001***
Rural/urban status	1.195	0.979	1.459	0.079
Household income	0.887	0.779	1.011	0.072
Tumor stage	1.563	1.335	1.829	<0.001***

**, P<0.010; ***, P<0.001. HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy.

1.258; 95% CI: 1.092–1.450; P=0.002), coexistence of other malignancy (HR, 1.515; 95% CI: 1.328–1.728; P<0.001), age (HR, 2.146; 95% CI: 2.020–2.280, P<0.001), marital status (HR, 0.741; 95% CI: 0.661–0.830, P<0.001). The sex (P=0.077), year of diagnosis (P=0.230), laterality (P=0.616), rural/urban status (P=0.079), and household income (P=0.072) were found no significant correlation with OS.

And the multivariable Cox analysis showed age (P<0.001), sex (P<0.001), tumor site (P<0.001), tumor histology (P<0.001), coexistence of other malignancy (P=0.018), surgery (P=0.01), RT (P<0.001), and marital status (P<0.001) were identified as independent prognosis factors (*Figure 2*). The Kaplan-Meier curve analysis was depicted to further verify the prognostic abilities of these factors (*Figure 3*), showing that longer OS was related to age (P<0.0001), tumor site (P<0.0001), tumor histology (P<0.0001), coexistence of other malignancy (P<0.0001), surgery (P=0.00022), and RT (P<0.0001).

Establishment and validation of the nomogram

To predict the rates of OS for the periods of 2, 5, 10, and 15 years, a nomogram was created based on seven independent prognosis factors that showed significance. These factors included age, gender, tumor site, tumor histology, presence of other malignancy, surgical intervention, and RT for patients with POAL. The nomogram, shown in *Figure 4*, revealed that age was the most prominent contributor to prognosis, followed by tumor histology, tumor site, RT, surgical intervention, and gender. Each prognostic parameter was attributed a score based on the corresponding scoring table. After adding up the individual scores and consulting the comprehensive score table, the calculated likelihood of survival at each given time interval could be readily ascertained by tracing a vertical line down the chart. To assess the validity of the nomogram's predictive capabilities, we utilized calibration curves and C-indexes to evaluate its performance. Calibration curves were generated for survival probabilities at 24, 60, 120, and 180 months for both training (*Figure 5*) and testing (*Figure 6*) samples, demonstrating favorable agreement between ideal and calibration curves. C-indexes were 0.77 (95% CI: 0.74–0.80) and 0.77 (95% CI: 0.72–0.81) for the training and testing groups, respectively, indicating strong accuracy of the model. The ROC curve was used to evaluate the sensitivity and specificity of the nomogram for the training and testing samples at survival probabilities of 24, 60, 120, and

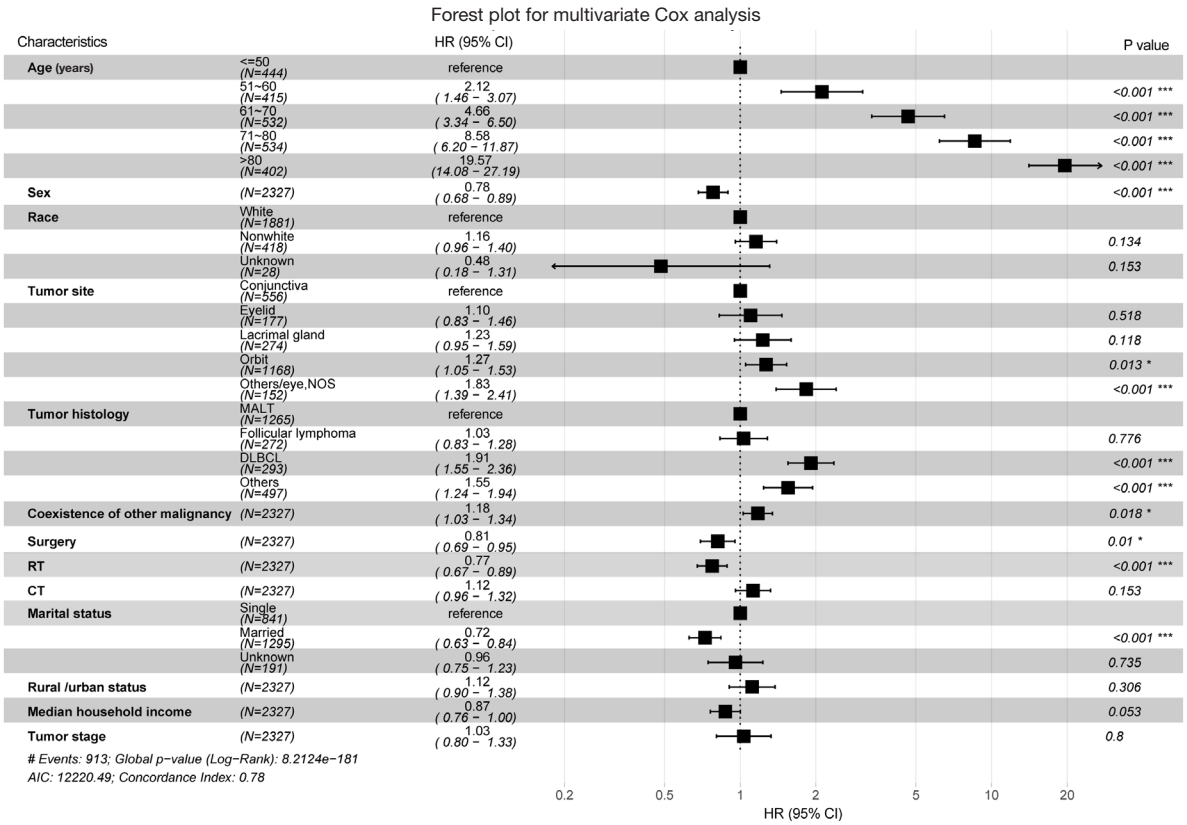

Figure 2 Forest plot for the multivariable Cox analysis. *, P<0.05; ***, P<0.001. HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; RT, radiotherapy; CT, chemotherapy; AIC, Akaike information criterion.

180 months, as shown in *Figures 7,8*. The C-indexes for the training and testing groups were 0.77 (95% CI: 0.74–0.80) and 0.77 (95% CI: 0.72–0.81), respectively, indicating a high level of accuracy for the model. The ROC curve was employed to assess the sensitivity and specificity of the nomogram in the training and testing samples, with survival probabilities of 24, 60, 120, and 180 months, illustrated in *Figures 7,8*. *Figure 9* displays the AUC curves over time for both the training and testing groups. AUC values served as a standard metric for evaluating a model's predictive prowess, with higher scores indicating superior performance. The time-based AUC values for both the training and testing groups consistently remained above 0.75 in this nomogram., indicating the favorable performance of our survival prediction model.

Online dynamic nomogram establishment

Finally, we further created an online dynamic survival calculator based on the nomogram model. Healthcare professionals can access the nomogram easily through our website (https://helloshinyweb.shinyapps.io/eye_dynamic_nomogram/) to draw individual survival curves and predict survival rates at different time points. *Figure 10* represents a screenshot of the online tool.

Discussion

Due to the low occurrence rate of POAL and the scarcity of relevant research data, there is limited analysis of CS and prognosis factors within the current literature (27). As POAL is not commonly understood, it can often be misdiagnosed in the early stages, and medical professionals may struggle to provide relatively accurate survival predictions for affected patients (19,28,29). Therefore, it is essential to develop a novel predictive tool based on common clinical characteristics to evaluate patient survival. This research examines CS among patients with POAL using data from the SEER database in the United States.

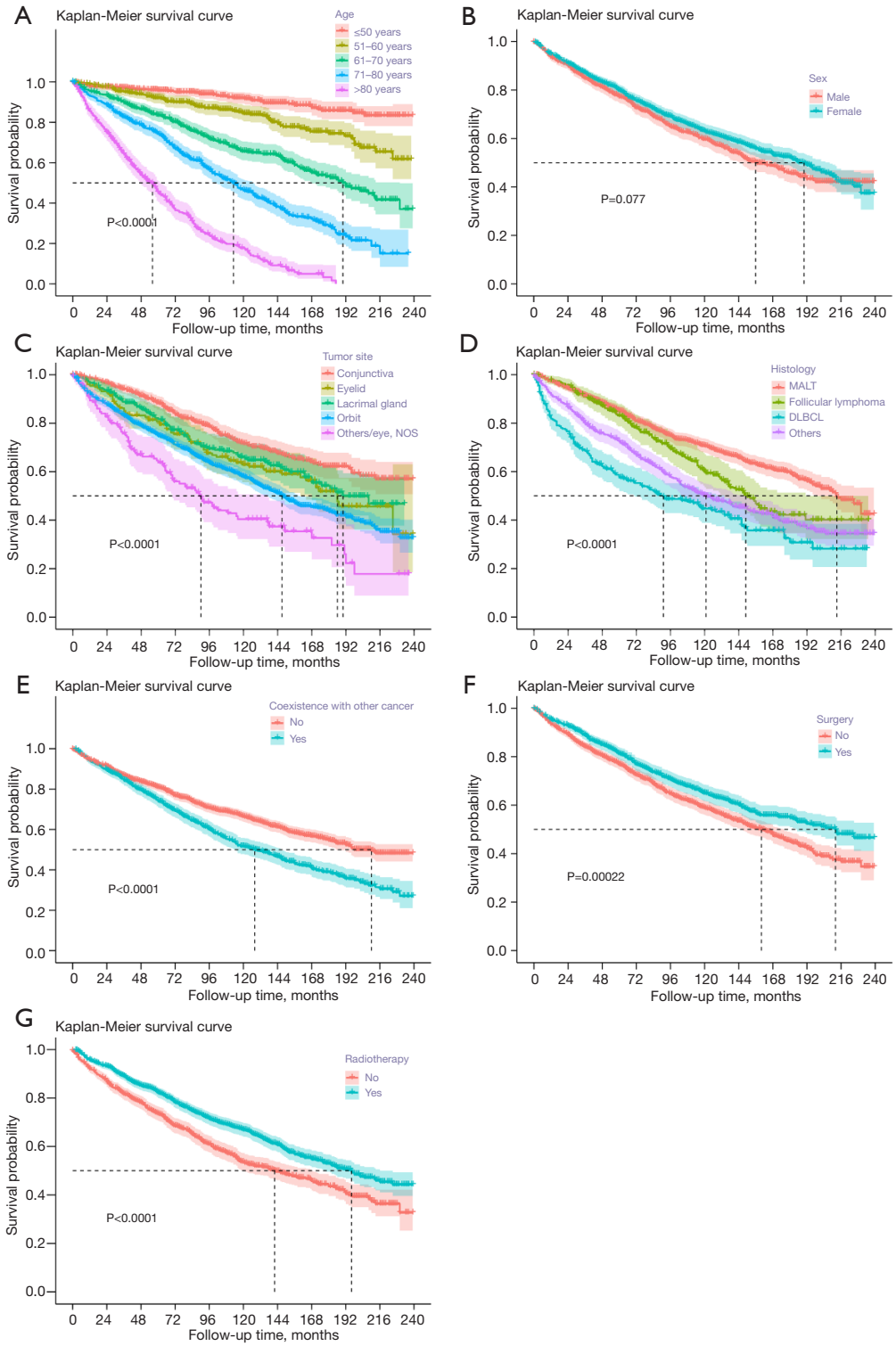

Figure 3 Kaplan-Meier survival curves depicting the relationship between seven significant predictors in multivariate analysis are displayed: (A) age; (B) sex; (C) tumor site; (D) histology; (E) coexistence with other cancers; (F) surgery; and (G) RT. P values resulting from the log-rank test are provided alongside the curves. NOS, not otherwise specified; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; RT, radiotherapy.

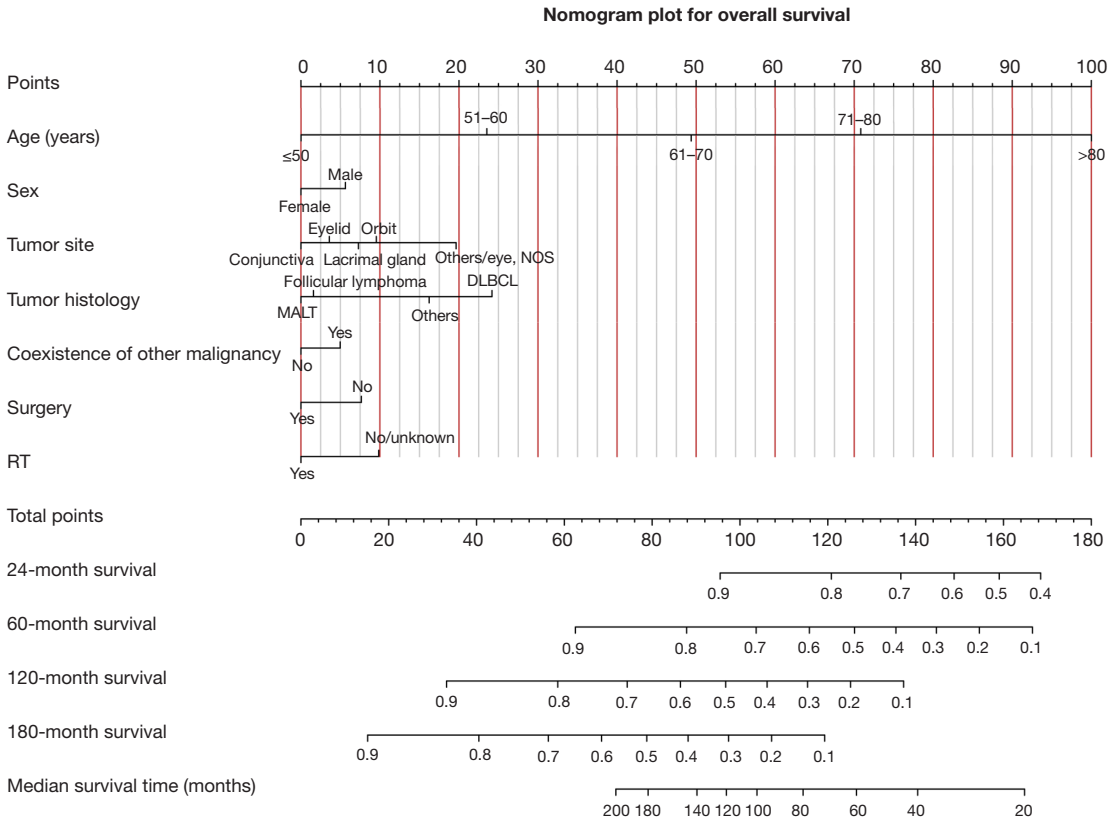

Figure 4 A nomogram model uses seven significant predictors to accurately predict survival rates at various time points, including 2, 5, 10, and 15 years, as well as the median survival time. NOS, not otherwise specified; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; RT, radiotherapy.

Univariate and multivariate Cox analyses were employed to identify potential prognostic factors. Utilizing significant prognostic factors, we have succeeded in constructing and validating a new POAL patient nomogram model to assist clinicians in providing personalized survival predictions.

The cause of POALs is not fully understood, which makes treatment challenging and highlights the need for further research (19). Some researchers suggested that chronic inflammation or autoimmune disorders might contribute to the development of extranodal reactive lymphoid hyperplasia (30). And prolonged exposure to such stimuli may lead to genetic instability and subsequent lymphocyte clonal transformation, ultimately resulting in POALs. While Ferreri *et al.* identified an association between *Chlamydophila psittaci* (*Cps*) and POALs, it is worth noting that the reported prevalence of *Cps* can vary significantly across different regions (28,31).

There are many prognostic factors related to POALs, including pathological type, primary site, clinical stage, etc. (32-34). Among them, the pathological type is the key factor in determining prognosis. Elderly patients often have more comorbidities and cannot tolerate highly toxic intensive treatment, which may directly have a negative impact on survival time.

Different pathological subtypes of lymphoma cells have varying levels of invasiveness, leading to differing degrees of malignancy and outcomes. Currently, there is no standardized protocol or set of guidelines for the treatment of POAL (19,28,30). Researches have shown that surgical treatment alone was more likely to result in long-term recurrence (28,35). Thus, a combination of surgery, radiation, and CT is commonly utilized in the treatment of POAL (27). The treatment plan for POAL is based on the patient's age, cancer stage, histologic type, and clinical manifestations at the time of diagnosis (19,36). The particular surgical method employed depends on the location, scope, and type of the lesion. Radiation therapy is now considered a feasible option for treating low-grade malignant POAL, providing a high

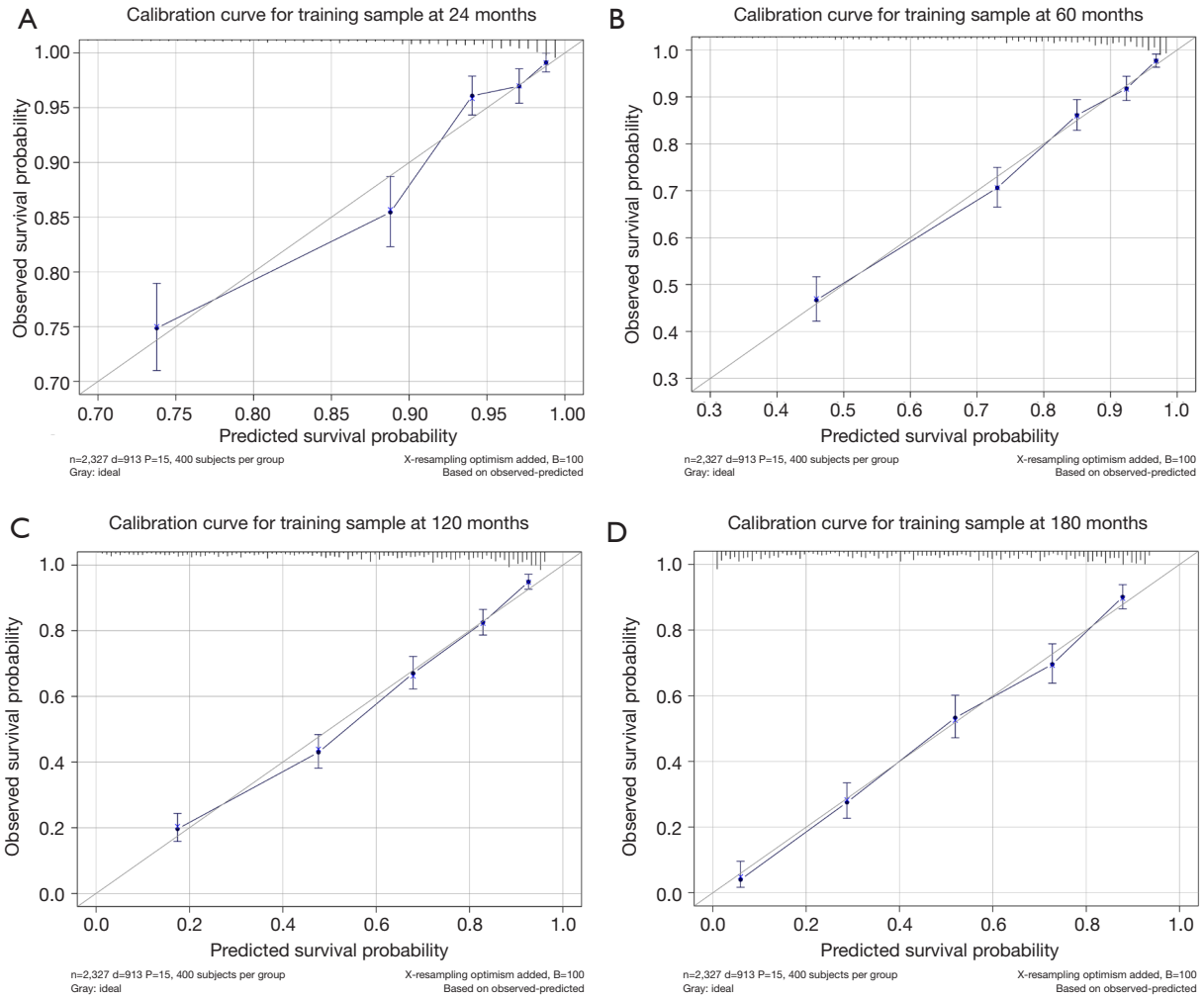

Figure 5 The calibration curves for the training group were 24 (A), 60 (B), 120 (C), and 180 (D) months. The consistency of the predicted and actual survival rates among the curves shows commendable performance.

rate of local remission whilst avoiding systemic side effects often associated with CT (35,36). Patients with various POAL subtypes have seen higher remission rates after receiving radiation therapy. In cases where there is highly malignant ocular adnexal lymphoma and/or systemic involvement, CT is necessary to reduce side effects and prolong survival (35). There are now numerous new treatment methodologies being employed for POAL treatment, providing patients with an increasing number of options. *Cps* infection is one of the potential pathogenic factors associated with POALs, making the treatment of primary infections a major focus of research for managing POALs (31). Radioimmunotherapy, which involves monoclonal antibodies coupled with radioactive nuclides targeted at human lesions, has been shown to provide maximum anti-tumor effects with minimal risk of damage to other areas of the body (37,38). This is a viable treatment alternative for patients with refractory and recurrent B-cell-derived ocular lymphomas. However, this therapy is yet to become a standard treatment, and as such, its use is relatively limited.

Due to the limited incidence rate of POALs, there is insufficient POAL data in literature and a lack of prognostic models at present (39). Recently, nomogram models have been recommended as crucial tools for personalized patient survival prediction in clinical management (34,40,41). Consequently, following multivariate analysis, we identified seven optimal variables and developed high-performance predictive models for POAL patients over 2, 5, 10, and 15 years. Our nomogram demonstrated excellent predictive proficiency for the clinical outcomes of these patients in

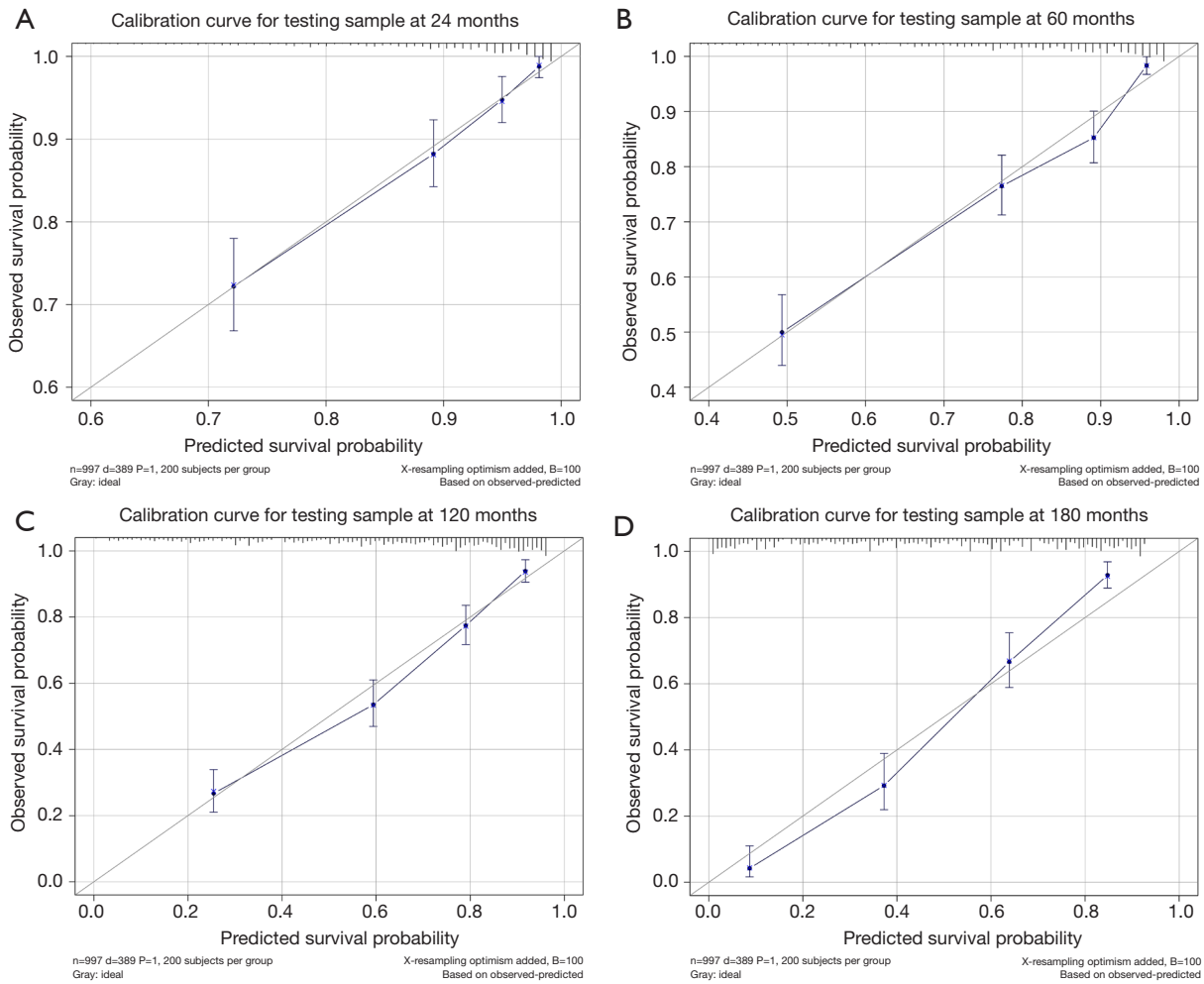

Figure 6 The calibration curves for the testing group were 24 (A), 60 (B), 120 (C), and 180 (D) months. The consistency of the predicted and actual survival rates among the curves shows commendable performance.

both the training and testing groups. Furthermore, the reliability and accuracy of our prediction model were confirmed with the use of the C-index, ROC, AUC, and calibration curve to verify the predicted values. To facilitate the model's clinical application, we developed an online survival calculator, accessible through the webpage (https://helloshinyweb.shinyapps.io/eye_dynamic_nomogram/). By inputting patient variables and time, survival probability with a 95% CI can be quickly obtained.

There are a few limitations worth noting in this study. To begin with, as a retrospective study, some degree of selection bias is unavoidable. Secondly, to ensure more reliable results, it is advisable to use another large-scale independent dataset for external validation. Moreover, the SEER database lacks detailed data on certain critical variables, such as quality of life, vision, and preoperative laboratory results, which are significant for POAL patient prognosis and may impact the predictive model. Lastly, advancements in lymphoma examination and diagnostic techniques may affect our findings. Nonetheless, we validated our results in the validation cohort and observed the nomogram's good performance, delivering useful information on POAL prognostic factors and patient survival.

Conclusions

In this study, we examined possible prognostic factors in patients diagnosed with POAL and created a dependable nomogram for predicting their OS. The nomogram demonstrated clinical utility and could assist healthcare professionals in evaluating risk factors for poor prognosis and developing personalized treatment strategies. Future

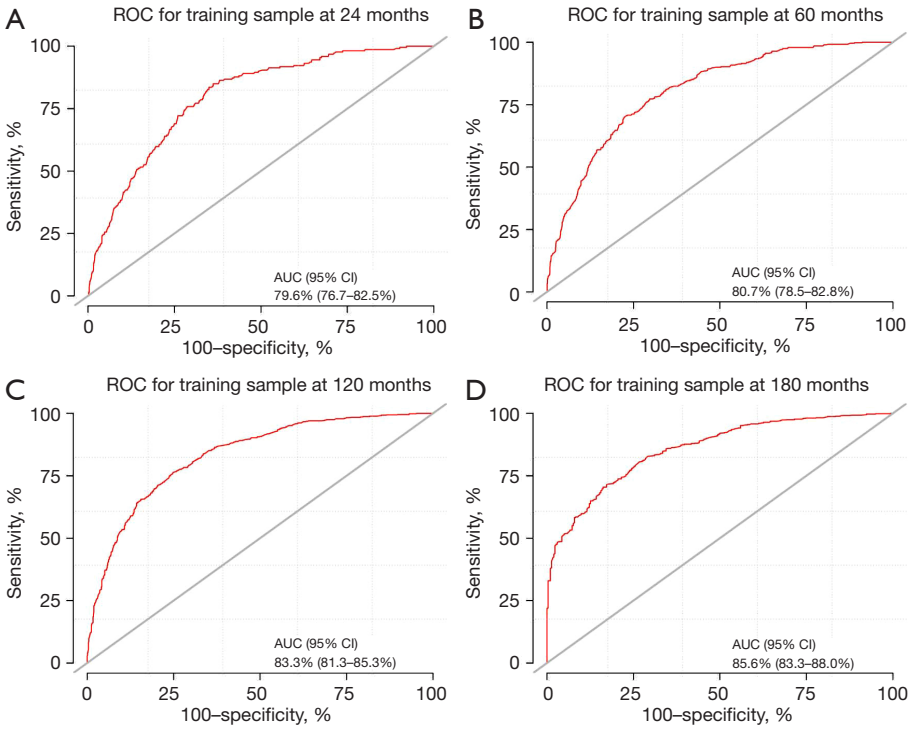

Figure 7 The ROCs curve with the AUC for the training group at different time intervals: 24 (A), 60 (B), 120 (C), and 180 (D) months. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.

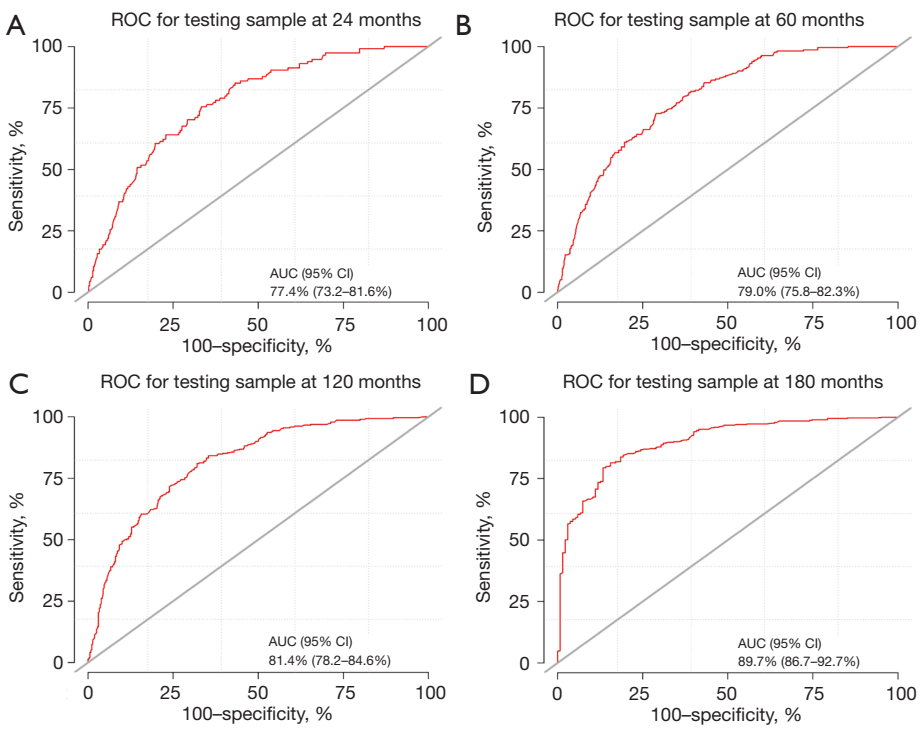

Figure 8 The ROCs curve with the AUC for the testing group at different time intervals: 24 (A), 60 (B), 120 (C), and 180 (D) months. ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.

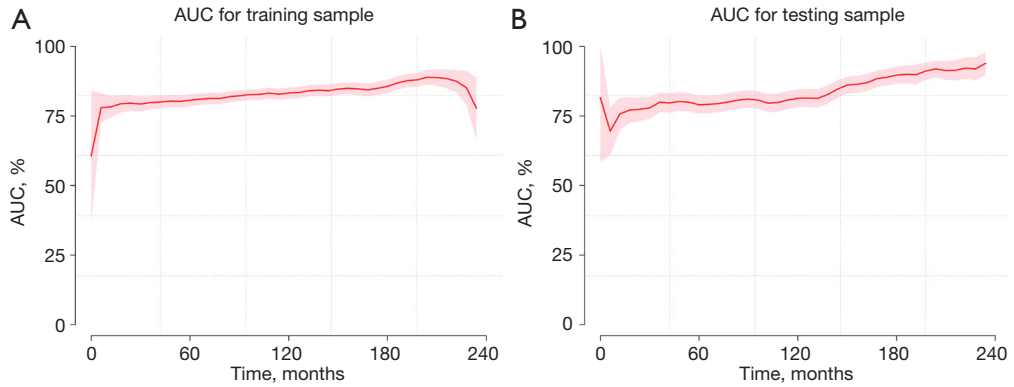

Figure 9 Time-dependent AUCs have been plotted for the training (A) and testing (B) groups. AUC, area under the ROC curve; ROC, receiver operating characteristic.

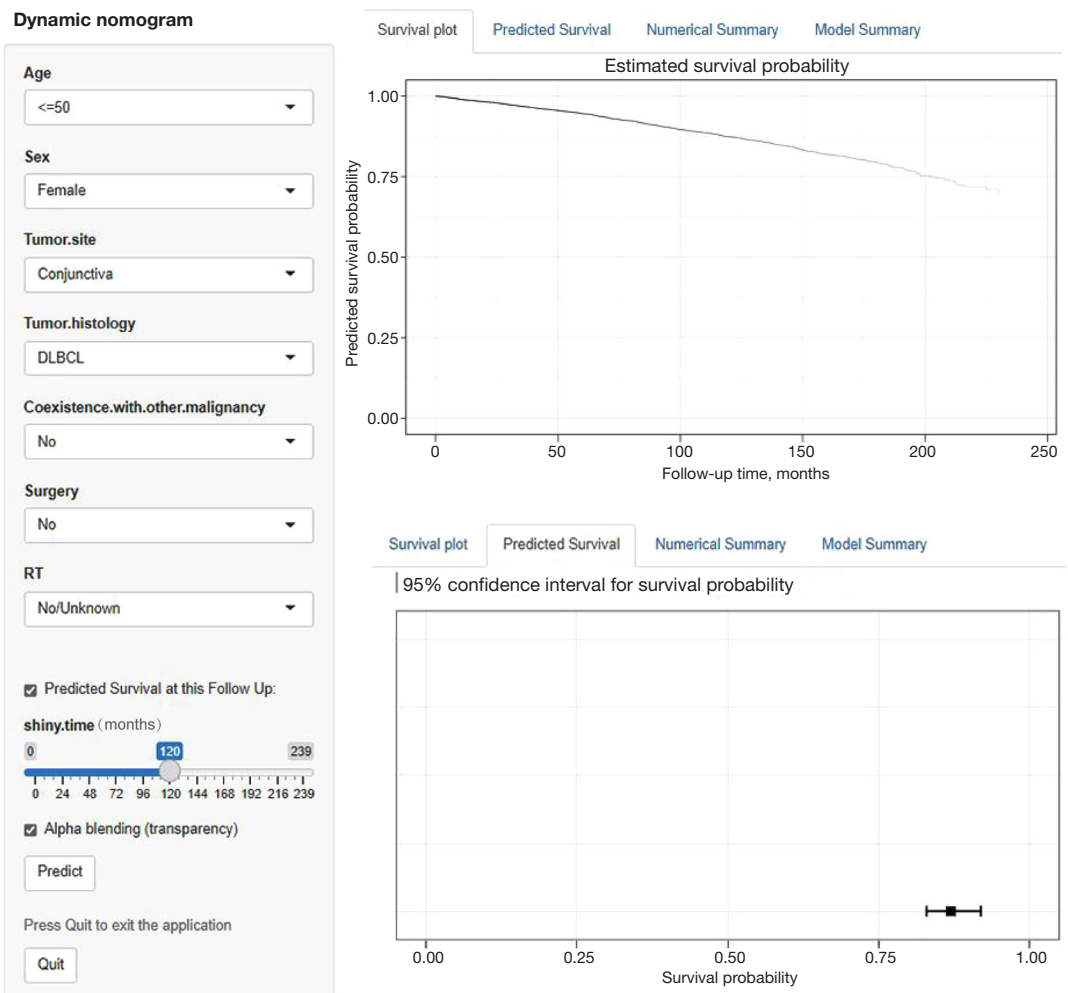

Figure 10 A snapshot of the interactive online nomogram. Upon specifying items, medical professionals could effortlessly plot the survival curve for an individual patient and forecast the survival rate at each point in time with ease and precision. DLBCL, diffuse large B-cell lymphoma; RT, radiotherapy.

research is necessary to validate our findings.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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