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Prognostic Factors and Prediction of Survival for Patients with Brain Metastases of Lung Adenocarcinoma

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Background: The study aimed to identify risk factors associated with overall survival (OS) of patients with lung adenocarcinoma (LACA) with brain metastasis and developed a prognostic tool (nomogram) for these patients.

Methods: LACA patients with brain metastases between 2010 and 2013 were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Kaplan-Meier analysis and a Cox regression model were used to assess the prognostic effect of variables on survival rate. A nomogram was developed to predict 3-, 6- and 9-month OS rates.

Results: 2,631 LACA patients with brain metastases were studied. A nomogram was developed by using variables that affected OS and was validated by internal bootstrap resampling, which revealed that the nomogram had satisfactory discrimination.

Conclusions: The nomogram was able to predict 3-, 6- and 9-month OS for patients with LACA and brain metastases. (J Nippon Med Sch 2021; 88: 319–325)

Key words: nomogram, lung adenocarcinoma, brain metastases, hazards model, SEER database

Introduction

Lung carcinoma is one of the most prevalent cancers worldwide. Because of its association with serious health problems, lung carcinoma has gained considerable attention in recent years[1–3]. In 2012, around 1.8 million people were diagnosed with lung carcinoma, and lung carcinoma caused 1.6 million deaths worldwide[4,5]. Non-small cell carcinoma (NSCLC) is the most prevalent lung carcinoma, and about 85% of patients are diagnosed with NSCLC, particularly lung adenocarcinoma (LACA, a histologic subtype of NSCLC)[6,7]. Brain metastasis occurs in about 20% to 40% of cancers[8]. Intracranial involvement occurs in about 40% to 60% of LACA patients and is present in about 10% of cases at first diagnosis[9,10]. Because of the severity of the disease, a feasible grading system is needed in order to stratify prognoses for patients with brain metastases of LACA.

Nomograms are a graphical tool that is extensively used to predict prognosis[11,12]. They can estimate the survival rate of individual patients more accurately by integrating important prognostic variables. However, cloud data on imaging of LACA patients with brain metastases are limited. Thus, we used data from the Surveillance, Epidemiology, and End Results (SEER) database to identify risk factors associated with overall survival (OS) and develop a nomogram for predicting the prognoses of patients with LACA and brain metastases.

Materials and Methods

Data Source

Data on cancer prevalence, incidence, mortality, and treatment were from the SEER database, which covered about 30% of the US population across 17 geographical regions in the United States[13]. Information on patients with brain metastases of LACA was retrieved by using SEER*Stat software (version 8.3.5)[14]. The Ethics Committee of the Institutional Review Board of Ningbo No. 2 Hospital approved this study and the consent form[15].

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This study was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 2,631 patients who had brain metastases of LACA during the period from January 2010 through December 2013 were included. The exclusion criteria were (1) age younger than 18 years at diagnosis; (2) diagnosis at autopsy or by death certification; (3) presence of multiple primary cancers or a past history of LACA; (4) missing or incorrect data on the rate of survival, tumor grade, duration of follow-up, or main cause of death.

Variables

Clinical and demographic variables were extracted with the SEER program, including race, sex, age, year of diagnosis, grade, history of surgery, history of radiotherapy, history of chemotherapy, cause of death, and follow-up information. Patients were classified by age at diagnosis as younger and older than 60 years. Race was classified as black, white, and other. The primary endpoint was OS, which was characterized as the time interval from diagnosis of LACA to death or last follow-up, with no restriction regarding the causes of mortality.

Statistical Analysis

Categorical variables are expressed by frequency and scale, followed by comparison with the Fisher exact test or chi-square test. The log-rank test was used to compare survival among subgroups. Cox analysis was used to calculate 95% confidence intervals (CIs) and hazard ratios. SPSS version 25.0 (Chicago, IL, USA) and R-3.5.1 (www.r-project.org) were used for the statistical analysis[16]. The nomogram for predicting OS was developed based on the Cox regression, and the R packages rms and mstate were used to frame the model[17]. The C-index for OS in the nomogram model measured variations in prognostic power between the observed and predicted data and was used to analyze nomogram discrimination[18]. A larger C-index indicates greater capability for patients with various survival outcomes[19]. The calibration plot and C-index were obtained by regression analysis. A calibration curve (along the 45-degree line) shows an appropriate calibration model, ie, one with a high level of similarity between predicted probabilities and actual results. All p-values are two-sided. A P-value of less than 0.05 was regarded as statistically significant.

Results

Patient Characteristics

A total of 2,631 patients with brain metastases of LACA were identified during the period from 2010 through 2013. **Table 1** shows the demographic and clinical features of the patients, 49.7% of whom were male. Most patients were white (75.9%) and older than 60 years (61.0%). Tumor grade was poorly differentiated, moderately differentiated, and well-differentiated in 64.5%, 29.5%, and 4.7% of cases, respectively.

Table 1 Baseline characteristics of the patients

Variables	All patients (n = 2,631)	
	No.	%
Sex		
Female	1,324	50.3
Male	1,307	49.7
Age		
≤60	1,027	39.0
>60	1,604	61.0
Race		
White	1,997	75.9
Black	335	12.7
Other[a]	299	11.4
Grade		
I	123	4.7
II	776	29.5
III	1,696	64.5
IV	36	1.4
Surgery history		
No	2,444	92.9
Yes	187	7.1
Radiotherapy history		
No	2,178	82.8
Yes	453	17.2
Chemotherapy history		
No	1,001	38.1
Yes	1,630	62.0

[a] Other includes American Indian/AK Native, Asian/Pacific Islander, and unknown.

Patients had previously been treated by surgery (7.1%), radiotherapy (17.2%), and chemotherapy (62.0%). By the end of follow-up, 2,303 (87.5%) patients had died, including 2,200 (95.5%) patients who died of brain metastasis of LACA and 103 (4.5%) who died of other causes.

Survival Analysis

Data from all 2,631 patients were included in Cox regression analyses to identify predictors of survival. As shown in **Figure 1**, survival differed by age, sex, and race, and tumor grade was a risk factor affecting survival. As shown in **Figures 1e～g**, history of surgery, history of radiotherapy, and history of chemotherapy were strongly associated with patient outcome.

We used Cox regression analysis to evaluate the effects of race, sex, age, grade, chemotherapy history, surgery history, and radiotherapy history (**Table 2**). In univariate

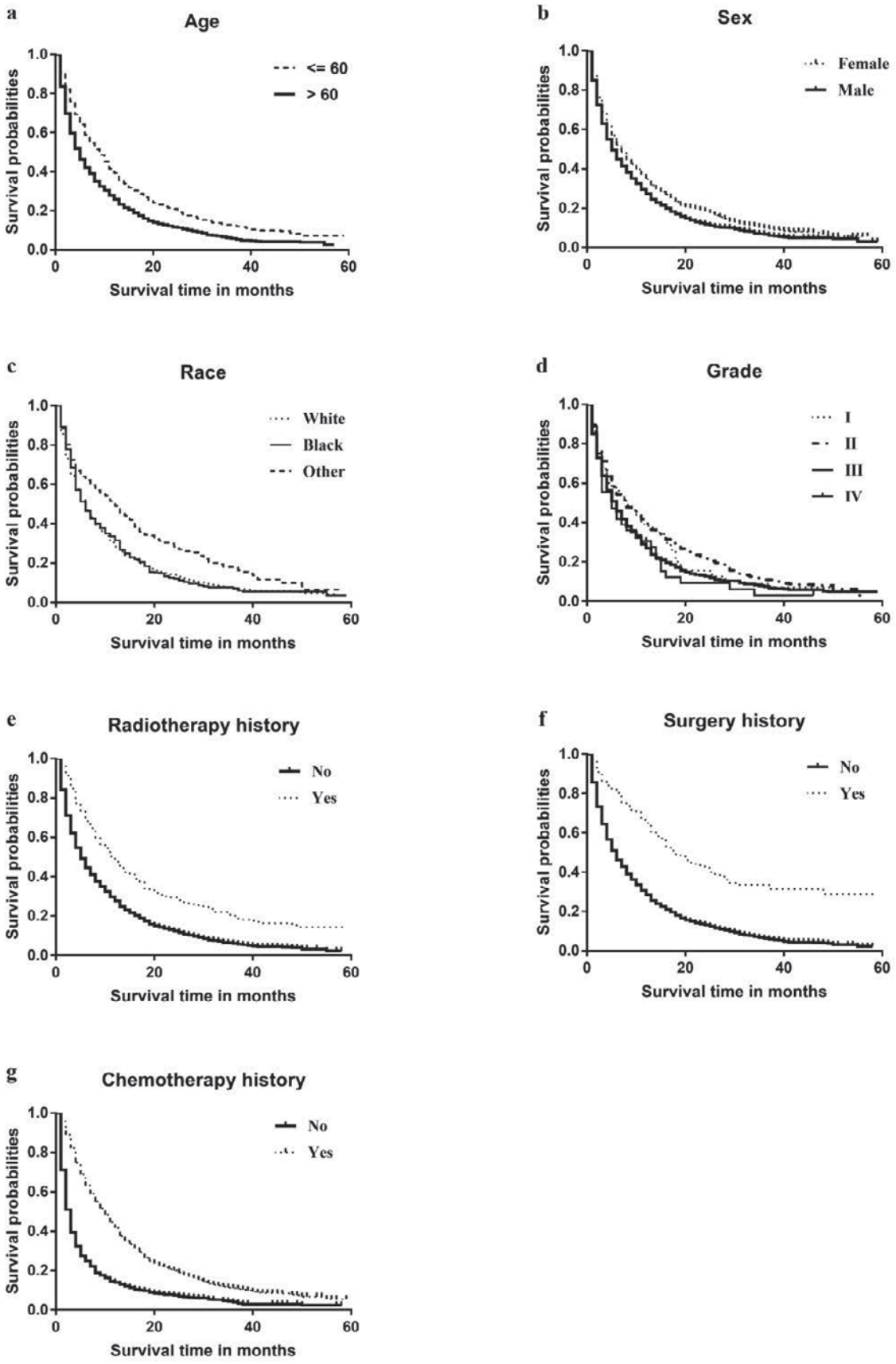

Fig. 1 Overall Kaplan–Meier survival curves for patients according to (a) age, (b) sex, (c) race, (d) grade, (e) radiotherapy history, (f) surgery history, and (g) chemotherapy history.

Table 2 Cox proportional hazards models of overall survival (OS)

Variables	Univariate		Multivariate	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Sex				
Female	1.00	<0.001	1.00	= 0.002
Male	1.20 (1.11-1.31)		1.14 (1.05-1.24)	
Age				
<60	1.00	<0.001	1.00	<0.001
≥60	2.16 (1.65-2.83)		1.27 (1.16-1.38)	
Race		<0.001		<0.001
White	1.00		1.00	
Black	0.99 (0.88-1.12)		0.94 (0.83-1.06)	
Other[a]	0.66 (0.58-0.76)		0.64 (0.56-0.73)	
Grade		<0.001		<0.001
I	1.00		1.00	
II	0.91 (0.74-1.11)		0.97 (0.79-1.19)	
III	1.17 (0.96-1.42)		1.27 (1.05-1.55)	
IV	1.27 (0.86-1.86)		1.33 (0.90-1.95)	
Surgery history				
No	1.00	<0.001	1.00	<0.001
Yes	0.40 (0.33-0.48)		0.45 (0.37-0.55)	
Radiotherapy history				
No	1.00	<0.001	1.00	<0.001
Yes	0.56 (0.50-0.63)		0.74 (0.65-0.84)	
Chemotherapy history				
No	1.00	<0.001	1.00	<0.001
Yes	0.46 (0.42-0.50)		0.46 (0.42-0.50)	

[a] Other includes American Indian/AK Native, Asian/Pacific Islander, and unknown.

analyses, all these variables were associated with OS. The independent prognostic variables were surgery history, radiotherapy history, chemotherapy history, age, sex, race, and grade ($p < 0.001$). After adjustment for other risk factors, a multivariate Cox regression model using step by step selection showed that the same variables identified in univariate analyses were independent predictors ($p < 0.01$).

Figure 2 shows the nomogram developed based on significant risk factors, as determined by multivariate analysis of OS at 3, 6, and 9 months. To measure 3-, 6- and 9-month OS rates, each factor was recognized based on total points at the top scale of the nomogram, and the total points were summed. Ultimately, 3-, 6- and 9-month OS rates were calculated by using the point scale at the bottom of the nomogram. Models showed significant precision, with a C-index of 0.697 (95% CI = 0.685-0.709) for the OS model, which indicates relatively good discriminating ability for predicting 3-, 6- and 9-month OS for LACA patients with brain metastases. The calibration curves based on bootstrap resampling validation were well standardized, ie, the points were close to the 45-degree line (**Fig. 3**).

Discussion

The present study analyzed 2,631 cases of LACA with brain metastases from the SEER database to develop a prognostic nomogram to predict OS at 3, 6, and 9 months. In a Cox model, age, sex, race, grade, surgery history, radiotherapy history, and chemotherapy history were independent prognostic factors. Internal bootstrap resampling was used to analyze the performance and discriminant features of the nomogram, which fit well with the actual observations of 3-, 6- and 9-month OS rate, as indicated by the C-index.

Because of its poor prognosis, high incidence, and high rate of recurrence, LACA with brain metastases is a large public health burden worldwide. However, there is no standard, efficient, international model for survival prediction. Hence, there is a compelling need for effective approaches that can identify patients at high risk for poor outcomes. Here, we developed a nomogram that defined significant prognostic factors that are readily accessible in clinical practice. The nomogram comprised independent prognostic factors from clinical practice. Sex, age, and race were previously identified as important prognostic variables for OS[20–22], and the present study

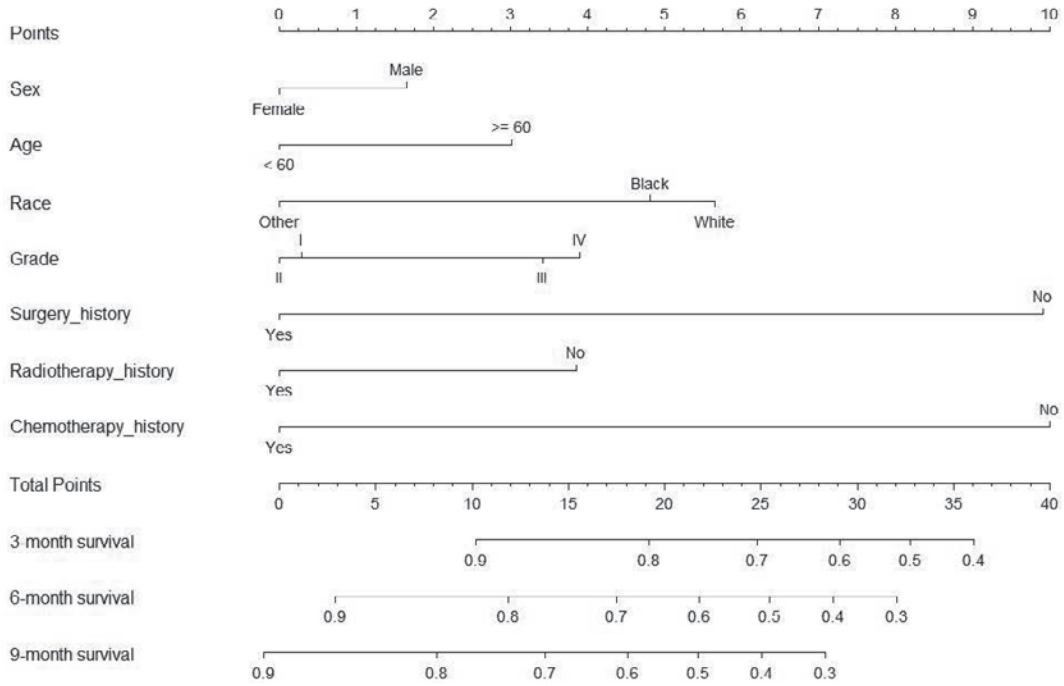

Fig. 2 Nomogram for predicting 3-, 6- and 9-month overall survival (OS) of LACA patients with brain metastases.

confirmed that survival was worse for older and male patients and better for married patients, possibly because they receive greater emotional support. Furthermore, grade, surgery history, radiotherapy history, and chemotherapy history were identified in this and past studies as independent factors for survival prediction[23,24].

Nomograms provide a basic graphical representation of complex models for quantification of individual risk and are comprehensively used in clinical practice and research[25]. Prediction of survival rate by nomograms is straightforward. First, for each clinical variable, a vertical line is drawn to the "points" line in the nomogram. Second, all "points" are added to obtain the "total points", and from "total points" a vertical line is drawn to the "OS" lines to determine survival. For instance, for a 61-year-old (3.1 points) male (1.8 points) with a grade I tumor (0.4 points) and a history of chemotherapy (0 points), the predicted 3-, 6- and 9-month OS would be 79%, 65%, and 54%, respectively. The present nomogram could enable pretreatment identification of patients at greater risk of death, thus improving clinical decision-making and patient follow-up.

The main advantages of this study are the rich, detailed samples and the simplicity of the models, which were confirmed as perfectly predictive. Data from all 2,631 suitable patients were included in the study, and the statistical data in underlined samples from population-based cancer registries are more general and authentic than those from single-center studies. Furthermore, the variables in the models can be acquired easily, and predictive hazard assessment for LACA patients with brain metastases was more complete. Our nomogram is accurate in predicting OS, and the nomogram presentation was confirmed by calibration.

As was the case for earlier studies of databases other than SEER, our study has some shortcomings associated with studies that use large population-based datasets. First, selection bias is a concern because of the retrospective review of the SEER database. Second, the SEER dataset does not have data on some clinical variables associated with prognosis, ie, vascular invasion, driver gene status, and Karnofsky performance status. Future studies should examine these other factors. Third, the predictive value calculated from nomograms is only for clinician reference, as not all prognostic factors are included in nomograms. Thus, precise prediction of prognosis is not possible in clinical practice.

Conclusions

In summary, using data from a large population we developed nomograms that were useful in predicting 3-, 6- and 9-month OS for LACA patients with brain metastases.

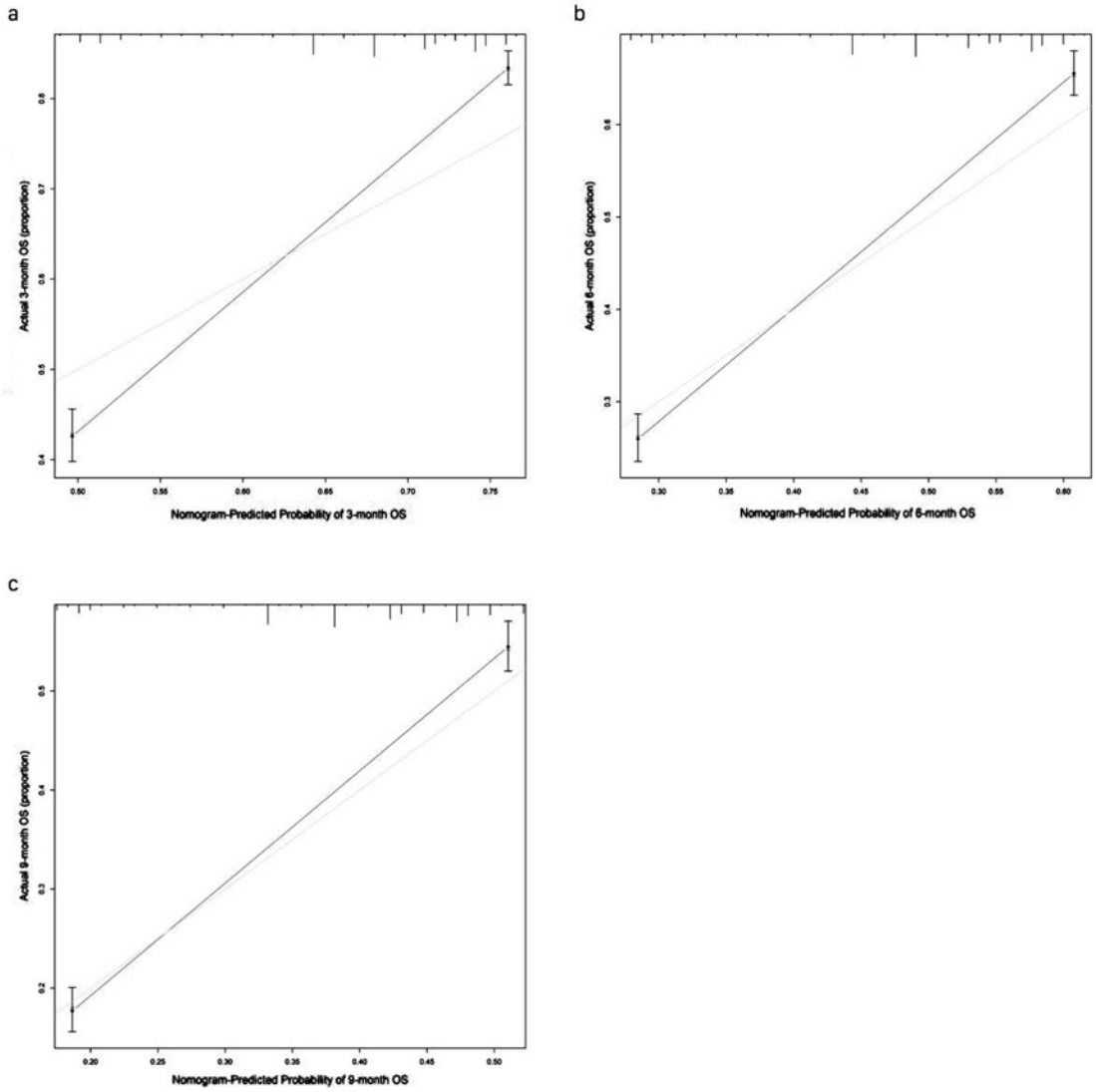

Fig. 3 Calibration plots of the nomogram for 3-, 6- and 9-month OS prediction (a, b, c). The X-axis shows nomogram-predicted probabilities of survival; the Y-axis shows actual OS values.

Authors' contributions: RJZ and DNG carried out the study analysis and data interpretation, and drafted the manuscript. MMW, YFR, YQD, and MLH participated in the analysis and interpretation of data, conceived the study, and helped in drafting the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare no conflicts of interest.

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