






## Research Article

# Development and Validation of a Prognostic Nomogram for Lung Adenocarcinoma: A Population-Based Study

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Received 23 June 2022; Revised 16 November 2022; Accepted 17 November 2022; Published 10 December 2022

Academic Editor: Nadeem Sarwar

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**Purpose.** To establish an effective and accurate prognostic nomogram for lung adenocarcinoma (LUAD). **Patients and Methods.** 62,355 LUAD patients from 1975 to 2016 enrolled in the Surveillance, Epidemiology, and End Results (SEER) database were randomly and equally divided into the training cohort ( $n = 31,179$ ) and the validation cohort ( $n = 31,176$ ). Univariate and multivariate Cox regression analyses screened the predictive effects of each variable on survival. The concordance index (C-index), calibration curves, receiver operating characteristic (ROC) curve, and area under the ROC curve (AUC) were used to examine and validate the predictive accuracy of the nomogram. Kaplan–Meier curves were used to estimate overall survival (OS). **Results.** 10 prognostic factors associated with OS were identified, including age, sex, race, marital status, American Joint Committee on Cancer (AJCC) TNM stage, tumor size, grade, and primary site. A nomogram was established based on these results. C-indexes of the nomogram model reached 0.777 (95% confidence interval (CI), 0.773 to 0.781) and 0.779 (95% CI, 0.775 to 0.783) in the training and validation cohorts, respectively. The calibration curves were well-fitted for both cohorts. The AUC for the 3- and 5-year OS presented great prognostic accuracy in the training cohort (AUC = 0.832 and 0.827, respectively) and validation cohort (AUC = 0.835 and 0.828, respectively). The Kaplan–Meier curves presented significant differences in OS among the groups. **Conclusion.** The nomogram allows accurate and comprehensive prognostic prediction for patients with LUAD.

## 1. Introduction

Lung cancer is the most common malignancy worldwide and is the leading cause of cancer-related death worldwide, accounting for 1.8 million deaths annually [1, 2]. Lung adenocarcinoma (LUAD) is the most common type of lung cancer, accounting for nearly 50% of non-small-cell lung cancers (NSCLC) [3, 4]. LUAD is characterized by a high degree of malignancy and poor prognosis [5]. In recent

years, the incidence and mortality of LUAD have increased, despite the introduction of novel therapeutic approaches including immunotherapy or molecular targeted therapy [6, 7]. Recently, several prognostic factors for the survival of LUAD patients have been reported [8–10]. The studies mainly focused on LUAD-related genes and biomarkers, but these results lack the integration of some critical clinical information. Therefore, it is necessary to identify high-risk prognostic factors for predicting the individualized survival

of patients with LUAD, and a nomogram is considered a good tool for predicting outcomes.

Nomograms, which can provide evidence-based, individualized, and highly accurate risk estimation, have been widely used for different types of cancer [11–13]. A nomogram is created by applying meaningful variables based on the results of regression analyses investigating potential prognostic factors, which contributed to better risk stratification and clinical decision-making [14–16]. The above makes the nomogram quite practical and easy to popularize.

The majority of previous nomograms in LUAD have focused on factors such as lesion size, lymph node metastasis, histological types, treatment factors, pathological stage, lymph node invasion, and age [17–19]. Nonetheless, there is a lack of comprehensive and accurate nomograms for predicting the survival of LUAD patients. The Surveillance, Epidemiology, and End Results (SEER) database is representative of the United States (US) population, with patient-level data abstracted from 18 geographically diverse populations including rural, urban, and regional populations [20]. It is widely used in cancer research [21, 22]. The SEER database contains rich information on LUAD patients; thus, it offers an excellent opportunity for LUAD study. Therefore, we used a cohort from the SEER database to develop a comprehensive, accurate, and effective nomogram for predicting the survival of LUAD patients.

## 2. Materials and Methods

**2.1. Data Sources.** Patients with LUAD were identified from the SEER database, a publicly available database, established in 1973. The database covers approximately 26% of the population of the US and includes 17 national population-based cancer registries [23]. Data from the SEER database includes demographic information as well as primary tumor site, tumor morphology, stage at diagnosis, the first course of cancer treatment, and follow-up information on the vital statistics of the patients with cancer. To include as much data as possible in the analysis, we retrieved database records from 1975 to 2016. All the patient information can be obtained from the supplementary section (supplementary 1. Date-AD and 2. Date-Code). (Available here).

**2.2. Study Design.** All included patients had data including definite LUAD diagnosis, age, sex, race, marital status, TNM staging, tumor size, grade, primary site, and overall survival (OS) information. LUAD was classified according to the International Classification of Diseases for Oncology, third edition (ICD-O-3), morphology codes: 8140, 8141, 8143, 8147, 8260, 8250–8257, 8323, 8480, 8481, 8550, 8570–8574, and 8576; and the site codes: C340–C343 and C348–C349. Patients with incomplete information listed above were excluded. The included patients were randomized into a training cohort ( $n = 31,179$ ) and a validation cohort ( $n = 31,176$ ) to develop and validate nomograms.

**2.3. Statistical Analysis.** All analyses were performed using R version 3.6.3 and R studio (<https://www.r-project.org/>). Cox

regression analysis was used for univariate and multivariate analyses.

A nomogram was created based on the risk factors identified from the multivariate analysis using packages of “rms,” “foreign,” and “survival” in R studio. The performance of the model was measured using the concordance index (C-index), calibration curves, receiver operating characteristic (ROC) curve, and the area under the ROC curve (AUC). The larger the C-index, the more accurate the prognostic prediction [24]. We use the “predict” function in the “survival” R package to calculate the risk score of the samples in the training cohorts. Based on the median risk score, the samples were then divided into a high-risk group and a low-risk group. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. During the internal validation of the nomogram, the C-index, calibration curves, and ROC curves were derived from the regression analysis using the same R package described above. A  $P$  value  $< 0.05$  was considered statistically significant.

## 3. Results

**3.1. Clinical Characteristics of Patients.** A total of 67,146 patients with LUAD were identified from the SEER database. Of these, 62,355 patients who satisfied the inclusion criteria were enrolled and randomly divided into the training ( $n = 31,179$ ) and validation ( $n = 31,176$ ) cohorts. The methods used for data collection and analysis are summarized in Figure 1. The clinical characteristics of patients are listed in Table 1.

**3.2. Independent Prognostic Factors in the Training Cohort.** The results of the univariate and multivariate analyses are presented in Table 2. The multivariate analyses demonstrated that age, sex, race, marital status, AJCC-N, AJCC-M, tumor size, grade, and the primary tumor site were independent risk factors for OS.

**3.3. Prognostic Nomogram for OS.** The nomogram was constructed using all significant independent factors derived from the regression analysis above and the AJCC-T (an important aspect of AJCC-TMN staging) for OS in the training cohort (Figure 2). The C-index of this model for OS prediction was 0.777 (95% confidence interval (CI), 0.773 to 0.781). Furthermore, the calibration plot for the probability of survival at 3 or 5 years presented good agreement between nomogram prediction and actual observation (Figures 3(a) and 3(b)). AUC for the 3- and 5-year OS was 0.832 and 0.827 in the training cohort (Figures 4(a) and 4(b)), respectively, showing good accuracy of the nomogram.

**3.4. Validation of the Nomogram.** In the validation cohort, the C-index of this model for OS prediction was 0.779 (95% CI, 0.775 to 0.783), slightly higher than that of the training cohort. The calibration curves also presented good agreement between prediction and observation for the 3- and 5-year survival probabilities (Figures 5(a) and 5(b)). The ROC curves showed good accuracy of the nomogram for predicting 3- or

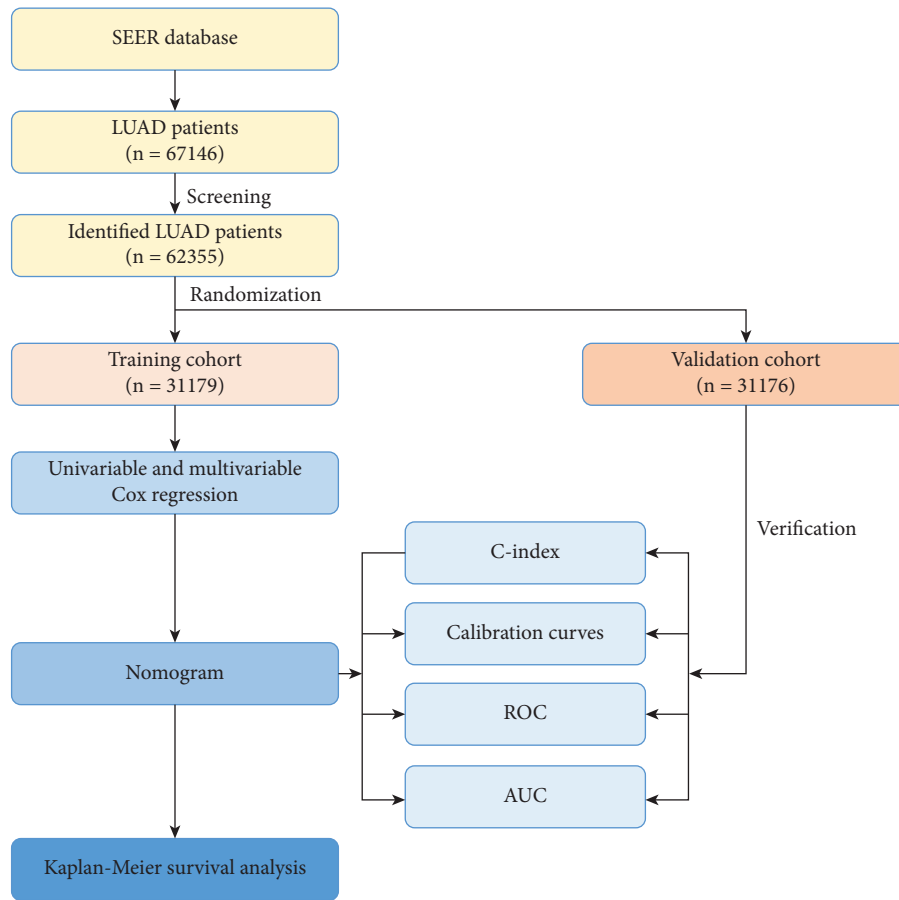


FIGURE 1: Data analysis workflow.

5-year OS, as shown in Figures 6(a) and 6(b) (AUC = 0.835 and 0.828, respectively).

**3.5. Survival and Prognostic Factors for OS.** The Kaplan–Meier analysis was conducted to identify vital prognostic factors that could be useful to predict the outcome. The effects of vital factors for predicting OS across all patients with LUAD are shown in Figure 7. We found survival rates were significantly higher in the low-risk group than in the high-risk group (Figure 7(a)). As shown in Figure 7(b), patients aged 60–69 years had the best survival, but patients over 80 years had the worst survival. Survival for the other age groups was between patients aged 60–69 years and patients over 80 years, in order of worsening survival, 50–59, <50, and 70–79 ( $P < 0.0001$ ). Male patients presented better survival than female patients ( $P < 0.0001$ ) (Figure 7(c)). Further analysis showed that other races were associated with better outcomes compared with white and black races ( $P < 0.0001$ ) (Figure 7(d)). Married patients (including married and domestic partners) showed better survival than single patients (including single, widowed, divorced, and separated), as shown in Figure 7(e) ( $P < 0.0001$ ). Better survival was observed in LUAD stage T1 than in other stages (Figure 7(f)) ( $P < 0.0001$ ). Different from the T stage, patients in the N0 stage exhibited better survival than in the N1, N2, or N3 stages (Figure 7(g)) ( $P < 0.0001$ ). The survival probability in the M0

stage was higher than in the M1 stage (including M1a and M1b) (Figure 7(h)) ( $P < 0.0001$ ). As illustrated in Figure 7(i), the smaller the tumor size, the better the survival generally. However, the not otherwise specified (NOS) group presented the worst survival probability ( $P < 0.0001$ ). In the plot association between grade level and survival, grade I had better survival than other grades (Figure 7(j)) ( $P < 0.0001$ ). However, patients with grade IV tumors achieved better survival than grade III patients. In Figure 7(k), patients with the primary site at the middle lobe showed better survival than those with primary sites at the lower lobe, upper lobe, overlapping lesion of the lung, lung NOS, or the mainstem bronchus ( $P < 0.0001$ ).

#### 4. Discussion

LAUD is a highly heterogeneous tumor in terms of pathology, biology, and clinical behavior, which leads to significant challenges to therapy and prognostic prediction [25, 26]. In the past, several different approaches have been attempted to predict the prognosis of LAUD patients, for example, using features from pathology images, molecule biomarkers based on bioinformatics analysis and laboratory data, and clinical staging [27–29]. Here, our research focused on the combination of pathology, bioinformatics, and clinical characteristics of LAUD patients and provided a more accurate assessment of the prognosis of LAUD

TABLE 1: Clinical characteristics of patients with lung adenocarcinoma.

Variables	Total ( $n = 62355$ )	Training cohort ( $n = 31179$ )	Validation cohort ( $n = 31176$ )
Age (years), $n$ (%)			
<50	2469 (3.96)	1246 (4.00)	1223 (3.92)
50–59	10101 (16.20)	5109 (16.39)	4992 (16.01)
60–69	19589 (31.42)	9762 (31.31)	9827 (31.52)
70–79	20425 (32.76)	10200 (32.71)	10225 (32.80)
≥80	9771 (15.67)	4862 (15.59)	4909 (15.75)
Sex, $n$ (%)			
Female	33618 (53.91)	16768 (53.78)	16850 (54.05)
Male	28737 (46.09)	14411 (46.22)	14326 (45.95)
Race, $n$ (%)			
Black	6773 (10.86)	3372 (10.81)	3401 (10.91)
White	50222 (80.54)	25170 (80.73)	25052 (80.36)
Others	5360 (8.60)	2637 (8.46)	2723 (8.73)
Marital status, $n$ (%)			
Married	35027 (56.17)	17527 (56.21)	17500 (56.13)
Single	27328 (43.83)	13652 (43.79)	13676 (43.87)
AJCC_T, $n$ (%)			
T0	43 (0.07)	19 (0.06)	24 (0.08)
T1	21609 (34.65)	10722 (34.39)	10887 (34.92)
T2	19632 (31.48)	9892 (31.73)	9740 (31.24)
T3	10844 (17.39)	5392 (17.29)	5452 (17.49)
T4	10227 (16.40)	5154 (16.53)	5073 (16.27)
AJCC_N, $n$ (%)			
N0	36208 (58.07)	18112 (58.09)	18096 (58.04)
N1	5687 (9.12)	2847 (9.13)	2840 (9.11)
N2	15450 (24.78)	7743 (24.83)	7707 (24.72)
N3	5010 (8.03)	2477 (7.94)	2533 (8.12)
AJCC_M, $n$ (%)			
M0	42862 (68.74)	21459 (68.83)	21403 (68.65)
M1	19493 (31.26)	9720 (31.17)	9773 (31.35)
Tumor size (cm), $n$ (%)			
≤3	32231 (51.69)	15990 (51.28)	16241 (52.09)
3–5	14814 (23.76)	7483 (24.00)	7331 (23.51)
5–7	6715 (10.77)	3362 (10.78)	3353 (10.76)
≥7	5070 (8.13)	2564 (8.22)	2506 (8.04)
NOS	3525 (5.65)	1780 (5.71)	1745 (5.60)
Grade, $n$ (%)			
I	11626 (18.64)	5783 (18.55)	5843 (18.74)
II	24877 (39.90)	12427 (39.86)	12450 (39.93)
III	25328 (40.62)	12681 (40.67)	12647 (40.57)
IV	524 (0.84)	288 (0.92)	236 (0.76)
Primary site, $n$ (%)			
Mainstem bronchus	940 (1.51)	482 (1.55)	458 (1.47)
Upper lobe	35977 (57.70)	17968 (57.63)	18009 (57.77)
Middle lobe	3150 (5.05)	1589 (5.10)	1561 (5.01)
Lower lobe	18737 (30.05)	9336 (29.94)	9401 (30.15)
Overlapping lesion of lung	623 (1.00)	309 (0.99)	314 (1.01)
Lung NOS	2928 (4.70)	1495 (4.79)	1433 (4.60)

AJCC\_T, American Joint Committee on Cancer\_Tumor; AJCC\_N, American Joint Committee on Cancer\_Node; AJCC\_M, American Joint Committee on Cancer\_Metastasis; NOS, not otherwise specified.

patients. We considered a nomogram to be an appropriate choice.

In our study, we evaluated the prognostic factors in the SEER database using Cox regression analysis (Tables 1 and 2). The SEER database provides a public population-based database, which means less inconsistency than that of institutions [30, 31]. In our study, age, sex, race, marital status, TNM stages, tumor size, grade, and primary site were considered and identified as predictors of OS in patients with

LAUD (Tables 1 and 2). With increasing T stages, hazard ratio (HR) values increased, although  $P$  values were not significant in the multivariate Cox regression analyses. We think the few patients in the T0 stage ( $n = 19$ ) in the training cohort may be attributed to the result (Table 1). Nonetheless, T staging still plays a crucial role in predicting the survival of lung cancer patients [32, 33]. Thus, we took the AJCC-T stage into account for the construction of the nomogram to avoid any inappropriate exclusion of this variable. In

TABLE 2: Univariate and multivariate Cox regression analyses in the training cohort.

Variables	Univariate			Multivariate		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age (years)						
<50	Ref			Ref		
50–59	1.021	0.938–1.110	0.637	1.245	1.144–1.355	<0.001
60–69	0.947	0.874–1.026	0.184	1.386	1.278–1.503	<0.001
70–79	1.083	1.000–1.174	0.049	1.817	1.670–1.970	<0.001
≥80	1.512	1.391–1.643	<0.001	2.529	2.325–2.751	<0.001
Sex						
Female	Ref			Ref		
Male	1.454	1.411–1.498	<0.001	1.401	1.358–1.445	<0.001
Race						
Black	Ref			Ref		
Others	0.716	0.667–0.768	<0.001	0.736	0.686–0.790	<0.001
White	0.848	0.810–0.889	<0.001	0.989	0.944–1.038	0.661
Marital status						
Married	Ref			Ref		
Single	1.190	1.155–1.226	<0.001	1.250	1.211–1.290	<0.001
AJCC_T						
T0	Ref			Ref		
T1	0.444	0.246–0.803	0.007	1.080	0.596–1.960	0.799
T2	0.868	0.480–1.568	0.639	1.193	0.657–2.165	0.562
T3	1.357	0.751–2.453	0.312	1.328	0.732–2.410	0.351
T4	1.971	1.091–3.562	0.025	1.401	0.772–2.541	0.267
AJCC_N						
N0	Ref			Ref		
N1	1.889	1.793–1.990	<0.001	1.401	1.328–1.478	<0.001
N2	3.353	3.239–3.471	<0.001	1.701	1.636–1.770	<0.001
N3	4.479	4.265–4.704	<0.001	1.743	1.651–1.841	<0.001
AJCC_M						
M0	Ref			Ref		
M1	4.949	4.798–5.105	<0.001	3.023	2.912–3.139	<0.001
Tumor size (cm)						
≤3	Ref			Ref		
3–5	2.003	1.929–2.080	<0.001	1.244	1.185–1.306	<0.001
5–7	2.962	2.828–3.103	<0.001	1.396	1.320–1.477	<0.001
≥7	3.555	3.381–3.737	<0.001	1.591	1.497–1.692	<0.001
NOS	5.692	5.384–6.017	<0.001	1.878	1.758–2.007	<0.001
Grade						
I	Ref			Ref		
II	1.478	1.407–1.553	<0.001	1.237	1.177–1.301	<0.001
III	2.922	2.787–3.064	<0.001	1.710	1.626–1.798	<0.001
IV	2.725	2.353–3.155	<0.001	1.613	1.392–1.870	<0.001
Primary site						
Mainstem bronchus	Ref			Ref		
Upper lobe	0.327	0.297–0.361	<0.001	0.750	0.680–0.828	<0.001
Middle lobe	0.311	0.276–0.349	<0.001	0.731	0.649–0.823	<0.001
Lower lobe	0.324	0.293–0.358	<0.001	0.775	0.701–0.857	<0.001
Overlapping lesion of lung	0.484	0.410–0.571	<0.001	0.878	0.744–1.037	0.126
Lung NOS	0.757	0.678–0.847	<0.001	0.845	0.755–0.946	0.003

AJCC\_T, American Joint Committee on Cancer\_Tumor; AJCC\_N, American Joint Committee on Cancer\_Node; AJCC\_M, American Joint Committee on Cancer\_Metastasis; NOS, not otherwise specified; HR, hazard ratio; CI, confidence intervals; Ref, reference.

addition, we used the AJCC 8th Edition for lung cancer to precisely classify the lesion sizes of LUAD patients and to define the relationship between tumor size and prognosis. The nomogram was then constructed based on the training cohorts to predict the 3- and 5-year OS of LAUD patients (Figure 1). The nomogram we established was more targeted for LUAD patients than the nomogram established for non-

small-cell lung cancer (NSCLC) patients [34]. The C-index of the nomogram was 0.777 (95% CI, 0.773 to 0.781) in the training cohorts, indicating a good concordance between prediction and actual OS. Furthermore, we found a good concordance in the calibration curves (Figures 2(a) and 2(b)) as well as for the ROC curves (Figures 3(a) and 3(b), AUC = 0.832 and 0.827, respectively) for 3- and 5-year OS.

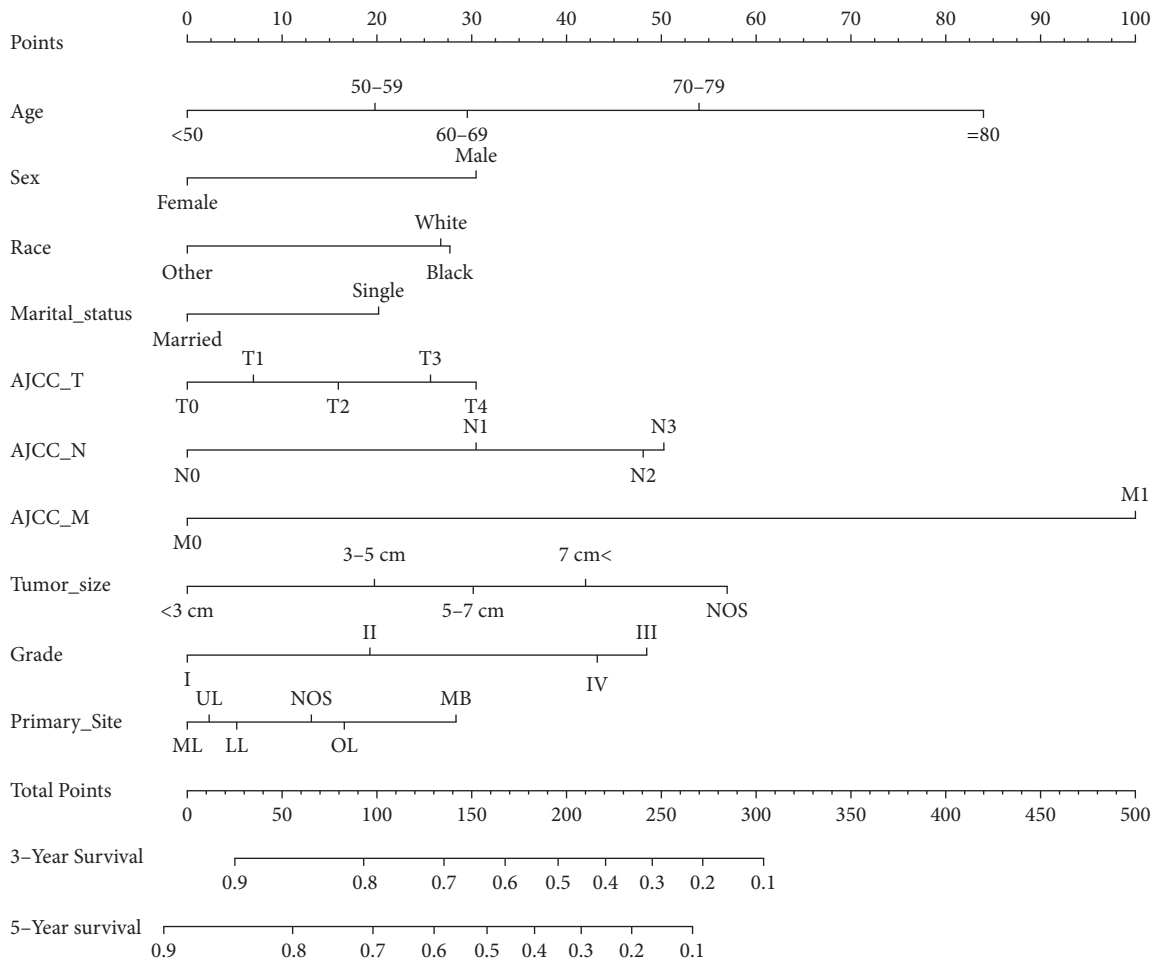


FIGURE 2: Lung adenocarcinoma survival nomogram. A nomogram-predicted survival risk based on age, sex, and other factors in patients with lung adenocarcinoma. A patient’s value is located on each variable axis, and the score corresponds to the number on the top line.

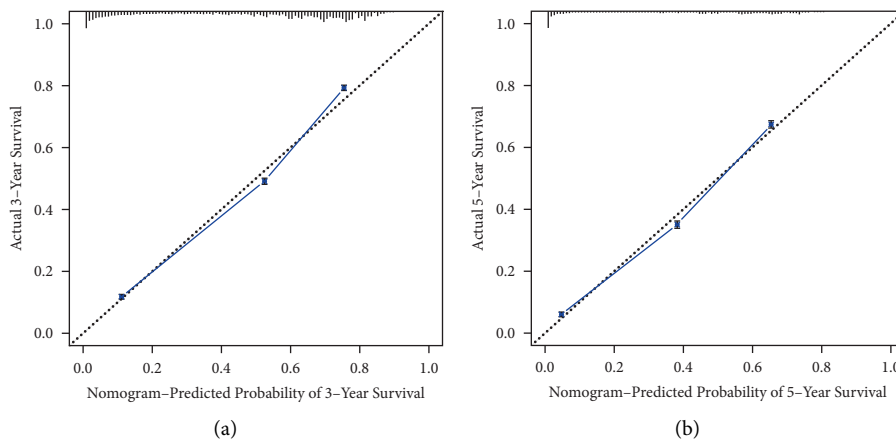


FIGURE 3: Calibration curves for training cohort. The calibration curves for predicting the overall survival of patient at (a) 3 and (b) 5 years in the training cohort. Nomogram-predicted probability of overall survival and actual survival proportion is plotted on the x-axis and y-axis, respectively.

All these results illustrated that the nomogram model achieved good predictive accuracy. We considered the relatively high predictive accuracy of the nomogram from three aspects. First, we choose an appropriate method, univariable

and multivariable Cox regression analyses, to analyze the relationship between predictive factors and prognosis. Second, the predictive factors we chose and identified are more closely associated with each LAUD patient. Most of

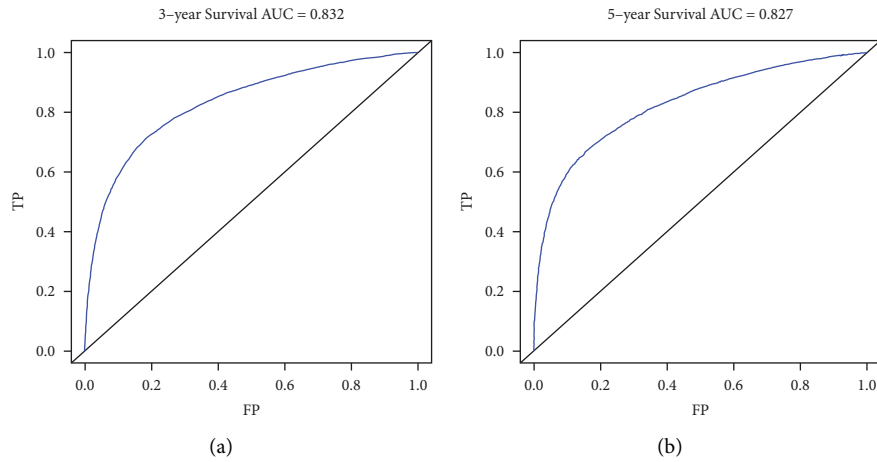


FIGURE 4: Receiver operating characteristic curves for training cohort. Receiver operating characteristic (ROC) curves for (a) 3 and (b) 5 years in the training cohort.

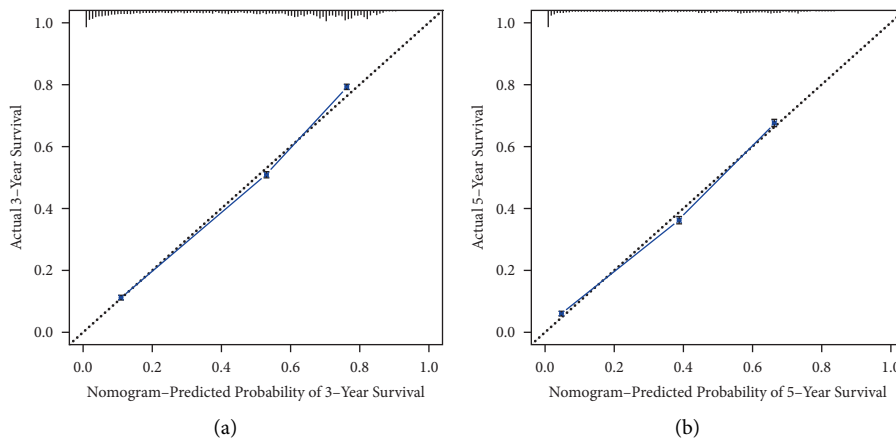


FIGURE 5: Calibration curves for validation cohort. The calibration curves for predicting the overall survival of patient at (a) 3 and (b) 5 years in the validation cohort. Nomogram-predicted probability of overall survival and actual survival proportion is plotted on the *x*-axis and *y*-axis, respectively.

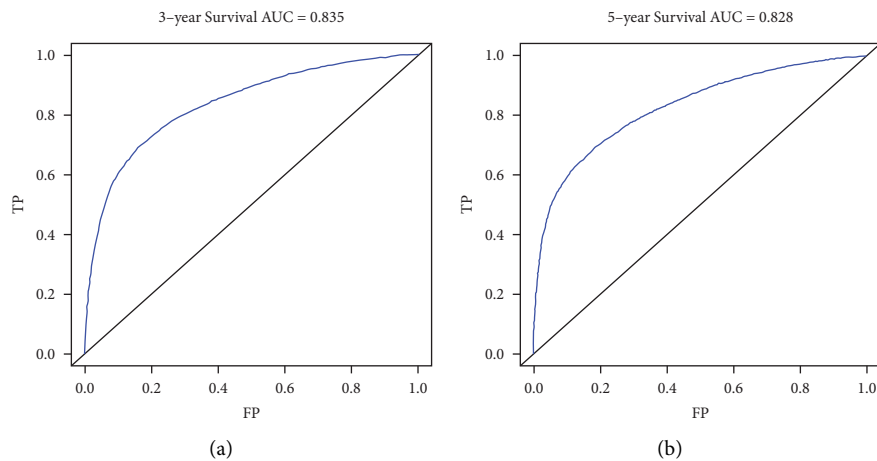


FIGURE 6: Receiver operating characteristic curves for validation cohort. Receiver operating characteristic (ROC) curves for (a) 3 and (b) 5 years in the validation cohort.

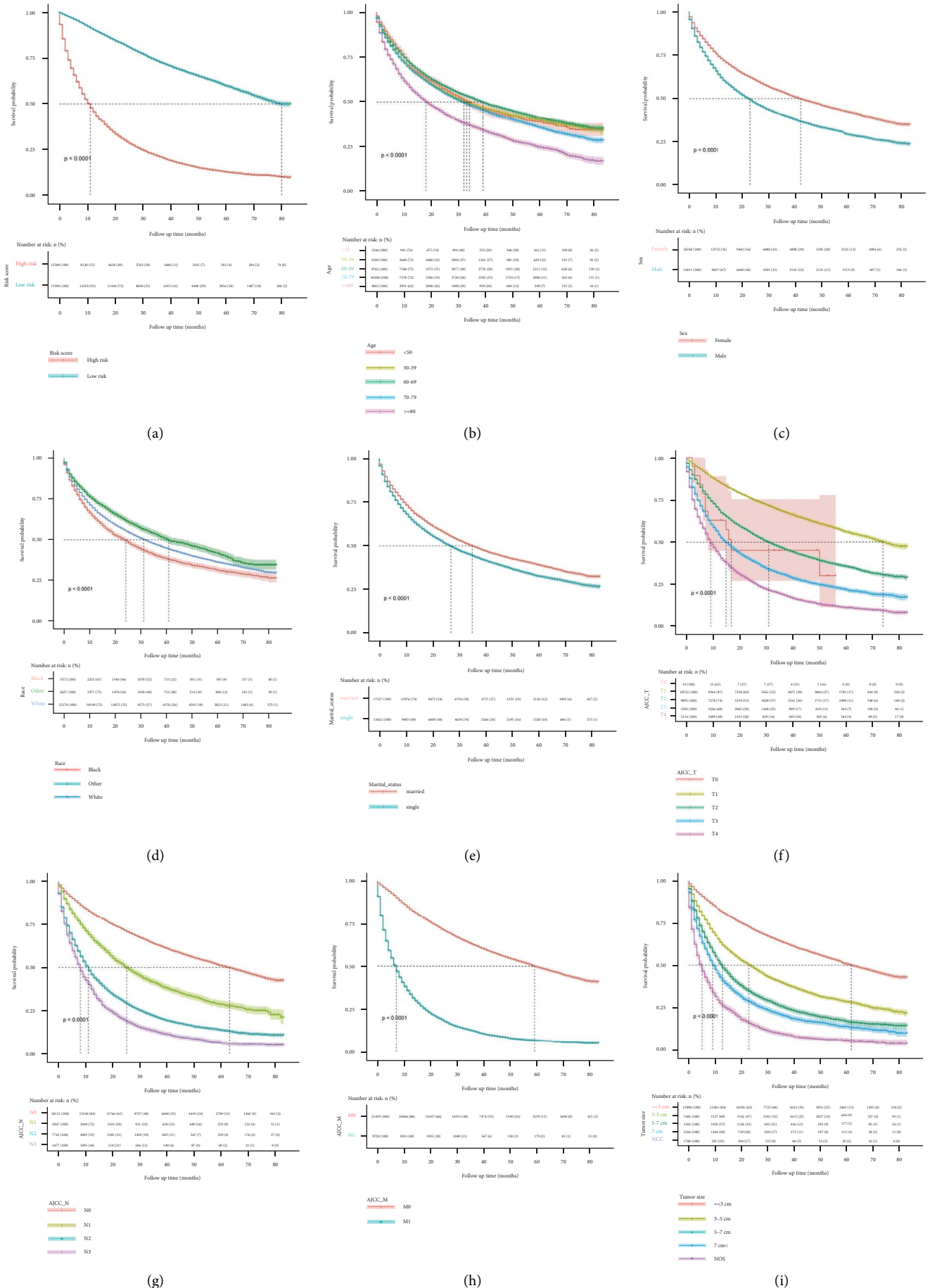


FIGURE 7: Continued.



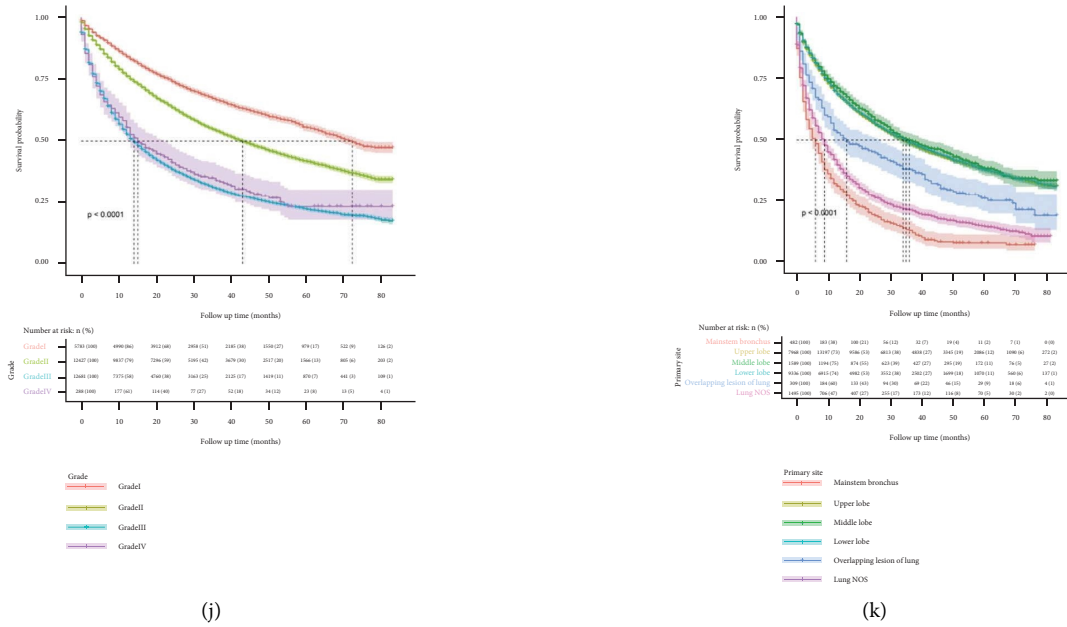


FIGURE 7: Kaplan–Meier survival curves of the training cohort. Kaplan–Meier survival curves for the training cohort on the basis of the nomogram. (a) Risk level; (b) age; (c) gender; (d) race; (e) marital status; (f) AJCC–T stage; (g) AJCC–N stage; (h) AJCC–M stage; (i) tumor size; (j) grade; (k) primary site.

these variables had been reported in previous studies as risk factors for NSCLC survival [35–41]. Thus, our nomogram integrated these closely related factors for all LAUD patients. Other factors, such as chronic obstructive pulmonary disease (COPD), cigarette smoking, and surgery, are not required for all LAUD patients [33]. So, we did not include those risk factors in the analysis. Third, to some extent, the large number of patients included in the analysis contributed to the accuracy of the model.

The C-index, calibration curves, ROC curves, and AUC values were also used to validate the predictive accuracy of the nomogram in the validation cohorts. The C-index was 0.779 (95% CI, 0.775 to 0.783) in the validation cohort, which was higher than the training cohort. The calibration lines overlapped more closely to the standard lines than the training cohort (Figures 4(a) and 4(b)). The AUC values under the ROC curves for the 3- and 5-year OS showed better concordance in the validation than in the training cohort (Figures 5(a) and 5(b), AUC = 0.835 and 0.828, respectively). Hence, in the current study, the C-indexes, calibration plots, ROC curves, and AUC values showed optimal agreement between prediction and actual observation, guaranteeing the repeatability and reliability of the constructed nomogram. Overall, the nomogram was able to predict the prognosis of LUAD patients effectively and precisely.

However, the primary limitation of our research is the lack of external validation. Some studies have examined the generalizability of their constructed nomograms via external validation [42]. But our model is based on a large set of globally representative data, which enhances its generalizability. Our use of random sampling and effective internal verification ensured the accuracy of the prediction. At the

same time, it is relatively difficult to collect enough LUAD patients for external validation in a short time. Larger multicenter studies will be needed in the future due to the lack of external validation in our study.

Furthermore, we investigated the impact of prognostic factors on patient survival. The cutoff value of the risk score determined by the Cox regression analyses was used to stratify patients into two groups. Patients with a low-risk score ( $\leq 0.798$ ) presented better survival, similar to previous studies on LUAD and NSCLC [42, 43]. In addition, according to the Kaplan–Meier analysis, age, sex, race, marital status, TNM stage, tumor size, grade, and primary tumor site were associated with survival.

The age stratification in our study was more detailed than in other studies, which is more conducive to analyzing the effect of different ages on patient survival. In our study, we concluded that age was closely correlated with LUAD survival. Older age predicted lower OS, which is consistent with other studies [44]. Furthermore, we demonstrated that female patients showed better survival, which is consistent with previous studies [45]. However, different results have been reported on whether age and sex have an impact on the survival of patients with LUAD. In the study by Pitz et al., sex but not age was an independent factor affecting prognosis, and women with LUAD showed better survival than men [46]. In contrast, Jubelirer et al. concluded that age, not sex, was the significant prognostic factor for LUAD [47]. Surprisingly, Zhao et al. concluded that neither age nor sex was a significant prognostic factor for LUAD patients [48]. We consider that these disagreements arose from an analysis of different databases or differences in study objectives.

The impact of race on the survival of patients with lung cancer has been reported previously. Several lines of

evidence have suggested that races other than white and black had the best survival [23, 49]. The same trend was observed in our study. However, it is controversial whether the white or black race can be associated with lower survival. Data from several studies demonstrated there was no significant difference in survival between white and black patients with lung cancer [23, 50]. Nonetheless, our study and other studies have reported that black patients with lung cancer experienced worse survival rate than white patients [49, 51]. Some evidence indicates that white patients may have a worse survival rate [52]. The great differences in smoking prevalence and hospital choices between black and white patients may partly explain these differences [53, 54].

It has been reported that marital status was a protective factor for survival among patients with lung cancer [55, 56]. The married patients in our study included married couples and those living with domestic partners, and singles were defined as single, widowed, divorced, and separated patients, which was a more detailed definition than previous studies [56, 57]. We highlighted the potentially significant social impact of marital status on the survival of LUAD patients. In the present study, a higher survival rate was shown in married patients. Similar results have been observed in other cancers, such as pancreatic and liver cancer [58, 59].

The TNM staging system is widely accepted as a tool to predict the prognosis of patients with cancer and provide therapy guidelines to doctors. Here, we did not include patients with stage Tx or Nx when assessing the impact of factors on prognosis to guarantee more accuracy and avoid potential errors caused by overdetailed classifications. Although the Kaplan–Meier curves showed that the higher T stage shortened the survival of the patients, patients at the T0 stage did not present the best survival in our study. We speculated that this is because of the lack of sufficient patients at the T0 stage. Patients at the N0 stage had better survival than those at higher N stages as shown in previous studies [60]. That means that lymph node metastasis exerted a negative impact on the survival of LUAD patients. The same tendency was also observed for patients at the M stage, that distant metastasis of LUAD reduces the survival rate. The same conclusion can be obtained from other studies [61]. Thus, higher TNM stages indicate poorer survival of LUAD patients.

We further confirmed the effect of tumor size on prognosis based on the 8th edition of the AJCC. Compared with the 7th edition, the latest staging criteria place greater emphasis on the importance of tumor size for a patient's prognosis [62, 63]. Hence, using the most recent criteria, one can effectively analyze the effect of tumor size on prognosis. In the present study, smaller tumor size was associated with a better prognosis, while the NOS group presented the worst. A previous study also established that the tumor size in lung cancer was negatively correlated with survival [23]. However, a majority of studies have not considered the NOS group [51]. We attributed this phenomenon to the complex workup and uncertain classification of the NOS group. Taken together, our specific classification in tumor size made it suitable to predict the prognosis of LUAD patients.

To date, several studies have indicated that the differentiation of the tumor was associated with survival in patients with lung cancer [64, 65]. The general rule emerging from these studies was that the poorer the differentiation of the tumor, the shorter the survival of the patients with lung cancer. Our results validated most of these findings. However, to our surprise, tumors with grade IV differentiation showed even better survival than grade III. We attributed this difference to the limited number of patients in grade IV included in our study ( $n = 288$ ). More patients in grade IV should be included in the future study.

Previous studies have explored the relationship between the primary site of NSCLC and prognosis [66]. However, conclusions from clinical studies remain controversial. Wang et al. reported that patients with lung cancer in the lower lobe had worse survival than tumors in the upper lobes [67]. Li et al. demonstrated that patients with NSCLC located in the main bronchus experienced worse outcomes than at other locations [68]. However, some studies have indicated that the primary site could not contribute to predicting the survival of NSCLC at stages I/II [69]. In the current study, we found that patients with lower and upper lobe tumors showed poorer survival than middle lobe tumors, and mainstem bronchus tumors showed the worst prognosis. Different from the grouping used in previous studies, we added the NOS group to provide additional guidelines for LUAD patients. The survival time of the lung NOS group fell between the mainstem bronchus and overlapping lesions of the other lung groups. Overall, this evidence suggests that the tumor primary site has a significant impact on prognosis and should be considered in prognosis assessment.

## 5. Conclusion

In conclusion, we established and validated a novel nomogram for predicting the survival of LUAD patients. Younger age, female sex, race other than white and black, married status, lower risk score, lower TNM staging, smaller tumor size, and high differentiation grade of the tumor were associated with good survival. Using this model, clinicians may evaluate the survival of LUAD individuals more precisely. In the future, the underlying mechanisms leading to these results should be studied to improve our understanding of LUAD.

## Data Availability

The data used to support the findings of this study are from publicly available datasets and are available at <https://seer.cancer.gov/data/>.

## Ethical Approval

Institutional review board approval was waived for this study because the SEER database is a public anonymized database. The author Bin Xie has gotten access to the SEER database (accession number: 16037-Nov2018).

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

BX, QD, and QC conceptualized and designed the study. BX, XC, and KS contributed to the provision of study materials for patients. QC and S-YH provided administrative support. BX, QD, B-SY, A-QG, S-SY, Z-YD, and H-YX contributed to the collection and assembly of data. BX, JX, and, YZ performed the statistical analysis. All authors contributed to the manuscript revision, read, and approved the submitted version.

## Acknowledgments

This work was supported by the grants from National Multidisciplinary Cooperative Diagnosis and Treatment Capacity Building Project for Major Diseases (Lung Cancer, no. z027002), the National Natural Science Foundation of China (no. 81770045), the National Natural Science Foundation of China (no. 82100051), and Natural Science Foundation of Hunan Province, China (no. 2021JJ40973).

## Supplementary Materials

The first Excel table named "1. Date-AD" in the supplementary materials section contains all the patient information sorted out, such as age and gender. The second Excel table named "2. Date\_Code" is the code used to convert the data downloaded from the public data into a useable format. (*Supplementary Materials*)

## References

- [1] H. J. de Koning, C. M. van der Aalst, P. A. de Jong et al., "Reduced lung-cancer mortality with volume CT screening in a randomized trial," *New England Journal of Medicine*, vol. 382, no. 6, pp. 503–513, 2020.
- [2] K. Li, X. Zang, X. Meng, Y. Li, Y. Xie, and X. Chen, "Targeted delivery of quercetin by biotinylated mixed micelles for non-small cell lung cancer treatment," *Drug Delivery*, vol. 29, no. 1, pp. 970–985, 2022.
- [3] A. Sinjab, G. Han, W. Treekitkarnmongkol et al., "Resolving the spatial and cellular architecture of lung adenocarcinoma by multiregion single-cell sequencing," *Cancer Discovery*, vol. 11, no. 10, pp. 2506–2523, 2021.
- [4] X. Hua, W. Zhao, A. C. Pesatori et al., "Genetic and epigenetic intratumor heterogeneity impacts prognosis of lung adenocarcinoma," *Nature Communications*, vol. 11, no. 1, p. 2459, 2020.
- [5] X. Zhou, D. Hua, C. Gao, Y. Zhang, L. Qiu, and L. Wang, "Icotinib and pemetrexed in treatment of lung adenocarcinoma and the effects on prognostic survival rate of patients," *Oncology Letters*, vol. 18, no. 4, pp. 4153–4159, 2019.
- [6] X. Tang, C. Qi, H. Zhou, and Y. Liu, "A novel metabolic-immune related signature predicts prognosis and immunotherapy response in lung adenocarcinoma," *Heliyon*, vol. 8, no. 8, Article ID e10164, 2022.
- [7] O. Ondič, N. Ptakova, V. Janovsky et al., "Patients with neuregulin 1 (NRG1) rearranged cancer are suitable for the theranostic approach and targeted therapy," *Klinická Onkologie*, vol. 35, no. 4, pp. 271–275, 2022.
- [8] Y. Huang, L. Qiu, X. Liang et al., "Identifying a 6-gene prognostic signature for lung adenocarcinoma based on copy number variation and gene expression data," *Oxidative Medicine and Cellular Longevity*, vol. 2022, Article ID 6962163, 15 pages, 2022.
- [9] Y. Liu, G. Ma, J. Liu et al., "SLC7A5 is a lung adenocarcinoma-specific prognostic biomarker and participates in forming immunosuppressive tumor microenvironment," *Heliyon*, vol. 8, no. 10, Article ID e10866, 2022.
- [10] Y. Wang, J. Feng, Y. Liu, and T. Han, "A risk-assessing signature based on hypoxia- and immune-related genes for prognosis of lung adenocarcinoma patients," *Computational and Mathematical Methods in Medicine*, vol. 2022, Article ID 7165913, 2022.
- [11] Y. Liu, H. Duan, D. Dong et al., "Development of a deep learning-based nomogram for predicting lymph node metastasis in cervical cancer: a multicenter study," *Clinical and Translational Medicine*, vol. 12, no. 7, p. e938, 2022.
- [12] M. Lin, Y. Jin, J. Jin, B. Wang, X. Hu, and J. Zhang, "A risk stratification model for predicting brain metastasis and brain screening benefit in patients with metastatic triple-negative breast cancer," *Cancer Medicine*, vol. 9, no. 22, pp. 8540–8551, 2020.
- [13] P. Li, W. Huang, F. Wang et al., "Nomograms based on inflammatory biomarkers for predicting tumor grade and micro-vascular invasion in stage I/II hepatocellular carcinoma," *Bioscience Reports*, vol. 38, no. 6, Article ID BSR20180464, 2018.
- [14] X. P. Liu, X. Jin, S. S. Ahmadian et al., "Clinical significance and molecular annotation of cellular morphometric subtypes in lower grade gliomas discovered by machine learning," *Neuro-Oncology*, vol. 24, Article ID noac154, 2022.
- [15] M. Peters, D. Eldred-Evans, P. Kurver et al., "Predicting the need for biopsy to detect clinically significant prostate cancer in patients with a magnetic resonance imaging-detected prostate imaging reporting and data system/likert  $\geq 3$  lesion: development and multinational external validation of the imperial rapid access to prostate imaging and diagnosis risk score," *European Urology*, vol. 82, no. 5, pp. 559–568, 2022.
- [16] X. Li, Y. Fan, Y. Dong et al., "Development and validation of nomograms predicting the overall and the cancer-specific survival in endometrial cancer patients," *Frontiers of Medicine*, vol. 7, Article ID 614629, 2020.
- [17] R. Shi, X. Bao, K. Unger et al., "Identification and validation of hypoxia-derived gene signatures to predict clinical outcomes and therapeutic responses in stage I lung adenocarcinoma patients," *Theranostics*, vol. 11, no. 10, pp. 5061–5076, 2021.
- [18] Q. Huang, T. Qu, L. Qi et al., "A nomogram-based immunoserum scoring system predicts overall survival in patients with lung adenocarcinoma," *Cancer Biol Med*, vol. 18, no. 2, pp. 517–529, 2021.
- [19] P. R. Bucciarelli, K. S. Tan, N. P. Chudgar et al., "BRMS1 expression in surgically resected lung adenocarcinoma predicts future metastases and is associated with a poor prognosis," *Journal of Thoracic Oncology*, vol. 13, no. 1, pp. 73–84, 2018.
- [20] W. Liang, J. He, Y. Shen et al., "Impact of examined lymph node count on precise staging and long-term survival of resected non-small-cell lung cancer: a population study of the us SEER database and a Chinese multi-institutional registry," *Journal of Clinical Oncology*, vol. 35, no. 11, pp. 1162–1170, 2017.

- [21] K. M. Doll, A. Rademaker, and J. A. Sosa, "Practical guide to surgical data sets: surveillance, Epidemiology, and End results (SEER) database," *JAMA surgery*, vol. 153, no. 6, pp. 588–589, 2018.
- [22] P. V. Shah, J. N. Choi, L. Fiessinger, B. Nardone, C. V. Nguyen, and W. Liszewski, "Utilization of immunotherapy among patients with stage 4 melanoma: an analysis of the National Cancer Database from 2012 to 2016," *Journal of the American Academy of Dermatology*, vol. 84, no. 3, pp. 811–814, 2021.
- [23] W. Liu and J. Wu, "Lung cancer with bone metastases in the United States: an analysis from the Surveillance, Epidemiologic, and End Results database," *Clinical & Experimental Metastasis*, vol. 35, no. 8, pp. 753–761, 2018.
- [24] F. D. Huitzil-Melendez, M. Capanu, E. M. O'Reilly et al., "Advanced hepatocellular carcinoma: which staging systems best predict prognosis?" *Journal of Clinical Oncology*, vol. 28, no. 17, pp. 2889–2895, 2010.
- [25] A. Sinha, Y. Zou, A. S. Patel et al., "Early-stage lung adenocarcinoma MDM2 genomic amplification predicts clinical outcome and response to targeted therapy," *Cancers*, vol. 14, no. 3, p. 708, 2022.
- [26] K. Guidry, V. Vasudevaraja, K. Labbe et al., "DNA methylation profiling identifies subgroups of lung adenocarcinoma with distinct immune cell composition, DNA methylation age, and clinical outcome," *Clinical Cancer Research*, vol. 28, no. 17, pp. 3824–3835, 2022.
- [27] S. G. Wu, T. H. Chang, M. F. Tsai et al., "IGFBP7 drives resistance to epidermal growth factor receptor tyrosine kinase inhibition in lung cancer," *Cancers*, vol. 11, no. 1, p. 36, 2019.
- [28] Q. Yan, B. Hu, H. Chen et al., "A novel algorithm for lung adenocarcinoma based on N6 methyladenosine-related immune long noncoding RNAs as a reliable biomarker for predicting survival outcomes and selecting sensitive anti-tumor therapies," *Journal of Clinical Laboratory Analysis*, vol. 36, no. 9, Article ID e24636, 2022.
- [29] Z. Sun, Y. Zeng, T. Yuan, X. Chen, H. Wang, and X. Ma, "Comprehensive analysis and reinforcement learning of hypoxic genes based on four machine learning algorithms for estimating the immune landscape, clinical outcomes, and therapeutic implications in patients with lung adenocarcinoma," *Frontiers in Immunology*, vol. 13, Article ID 906889, 2022.
- [30] A. K. Ganti, A. B. Klein, I. Cotalra, B. Seal, and E. Chou, "Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US," *JAMA Oncology*, vol. 7, no. 12, pp. 1824–1832, 2021.
- [31] Y. Wang, Z. Pang, X. Chen et al., "Survival nomogram for patients with initially diagnosed metastatic non-small-cell lung cancer: a SEER-based study," *Future Oncology*, vol. 15, no. 29, pp. 3395–3409, 2019.
- [32] W. Lim, C. A. Ridge, A. G. Nicholson, and S. Mirsadraee, "The 8(th) lung cancer TNM classification and clinical staging system: review of the changes and clinical implications," *Quantitative Imaging in Medicine and Surgery*, vol. 8, no. 7, pp. 709–718, 2018.
- [33] P. Bertoglio, V. Aprile, L. Ventura et al., "Impact of high-grade patterns in early-stage lung adenocarcinoma: a multicentric analysis," *Lung*, vol. 200, no. 5, pp. 649–660, 2022.
- [34] Y. Zhang, L. Zeng, X. Zhang et al., "Clinical and molecular feature-based nomogram model for predicting benefit from bevacizumab combined with first-generation EGFR-tyrosine kinase inhibitor (TKI) in EGFR-mutant advanced NSCLC," *BMC Medicine*, vol. 19, no. 1, p. 245, 2021.
- [35] J. Deng, Z. Ren, J. Wen et al., "Construction of a nomogram predicting the overall survival of patients with distantly metastatic non-small-cell lung cancer," *Cancer Management and Research*, vol. 10, pp. 6143–6156, 2018.
- [36] S. L. Zhang, W. R. Wang, Z. J. Liu, and Z. M. Wang, "Marital status and survival in patients with soft tissue sarcoma: a population-based, propensity-matched study," *Cancer Medicine*, vol. 8, no. 2, pp. 465–479, 2019.
- [37] J. Yang, A. Peng, B. Wang et al., "The prognostic impact of lymph node metastasis in patients with non-small cell lung cancer and distant organ metastasis," *Clinical & Experimental Metastasis*, vol. 36, no. 5, pp. 457–466, 2019.
- [38] Y. Liao, X. Fan, and X. Wang, "Effects of different metastasis patterns, surgery and other factors on the prognosis of patients with stage IV non-small cell lung cancer: a Surveillance, Epidemiology, and End Results (SEER) linked database analysis," *Oncology Letters*, vol. 18, no. 1, pp. 581–592, 2019.
- [39] H. Zheng, Y. Zhang, Y. Zhan et al., *Cancer Management and Research*, vol. 11, pp. 6139–6150, 2019.
- [40] Y. Zhong, Y. She, J. Deng et al., "Deep learning for prediction of N2 metastasis and survival for clinical stage I non-small cell lung cancer," *Radiology*, vol. 302, no. 1, pp. 200–211, 2022.
- [41] S. Garinet, P. Wang, A. Mansuet-Lupo, L. Fournel, M. Wislez, and H. Blons, "Updated prognostic factors in localized NSCLC," *Cancers*, vol. 14, no. 6, p. 1400, 2022.
- [42] Z. Zuo, G. Zhang, P. Song et al., "Survival nomogram for stage IB non-small-cell lung cancer patients, based on the SEER database and an external validation cohort," *Annals of Surgical Oncology*, vol. 28, no. 7, pp. 3941–3950, 2021.
- [43] L. Lin and W. Zhang, "Development and validation of endoplasmic reticulum stress-related eight-gene signature for predicting the overall survival of lung adenocarcinoma," *Translational Cancer Research*, vol. 11, no. 7, pp. 1909–1924, 2022.
- [44] Z. Li, J. Wei, H. Cao, M. Song, Y. Zhang, and Y. Jin, "A predictive web-based nomogram for the early death of patients with lung adenocarcinoma and bone metastasis: a population-based study," *Journal of International Medical Research*, vol. 49, no. 9, Article ID 030006052110477, 2021.
- [45] T. Fan, C. Li, and J. He, "Prognostic value of immune-related genes and comparative analysis of immune cell infiltration in lung adenocarcinoma: sex differences," *Biology of Sex Differences*, vol. 12, no. 1, p. 64, 2021.
- [46] M. W. Pitz, G. Musto, and S. Navaratnam, "Sex as an independent prognostic factor in a population-based non-small cell lung cancer cohort," *Canadian Respiratory Journal*, vol. 20, no. 1, pp. 30–34, 2013.
- [47] S. J. Jubelirer, N. L. Varela, C. A. Welch, and M. K. Emmett, "Does sex make a difference in survival of patients undergoing resection for early stage non-small cell lung cancer (NSCLC)?" *West Virginia Medical Journal*, vol. 105, no. 4, pp. 18–22, 2009.
- [48] J. Zhao, C. Guo, Z. Ma, H. Liu, C. Yang, and S. Li, "Identification of a novel gene expression signature associated with overall survival in patients with lung adenocarcinoma: a comprehensive analysis based on TCGA and GEO databases," *Lung Cancer*, vol. 149, pp. 90–96, 2020.
- [49] L. Ellis, A. J. Canchola, D. Spiegel, U. Ladabaum, R. Haile, and S. L. Gomez, "Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics," *Journal of Clinical Oncology*, vol. 36, no. 1, pp. 25–33, 2018.
- [50] B. Wang, L. Chen, C. Huang et al., "The homogeneous and heterogeneous risk factors for occurrence and prognosis in

- lung cancer patients with bone metastasis,” *Journal of bone oncology*, vol. 17, Article ID 100251, 2019.
- [51] C. Zhan, T. Jiang, X. Yang, W. Guo, and L. Tan, “[Clinical characteristics and prognostic factors of lung adenocarcinoma in SEER database between 2010 and 2015],” *Zhongguo fei ai za zhi = Chinese journal of lung cancer*, vol. 21, no. 8, pp. 600–609, 2018.
- [52] Z. Lin, W. Huang, Z. Xie, Y. Yi, and Z. Li, “Expression, clinical significance, immune infiltration, and regulation network of miR-3940-5p in lung adenocarcinoma based on bioinformatic analysis and experimental validation,” *International Journal of General Medicine*, vol. 15, pp. 6451–6464, 2022.
- [53] K. Steenland, S. Hu, and J. Walker, “All-cause and cause-specific mortality by socioeconomic status among employed persons in 27 US states, 1984–1997,” *American Journal of Public Health*, vol. 94, no. 6, pp. 1037–1042, 2004.
- [54] C. S. Lathan, B. A. Neville, and C. C. Earle, “Racial composition of hospitals: effects on surgery for early-stage non-small-cell lung cancer,” *Journal of Clinical Oncology*, vol. 26, no. 26, pp. 4347–4352, 2008.
- [55] A. A. Aizer, M. H. Chen, E. P. McCarthy et al., “Marital status and survival in patients with cancer,” *Journal of Clinical Oncology*, vol. 31, no. 31, pp. 3869–3876, 2013.
- [56] H. Wen, X. Lin, and D. Sun, “Gender-specific nomogram models to predict the prognosis of male and female lung adenocarcinoma patients: a population-based analysis,” *Annals of Translational Medicine*, vol. 9, no. 22, p. 1654, 2021.
- [57] H. Zhou, Y. Zhang, Z. Qiu et al., “Nomogram to predict cause-specific mortality in patients with surgically resected stage I non-small-cell lung cancer: a competing risk analysis,” *Clinical Lung Cancer*, vol. 19, no. 2, pp. e195–e203, 2018.
- [58] Y. Liang, X. Wu, C. Lu, and F. Xiao, “Impact of marital status on the prognosis of liver cancer patients without surgery and the critical window,” *Annals of Palliative Medicine*, vol. 10, no. 3, pp. 2990–2999, 2021.
- [59] Z. H. Chen, K. B. Yang, Y. Z. Zhang et al., “Assessment of modifiable factors for the association of marital status with cancer-specific survival,” *JAMA Network Open*, vol. 4, no. 5, Article ID e2111813, 2021.
- [60] W. Li, D. Ou, J. Zhang, and M. Ye, “Construction of lymph node metastasis-related prognostic model and analysis of immune infiltration mode in lung adenocarcinoma,” *Computational and Mathematical Methods in Medicine*, vol. 2022, Article ID 3887857, 10 pages, 2022.
- [61] C. Ma, S. Peng, B. Zhu, S. Li, X. Tan, and Y. Gu, “The nomogram for the prediction of overall survival in patients with metastatic lung adenocarcinoma undergoing primary site surgery: a retrospective population-based study,” *Frontiers Oncology*, vol. 12, Article ID 916498, 2022.
- [62] S. Shi, H. Xie, W. Yin et al., “The prognostic significance of the 8th edition AJCC TNM staging system for non-small-cell lung cancer is not applicable to lung cancer as a second primary malignancy,” *Journal of Surgical Oncology*, vol. 121, no. 8, pp. 1233–1240, 2020.
- [63] F. C. Detterbeck, W. A. Franklin, A. G. Nicholson et al., “The IASLC lung cancer staging project: background data and proposed criteria to distinguish separate primary lung cancers from metastatic foci in patients with two lung tumors in the forthcoming eighth edition of the TNM classification for lung cancer,” *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, vol. 11, no. 5, pp. 651–665, 2016.
- [64] C. Y. Liu, J. J. Hung, B. Y. Wang, W. H. Hsu, and Y. C. Wu, “Prognostic factors in resected pathological N1-stage II non-small cell lung cancer,” *European Respiratory Journal*, vol. 41, no. 3, pp. 649–655, 2013.
- [65] F. Yang, Y. Zhao, X. Huang, J. Zhang, and T. Zhang, “A cell differentiation trajectory-related signature for predicting the prognosis of lung adenocarcinoma,” *Genetics Research*, vol. 2022, Article ID 3483498, 11 pages, 2022.
- [66] L. Li, B. Xu, J. Wu, and Q. B. Song, “[Survival benefit of primary site surgery acquired by stage non-small cell lung cancer: a retrospective study based on seer database],” *Zhonghua Zhongliu Zazhi*, vol. 43, no. 3, pp. 335–344, 2021.
- [67] B. Y. Wang, J. Y. Huang, C. Y. Cheng, C. H. Lin, J. L. Ko, and Y. P. Liaw, “Lung cancer and prognosis in taiwan: a population-based cancer registry,” *Journal of Thoracic Oncology*, vol. 8, no. 9, pp. 1128–1135, 2013.
- [68] C. Li, J. Liu, J. Lin, Z. Li, X. Shang, and H. Wang, “Poor survival of non-small-cell lung cancer patients with main bronchus tumor: a large population-based study,” *Future Oncology*, vol. 15, no. 24, pp. 2819–2827, 2019.
- [69] V. Puri, N. Garg, E. E. Engelhardt et al., “Tumor location is not an independent prognostic factor in early stage non-small cell lung cancer,” *The Annals of Thoracic Surgery*, vol. 89, no. 4, pp. 1053–1059, 2010.