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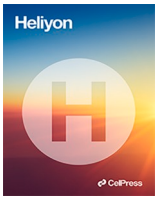

Survival analysis and clinicopathological features of patients with stage IA lung adenocarcinoma

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ABSTRACT

Background: With the development of medical technology and change of life habits, early-stage lung adenocarcinoma (LUAD) has become more common. This study aimed to systematically analyzed clinicopathological factors associated to the overall survival (OS) of patients with Stage IA LUAD.

Methods: A total of 5942 Stage IA LUAD patients were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Kaplan-Meier methods and log-rank tests were used to compare the differences in OS. A nomogram constructed based on the Cox regression was evaluated by Concordance index (C index), calibration curve, decision curve analysis (DCA) and area under curve (AUC). And 136 patients were recruited from Shandong Province Hospital for external validation.

Results: Cox analysis regression indicated that 12 factors, such as Diagnosis to Treatment Interval (DTI) and Income Level, were independent prognostic factors and were included to establish the nomogram. The C-index of our novel model was 0.702, 0.724 and 0.872 in the training, internal and external validation cohorts, respectively. The 3-year and 5-year survival AUCs and calibration curves showed excellent agreement in each cohort. Some new factors in the SEER database, including DTI and Income Level, were firstly confirmed as independent prognostic factors of Stage IA LUAD patients. The distribution of these factors in the T1a, T1b, and T1c subgroups differed and had different effects on survival.

Conclusion: We summarized 12 factors that affect prognosis and constructed a nomogram to predict OS of Stage IA LUAD patients who underwent operation. For the first time, new SEER database parameters, including DTI and Income Level, were proved to be survival-related.

Abbreviations: NSCLC, Non-small cell lung cancer; LUAD, Lung adenocarcinoma; SEER, The Surveillance Epidemiology and End Results; C index, Concordance index; CI, Confidential interval; AUC, Area under curve; LDCT, low-dose helical computed tomography; DTI, Diagnosis to Treatment Interval; ELN, Examined lymph node; TNM, Tumor Node and Metastasis; OS, Overall Survival; ROC, Receiver Operating Characteristic; DCA, Decision Curve Analysis; SABR, Stereotactic Ablative Radiotherapy.

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1. Introduction

Lung cancer remains one of the major causes of cancer-related deaths worldwide, which threatens human health seriously, according to the latest global cancer statistics [1]. Over the last few decades, significant changes have taken place in the constituent ratio of lung cancer patients. Approximately 80 % of patients are diagnosed as non-small cell lung cancer (NSCLC) [2] and about 20 %–25 % of which are classified as early-stage (stage I or II) tumor [3]. Similarly, lung adenocarcinoma (LUAD), which represents 40 % of NSCLC, has a similar early-stage ratio [4,5]. Concurrently, these alterations suggest that the percentage of early-stage patients across all NSCLC patients, particularly among all LUAD patients, is rising annually [1].

Generally, for most early-stage lung cancer patients, their clinical manifestations are elusive and varied. As a result, a considerable number of patients are already diagnosed with advanced lung cancer at their first visit, which contributes to one of the main causes for the low overall survival rate of lung cancer patients [6]. Giving the credit to the progress in diagnostic and surgical techniques, survival for patients with NSCLC, especially early-stage LUAD, has improved significantly over the past few decades [1,7].

Meanwhile, as low-dose helical CT (LDCT) becomes more common, the detection rate of small pulmonary nodules is getting higher, and the detection rate of asymptomatic micro-invasive lung adenocarcinoma increases accordingly, but the false positive rate is as high as 26.6 % [8–10]. As for these patients, whether they should receive treatment and whether they will be overtreated are major problems.

It is still unclear under what circumstances patients can benefit more comprehensively in terms of economy, prognosis, and quality of life. Notably, there is significant variation in the demographic and clinicopathological data among patients with stage IA LUAD. And the prognosis of them differs considerably across different cases. According to previous research, we suggest that there are some potential prognostic factors, such as the Surgery Type, Diagnosis to Treatment Interval (DTI), number of Examined Lymph Node (ELN) and Income Level [11,12].

Surveillance, Epidemiology, and End Results (SEER) is representative of the US population, with patient-level data abstracted from

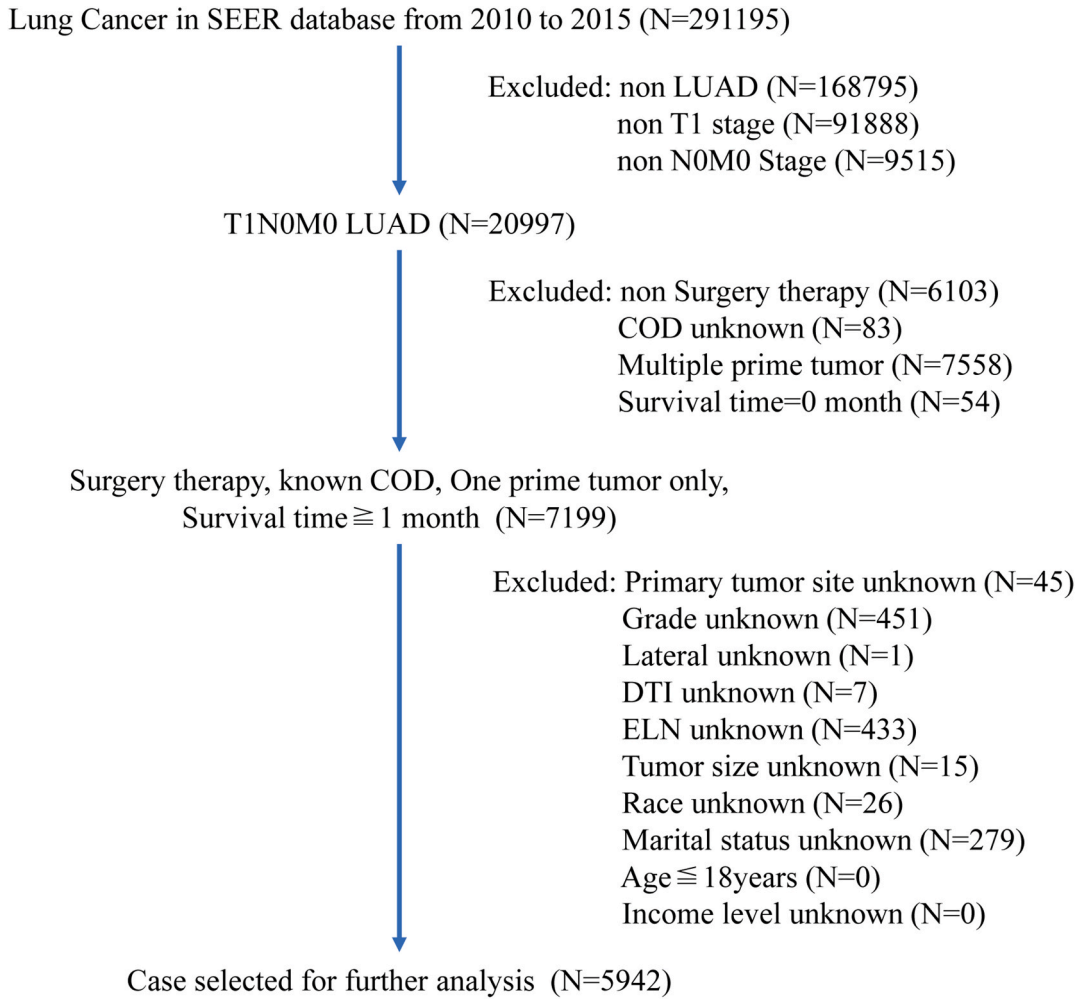

Fig. 1. The flowchart of study population selection in the study.

Table 1
Baseline characteristics of all patients from SEER database.

Characteristics	All cohorts (N = 5942), n (%)	
Age (years)		
Median (IQR)	66.76	(60–74)
≤54	680	(11.4)
55-64	1648	(27.7)
65-69	1169	(19.7)
70-74	1075	(18.1)
75-79	814	(13.7)
80-84	435	(7.3)
≥85	121	(2.0)
Sex		
Female	3638	(61.2)
Male	2304	(38.8)
Primary site		
Upper	3684	(62.0)
Middle	290	(4.9)
Lower	1953	(32.9)
Overlapping	15	(0.3)
Grade		
I	2054	(34.6)
II	2824	(47.5)
III/IV	1064	(17.9)
Lateral		
Left	2329	(39.2)
Right	3613	(60.8)
Histologic type		
Solid	44	(0.7)
BAC	531	(8.9)
Mucinous	287	(4.8)
Acinar	442	(7.4)
Others	520	(8.8)
AD, NOS	4118	(69.3)
Surgery		
Sublobar	1350	(22.7)
Lobectomy	4485	(75.5)
Extended	107	(1.8)
Radiotherapy		
No	5865	(98.7)
Yes	77	(1.3)
DTI (months)		
≤1	4213	(70.9)
2	1053	(17.7)
3	393	(6.6)
≥4	283	(4.8)
ELN count		
0	613	(10.3)
1-3	1113	(18.7)
4-6	1286	(21.6)
7-9	962	(16.2)
10-12	672	(11.3)
13-15	439	(7.4)
≥16	857	(14.4)
Tumor size (mm)		
1-10	728	(12.3)
11-15	1620	(27.3)
16-20	1566	(26.4)
21-25	1309	(22.0)
26-30	719	(12.1)
Race		
White	4860	(81.8)
Black	477	(8.0)
Others	605	(10.2)
Marital		
Married	3497	(58.9)
Widowed	868	(14.6)
Other unmarried	1577	(26.5)
Income level		
Low	1851	(31.2)
Middle	1866	(31.4)
High	2225	(37.4)

diverse populations that represent rural, urban, and regional populations. With the help of the SEER database, assessing clinical issue on a larger sample with long follow-up, which can effectively avoid biases, many prognosis-related factors have been explored deeply in recent years [13,14]. Besides, as a convenient tool to predict and quantify the probability of an individual patient developing a certain clinical event, nomogram is helpful in clinical decision making, risk stratification, personalized treatment and clinical trial design. Both the SEER database and nomogram have been extensively applied in clinical research [15–17]. However, nearly all of the current models for Stage IA LUAD patients have not included new statistical factors from the SEER database, such as DTI and Income Level [18,19].

Consequently, in this study, we systematically analyzed clinicopathological factors of Stage IA (T1N0M0) LUAD patients and identified 12 factors as independent prognostic factors, including DTI and Income Level, two novel factors in the SEER database. Then, based on these independent prognostic factors, a novel predictive model for Stage IA LUAD patients was established and validated. Our new model might support prognosis prediction and clinical decision making.

2. Results

2.1. Patient characteristics

A total of 5942 eligible patients from 2010 to 2015 were extracted from the SEER database (Fig. 1). All cases were confirmed to have Stage IA LUAD (diameter≤3 cm, T1N0M0) at the initial diagnosis. Most cases were female patients (N = 3638, 61.2 %). The median age of all patients was 66.76 years and the median follow-up time was 66 months. The baseline clinicopathological characteristics and treatment experience of all patients were summarized in Table 1. In the external validation cohort, 136 cases from 2012 to 2017 were collected from the Shandong Provincial Hospital and the baseline characteristics were in Supplementary Table 1.

All eligible cases from SEER were randomly divided into the training (N = 4754, 80 %) and internal validation cohorts (N = 1188, 20 %). At the end of follow-up, endpoint events had occurred in 1680/5942 (28.3 %), 1333/4754 (28.0 %), 347/1188 (29.2 %) and 39/136 (28.7 %) patients in the total, training, internal and external validation cohorts, respectively. The 3-year OS was 85.8 %, 84.1 % and 84.6 %, while the 5-year OS was 59.3 %, 60.0 % and 70.6 %, respectively, in the training, internal and external validation cohorts.

Kaplan-Meier survival analysis was conducted to assess the relationship between each factor and survival outcomes. The significant factors ($p < 0.05$) were: Age, Sex, Race, Differentiation Grade, Histologic Type, Surgery Type, Radiation Therapy, DTI, ELN, Tumor Size, Marital Status and Income Level (Fig. 2A-L). The following clinicopathology characteristics showed greater OS: Age≤54, Female, Grade I, Acinar cell Histology Type, Lobectomy, No Radiotherapy, DTI≤1 month, ELN≥16, Tumor size 1–10 mm, Married and High Income Level. Factors with no significant difference ($p \geq 0.05$) were Primary Tumor Site and Lateral, as shown in Supplementary Figs. 1A and B.

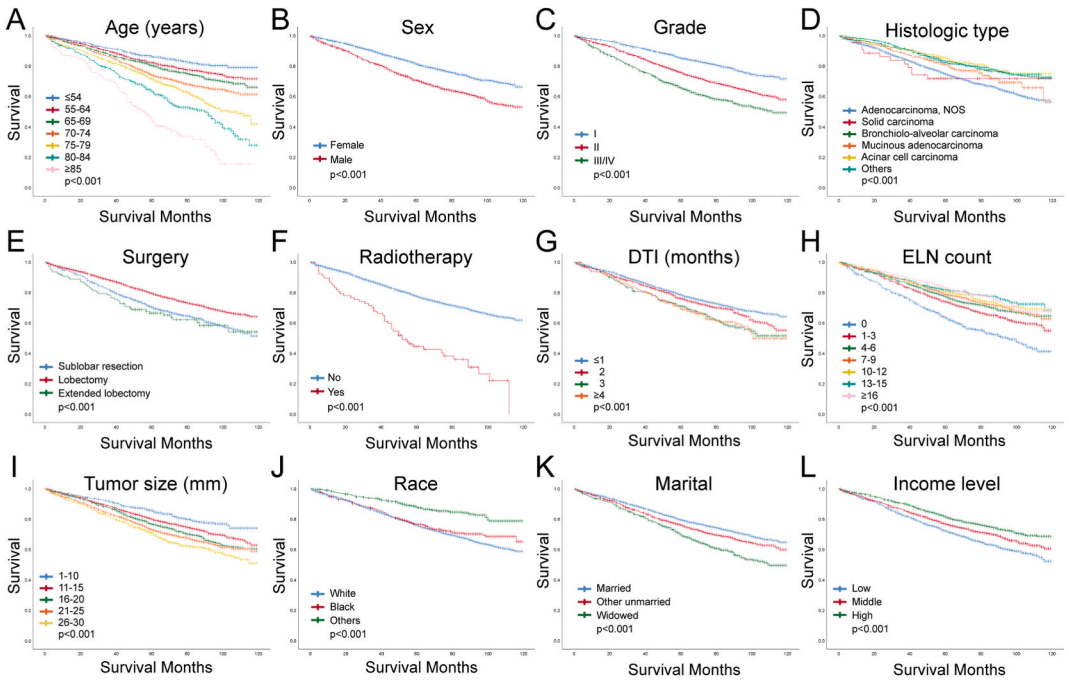

Fig. 2. Kaplan–Meier curves of OS for T1N0M0 patients stratified by (**A**) Age, $p < 0.001$; (**B**) Sex, $p < 0.001$; (**C**) Differentiation grade, $p < 0.001$; (**D**) Histologic type, $p < 0.001$; (**E**) Surgery type, $p < 0.001$; (**F**) Radiotherapy, $p < 0.001$; (**G**) DTI, $p < 0.001$; (**H**) ELN count, $p < 0.001$; (**I**) Tumor size, $p < 0.001$; (**J**) Race, $p < 0.001$; (**K**) Marital, $p < 0.001$; (**L**) Income level, $p < 0.001$.

Table 2
Univariate and multivariate Cox regression analysis in training cohort.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	(95 % CI)	*p* value	HR	(95 % CI)	*p* value
Age (years)			<0.001			<0.001
≤54	Reference			Reference		
55-64	1.270	(1.005–1.604)	0.046	1.227	(0.969–1.553)	0.018
65-69	1.459	(1.146–1.856)	0.002	1.495	(1.172–1.908)	0.001
70-74	1.883	(1.485–2.388)	<0.001	1.933	(1.518–2.462)	<0.001
75-79	2.452	(1.930–3.117)	<0.001	2.492	(1.948–3.187)	<0.001
80-84	3.339	(2.589–4.306)	<0.001	3.030	(2.327–3.945)	<0.001
≥85	5.648	(4.129–7.726)	<0.001	4.689	(3.376–6.513)	<0.001
Sex			<0.001			<0.001
Female	Reference			Reference		
Male	1.622	(1.456–1.806)	<0.001	1.673	(1.492–1.875)	<0.001
Primary site			0.493			
Upper	Reference					
Middle	1.028	(0.797–1.326)	0.834			
Lower	1.072	(0.956–1.202)	0.234			
Grade			<0.001			<0.001
I	Reference			Reference		
II	1.574	(1.379–1.795)	<0.001	1.525	(1.326–1.753)	<0.001
III/IV	2.390	(2.055–2.780)	<0.001	2.063	(1.752–2.428)	<0.001
Lateral			0.553			
Left	Reference					
Right	0.967	(0.867–1.079)	0.553			
Histologic type			<0.001			<0.001
AD, NOS	Reference			Reference		
Solid	1.076	(0.577–2.005)	0.819	0.806	(0.430–1.509)	0.486
BAC	0.620	(0.505–0.762)	<0.001	0.855	(0.689–1.062)	0.066
Mucinous	0.810	(0.621–1.055)	0.118	1.068	(0.813–1.403)	0.680
Acinar	0.579	(0.449–0.747)	<0.001	0.706	(0.545–0.914)	0.001
Others	0.661	(0.533–0.819)	<0.001	0.741	(0.596–0.921)	<0.001
Surgery			<0.001			0.022
Sublobar	Reference			Reference		
Lobectomy	0.664	(0.589–0.748)	<0.001	0.870	(0.753–1.006)	0.079
Extended	1.016	(0.708–1.457)	0.933	1.197	(0.826–1.736)	0.132
Radiotherapy			<0.001			<0.001
No	Reference			Reference		
Yes	2.956	(2.158–4.050)	<0.001	1.817	(1.316–2.508)	<0.001
DTI (months)			<0.001			<0.001
≤1	Reference			Reference		
2	1.161	(1.009–1.336)	0.037	1.127	(0.978–1.300)	0.061
3	1.484	(1.213–1.816)	<0.001	1.382	(1.126–1.696)	<0.001
≥4	1.693	(1.362–2.106)	<0.001	1.531	(1.227–1.909)	0.003
ELN count			<0.001			<0.001
0	Reference			Reference		
1-3	0.624	(0.524–0.743)	<0.001	0.688	(0.571–0.830)	<0.001
4-6	0.531	(0.446–0.632)	<0.001	0.622	(0.512–0.757)	<0.001
7-9	0.473	(0.391–0.573)	<0.001	0.570	(0.460–0.706)	<0.001
10-12	0.468	(0.377–0.581)	<0.001	0.571	(0.449–0.726)	<0.001
13-15	0.397	(0.306–0.516)	<0.001	0.473	(0.357–0.626)	<0.001
≥16	0.386	(0.313–0.476)	<0.001	0.454	(0.360–0.573)	<0.001
Tumor size (mm)			<0.001			<0.001
1-10	Reference			Reference		
11-15	1.288	(1.039–1.596)	0.021	1.237	(0.997–1.536)	0.016
16-20	1.513	(1.225–1.870)	<0.001	1.409	(1.136–1.748)	<0.001
21-25	1.752	(1.416–2.169)	<0.000	1.656	(1.330–2.062)	<0.001
26-30	2.029	(1.613–2.551)	<0.001	1.712	(1.349–2.173)	<0.001
Race			<0.001			<0.001
White	Reference			Reference		
Black	0.889	(0.727–1.088)	0.254	0.923	(0.751–1.133)	0.379
Others	0.478	(0.377–0.605)	<0.001	0.560	(0.440–0.713)	<0.001
Marital			<0.001			<0.001
Married	Reference			Reference		
Widowed	1.197	(1.055–1.357)	0.005	1.309	(1.147–1.494)	<0.001
Others	1.581	(1.370–1.824)	<0.001	1.321	(1.131–1.542)	<0.001
Income level			<0.001			<0.001
Low	Reference			Reference		
Middle	0.802	(0.705–0.912)	0.001	0.833	(0.731–0.950)	0.003
High	0.626	(0.549–0.714)	<0.001	0.729	(0.637–0.835)	<0.001

2.2. Univariate and multivariate analysis

The Cox regression analysis was performed in the training cohort to determine the accuracy of each variable in predicting the prognosis of Stage IA LUAD. Age, Sex, Race, Differentiation Grade, Histologic Type, Surgery Type, Radiation Therapy, DTI, ELN, Tumor Size, Marital Status and Income Level were all found to be associated with patients' prognosis in univariate analysis (Table 2). The significant factors in the univariate analysis were further examined in the multivariate analysis using the same exclusion criteria ($p < 0.05$). Finally, our novel predictive model for Stage IA LUAD patients was developed using statistically significant factors that included Age, Sex, Race, Differentiation Grade, Histologic Type, Surgery Type, Radiation Therapy, DTI, ELN, Tumor Size, Marital Status and Income Level as independent predictors of survival (Table 2). Clinicopathology factors including Age≤54, Female, Grade I, Acinar cell Histology Type, Lobectomy, No Radiotherapy, DTI≤1 month, ELN≥16, Tumor size 1–10 mm, Married and High Income Level, were protective factors. These findings indicated that, in addition to the usual clinicopathology factors, DTI and house income also played an important role in the survival of stage IA LUAD patients.

2.3. Nomogram development

According to the results of Cox multivariate analysis, 12 independent prognostic factors from training cohort (Table 2) were integrated into the nomogram (Fig. 3). Each of the parameters included in the nomogram was given a score on the point scale and the total score projected to the bottom scale represented the probabilities of 3- and 5-year OS. In detail, according to its vertical projection on the top 'Points' axis, the score for each factor was read out in full. A patient's position on the 'Total Points' axis was determined by

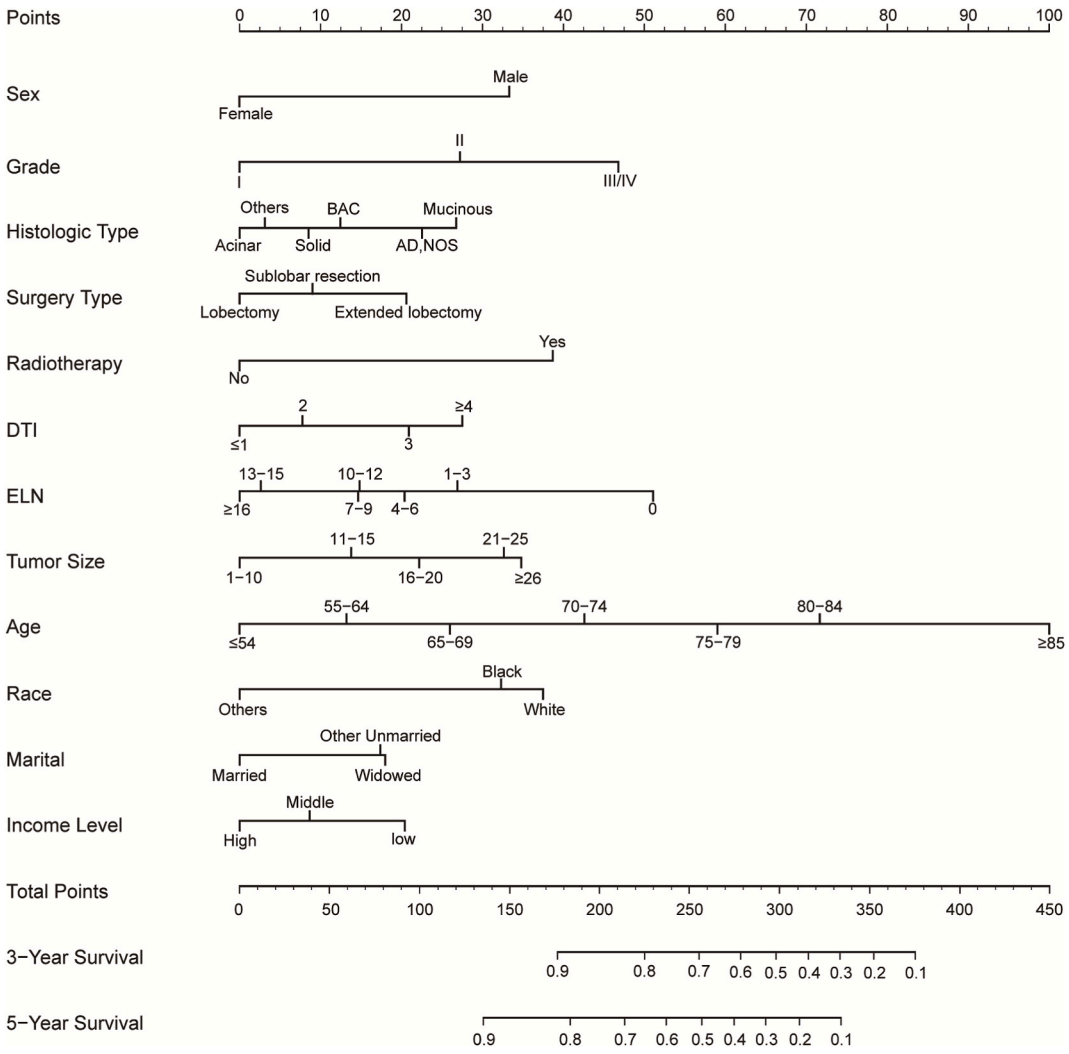

Fig. 3. Prognostic nomogram predicting the probability of 3- and 5-year overall survival (OS). Each subtype within these significant independent variables was assigned a score on the point scale. The sum of these points was located on the 'Total Points' axis.

the sum of the scores for the various factors. The vertical projection of this 'Total Points' position on '3-Year Survival' and '5-Year Survival' axes was the OS predicted by the nomogram. We then accessed the individual 3- and 5-year OS by calculating the total score.

2.4. Nomogram validation

C-index, ROC and DCA curves were used to evaluate the accuracy and discrimination of our nomogram. The C-index was 0.702 (95 % CI: 0.689–0.716), 0.724 (95 % CI: 0.697–0.751) and 0.872 (95%CI: 0.825–0.919), respectively, in the training, internal and external validation cohorts. The ROC of the nomogram was performed and the 3- and 5-year AUCs were 0.713 (95%CI: 0.692–0.735) and 0.711 (95%CI: 0.693–0.730) in the training cohort, respectively (Fig. 4A). In the internal validation cohort, the 3- and 5-year AUCs were 0.722 (95%CI: 0.682–0.761) and 0.729 (95%CI: 0.694–0.765), respectively (Fig. 4B). In the external validation cohort, the 3- and 5-year AUCs were 0.877 (95%CI: 0.804–0.951) and 0.830 (95%CI: 0.738–0.922), respectively (Fig. 4C). The 3- and 5-year OS calibration curves and plots showed agreement between the nomogram predictions and actual observations for 3- and 5-year OS in the training, internal and external validation cohorts, respectively (Fig. 4D–F).

To validate the superiority of the novel model, we compared the net benefit using the DCA curve. We explored two reported models that were also suitable for T1N0M0 LUAD [15,20]. Model 1 included factors: Sex, Differentiation Grade, Tumor Size, Age, Race; Model 2 included factors: Sex, Differentiation Grade, Tumor Size, Age, Race, Primary Site, Marital Status; T Stage included the particular stage (T1a, T1b and T1c) of patients diagnosed with 'T1N0M0' from TNM staging system. In Fig. 5, 'ALL' means intervention for all patients, 'None' means intervention for none patient. The higher the DCA curve, the better net benefit for patients in this model [21], and the results demonstrated that our novel model exhibited an increase in the net benefit according to the DCA of 3-year OS (Fig. 5A) and 5-year OS (Fig. 5B). These findings suggested that the novel model had good accuracy and higher clinical application value.

2.5. Subgroup analyses

In the total cohort, we performed a subgroup analysis based on the Tumor Size Chi-square test, which indicated that factors including Age, Sex, Differentiation Grade, Surgery Type, DTI, ELN and Income Level differed significantly ($p < 0.05$) among these subgroups (Table 3).

Patients with the following characteristics were more likely to be in Stage T1a than in T1b and T1c: Age (at diagnosis) < 70 years, Female, Grade I, sublobectomy, DTI≤1 month, ELN≤3 and High-Income Level. Correspondingly, for the patients with characteristics such as Age (at diagnosis) ≥70 years, Male, Grade II and III/IV, lobectomy/extended lobectomy, DTI>1 month, ELN>3 and Low/Middle-Income Level, the proportion in Stage T1c was the highest among three subgroups (Table 3).

For patients with characteristics such as Age (at diagnosis) < 70 years, Female, Grade I, DTI ≤1 month, Married, other race and

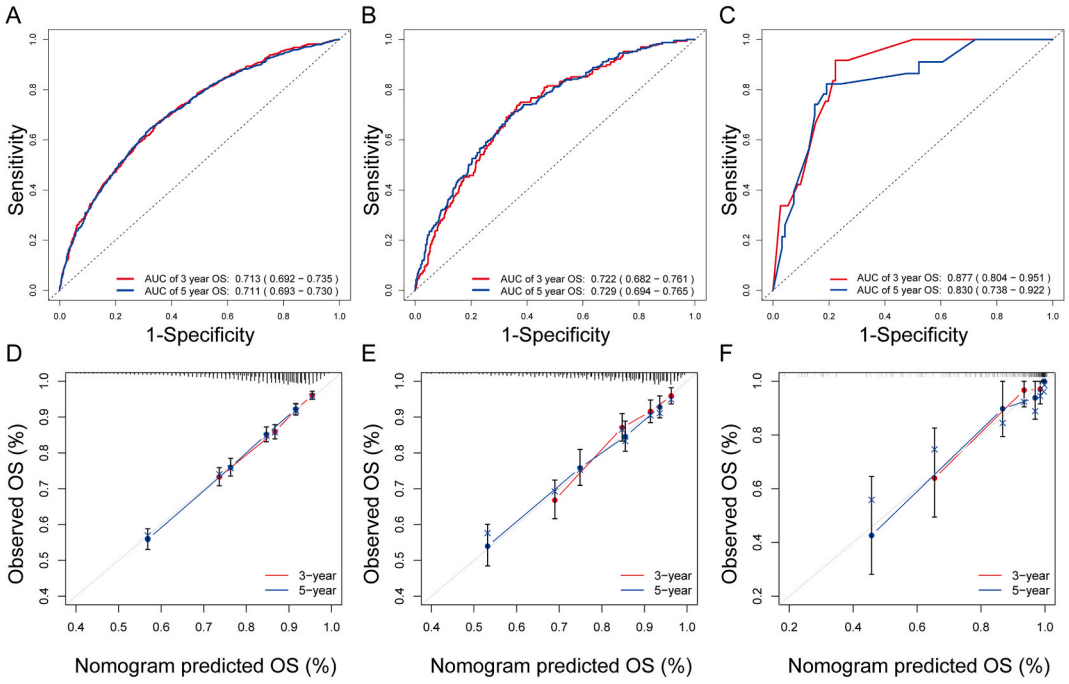

Fig. 4. ROC curves of training cohort (**A**), internal validation cohort (**B**) and external validation cohort (**C**) for 3- and 5-year OS based on the nomogram. The AUCs at 3 and 5 years were 0.713 and 0.711 (training cohort); 0.722 and 0.729 (internal validation cohort); 0.877 and 0.830 (external validation cohort), respectively; Calibration curves predicting the 3- and 5-year OS of patients in the training cohort (**D**), internal validation cohort (**E**) and external validation cohort (**F**).

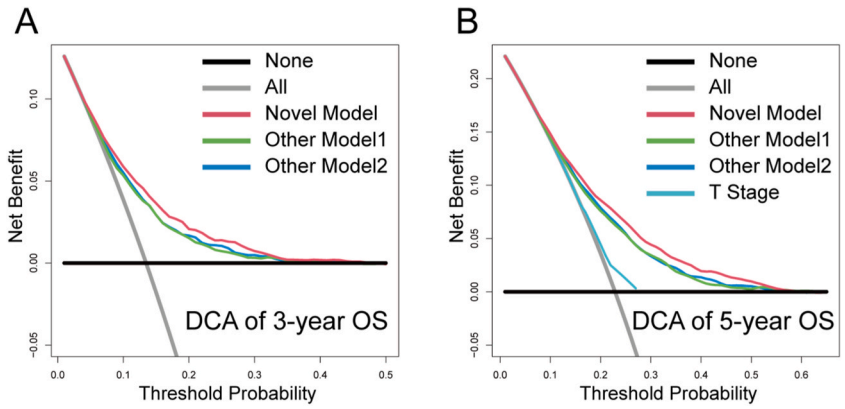

Fig. 5. Decision curve analyses (DCA) of our nomogram and other 2 reported models for 3-year overall survival (**A**); DCA of our nomogram, AJCC TNM staging method and other 2 reported models for 5-year overall survival. (**B**).

higher ELN counts, they would have the best OS whether they were in Stage T1a (Fig. 6 A-G), T1b (Fig. 7 A-G) or T1c (Fig. 8 A-G) (Tables 4 and 5). However, for the patients of Stage T1b and T1c, lobectomy was related to the best OS (Tables 4 and 5, Fig. 7H and 8H). But for the patients of T1a, surgery type had no apparent correlation to OS (Tables 4 and 5, Fig. 6H). Similarly, For the patients of Stage T1b (Fig. 7 I–K) and T1c (Fig. 8 I–K), factors including Acinar Histologic Type, No Radiotherapy and High-Income Level were associated with the best OS (Tables 4 and 5) But among the patients of T1a, factors such as Histologic Type, Radiotherapy and Income Level were not obviously related to OS (Tables 4 and 5, Fig. 6 I–K).

The accuracy of our nomogram in each subgroup was also evaluated by the C index and the AUC (Supplementary Fig. 2). All these analyses, which demonstrated heterogeneity among the three subgroups and the significance of DTI and house income in prognosis, merited more investigation. exploration.

3. Discussion

Lung cancer remains one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide [23]. LUAD patients showed us different characteristics in recent years, especially the increasing ratio of early-stage tumor [24]. This change was the result of numerous factors. First of all, improvement of diagnosis technology allowed patients to be diagnosed before the occurrence of local invasion or metastasis [25]. Besides, the improvement of clinical therapy, including the development of chemotherapy, target therapy, immunotherapy and thoracic surgery, inhibited tumor progression significantly [23,26,27]. Some life habits and environmental changes, like smoking and air pollution [28–30], contributed to the transition of the NSCLC histology. For stage IA LUAD patients, whose prognosis was related to tumor size, from T1a to T1c, 5-year OS was 90 %, 85 % and 80 %, respectively. And the main treatment for them was lung local resection surgery, including lobectomy and limited resection (segmentectomy and wide-wedge resection) [31]. Understanding stage IA LUAD patients and determining the best course of action for treatment required a methodical investigation of the prognosis-related characteristics of them.

In this study, based on the data base of SEER, we established a novel nomogram predicting the OS of Stage IA LUAD patients. We identified 12 independent risk factors, including Age, Sex, Race, Differentiation Grade, Histologic Type, Surgery Type, Radiation Therapy, DTI, ELN, Tumor Size, Marital Status and Income Level, by using univariate analysis and multivariate analysis. Factors in our predictive model can be conveniently obtained from clinical practices (Table 2).

Our results showed that the C-index of the nomogram in training, internal and external validation cohort was 0.702 (95%CI: 0.688–0.716), 0.724 (95%CI: 0.697–0.751) and 0.872 (95%CI: 0.825–0.919), respectively. The calibration, ROC and DCA of our novel model reached excellent agreement in each cohort (Figs. 4 and 5). However, the values of C-index and AUC of both external and internal validation cohorts were higher than those of the training cohort (Figs. 4 and 5). These counterintuitive results might be caused by the following factors: 1) The SEER database was a multicenter study with varying patient sources and different levels of diagnosis and treatment, which resulted in significant heterogeneity among patients. 2) Although we used random grouping, due to the smaller sample size of the internal validation cohort, the heterogeneity of it might be affected, which caused the higher C-index and AUC values. 3) Our external validation group was a single center cohort, in which patients received the same level of diagnosis and treatment, which led to higher homogeneity of the cohort and might result in higher C-index and AUC values. This unusual observation also appeared in some research using the SEER database and nomogram [17]. According to the recent research, there were 16 existing studies in which a nomogram was constructed to predict the prognosis of stage IA lung cancer patients. However, the majority of these studies focused on patients with NSCLC [32], and only 6 studies were conducted in the Stage IA LUAD [33]. Most studies had only a small sample size and included only a specific group of patients, which suppressed their generalizability.

It has been confirmed that the DTI is an independent prognostic factor for tumor patients. Usually, treatment delays in lung cancer patients portended poor outcomes [34,35]. This issue had been previously investigated in reports focusing on lung cancer but the findings were inconsistent. Some studies reported lower survival among patients were associated with shorter waiting time [22,36].

Table 3
Chi-square test for three subtypes of Stage IA LUAD patients.

Characteristics	T1a		T1b		T1c		Total		*p* value
Age(years)									<0.001
Mean	65.36		66.38		67.85		66.76		
Percentiles25	59		60		61		60		
Percentiles50	66		67		69		67		
Percentiles75	72		73		75		74		
≤54	91	(12.5)	384	(12.1)	205	(10.1)	680	(11.4)	
55-64	233	(32.0)	926	(29.1)	489	(24.1)	1648	(27.7)	
65-69	146	(20.1)	630	(19.8)	393	(19.4)	1169	(19.7)	
70-74	132	(18.1)	562	(17.6)	381	(18.8)	1075	(18.1)	
75-79	89	(12.2)	402	(12.6)	323	(15.9)	814	(13.7)	
80-84	32	(4.4)	217	(6.8)	186	(9.2)	435	(7.3)	
≥85	5	(0.7)	65	(2.0)	51	(2.5)	121	(2.0)	
Sex									0.001
Female	490	(67.3)	1947	(61.1)	1201	(59.2)	3638	(61.2)	
Male	238	(32.7)	1239	(38.9)	827	(40.8)	2304	(38.8)	
Primary tumor site									0.079
Upper	449	(61.7)	1932	(60.8)	1303	(64.5)	3684	(62.2)	
Middle	39	(5.4)	166	(5.2)	85	(4.2)	290	(4.9)	
Lower	240	(33.0)	1080	(34.0)	633	(31.3)	1953	(33.0)	
Grade									<0.001
I	353	(48.5)	1116	[22]	585	(28.8)	2054	(34.6)	
II	279	(38.3)	1536	(48.2)	1009	(49.8)	2824	(47.5)	
III/IV	96	(13.2)	534	(16.8)	434	(21.4)	1064	(17.9)	
Lateral									0.713
Left	276	(37.9)	1260	(39.5)	793	(39.1)	2329	(39.2)	
Right	452	(62.1)	1926	(60.5)	1235	(60.9)	3613	(60.8)	
Histologic Type									0.012
AD, NOS	505	(69.4)	2161	(67.8)	1452	(71.6)	4118	(69.3)	
Solid	6	(0.8)	22	(0.7)	16	(0.8)	44	(0.7)	
BAC	66	(9.1)	301	(9.4)	164	(8.1)	531	(8.9)	
Mucinous	45	(6.2)	154	(4.8)	88	(4.3)	287	(4.8)	
Acinar	58	(8.0)	263	(8.3)	121	(6.0)	442	(7.4)	
Others	48	(6.6)	285	(8.9)	187	(9.2)	520	(8.8)	
Surgery									<0.001
Sublobar	284	(39.0)	790	(24.8)	276	(13.6)	1350	(22.7)	
Lobectomy	439	(60.3)	2347	(73.7)	1699	(83.8)	4485	(75.5)	
Extended	5	(0.7)	49	(1.5)	53	(2.6)	107	(1.8)	
Radiotherapy									0.406
No	722	(99.2)	3145	(98.7)	1998	(98.5)	5865	(98.7)	
Yes	6	(0.8)	41	(1.3)	30	(1.5)	77	(1.3)	
DTI(months)									<0.001
≤1	583	(80.1)	2282	(71.6)	1348	(66.5)	4213	(70.9)	
2	86	(11.8)	559	(17.5)	408	(20.1)	1053	(17.7)	
3	35	(4.8)	201	(6.3)	157	(7.7)	393	(6.6)	
≥4	24	(3.3)	144	(4.5)	115	(5.7)	283	(4.8)	
ELN count									<0.001
0	134	(18.4)	335	(10.5)	144	(7.1)	613	(10.3)	
1-3	169	(23.2)	603	(18.9)	341	(16.8)	1113	(18.7)	
4-6	137	(18.8)	683	(21.4)	466	(23.0)	1286	(21.6)	
7-9	90	(12.4)	532	(16.7)	340	(16.8)	962	(16.2)	
10-12	70	(9.6)	349	(11.0)	253	(12.5)	672	(11.3)	
13-15	40	(5.5)	236	(7.4)	163	(8.0)	439	(7.4)	
≥16	88	(12.1)	448	(14.1)	321	(15.8)	857	(14.4)	
Race									0.046
White	617	(84.8)	2622	(82.3)	1621	(79.9)	4860	(81.8)	
Black	51	(7.0)	248	(7.8)	178	(8.8)	477	(8.0)	
Others	60	(8.2)	316	(9.9)	229	(11.3)	605	(10.2)	
Marital									0.245
Married	445	(61.1)	1873	(58.8)	1179	(58.1)	3497	(58.9)	
Widowed	194	(26.6)	852	(26.7)	531	(26.2)	1577	(26.5)	
Others	89	(12.2)	461	(14.5)	318	(15.7)	868	(14.6)	
Income level									<0.001
Low	191	(26.2)	1014	(31.8)	646	(31.9)	1851	(31.2)	
Middle	221	(30.4)	968	(30.4)	677	(33.4)	1866	(31.4)	
High	316	(43.4)	1204	(37.8)	705	(34.8)	2225	(37.4)	

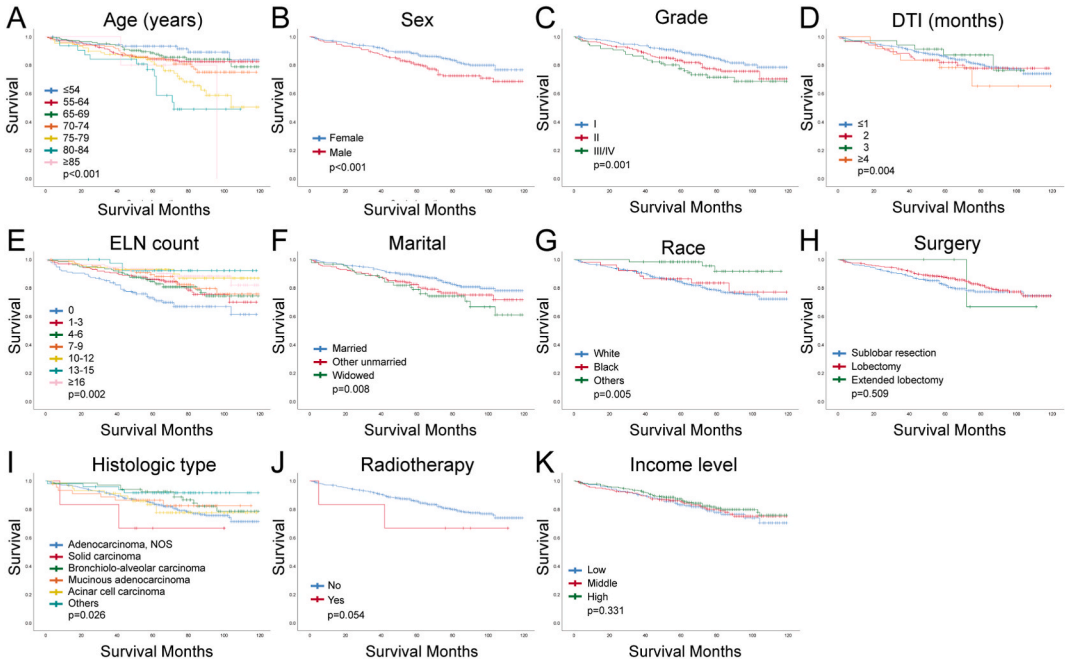

Fig. 6. Kaplan–Meier curves of OS for T1aN0M0 patients stratified by (**A**) Age, $p < 0.001$; (**B**) Sex, $p < 0.001$; (**C**) Differentiation grade, $p = 0.001$; (**D**) DTI, $p = 0.004$; (**E**) ELN count, $p = 0.002$; (**F**) Marital, $p = 0.008$; (**G**) Race, $p = 0.005$; (**H**) Surgery type, $p = 0.509$; (**I**) Histologic type, $p = 0.026$; (**J**) Radiotherapy, $p = 0.054$; (**K**) Income level, $p = 0.331$.

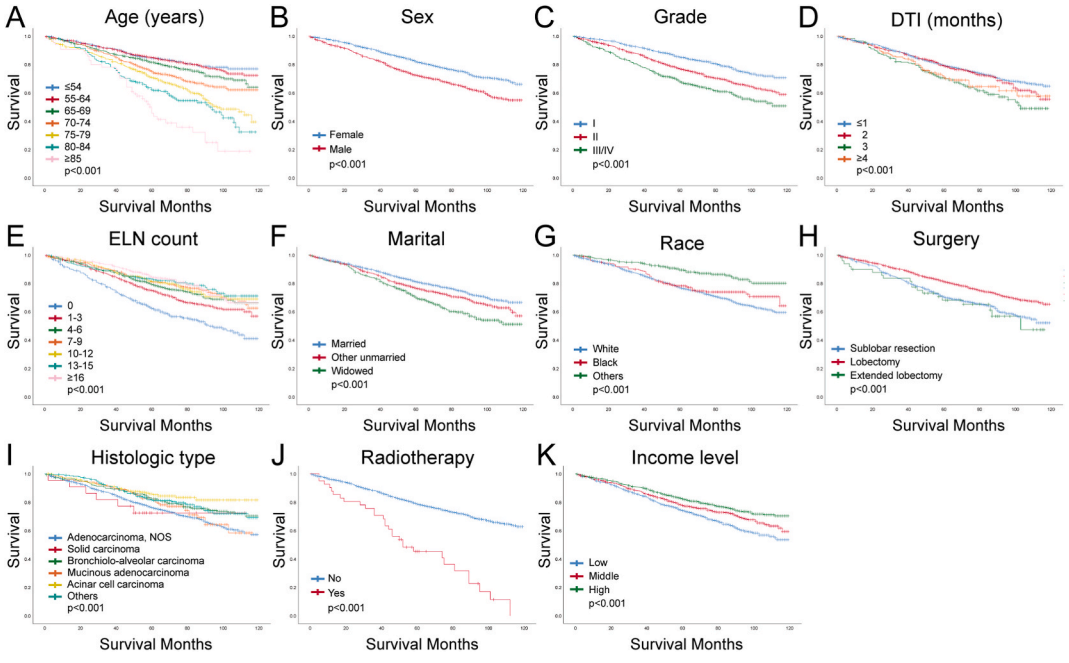

Fig. 7. Kaplan–Meier curves of OS for T1bN0M0 patients stratified by (**A**) Age, $p < 0.001$; (**B**) Sex, $p < 0.001$; (**C**) Differentiation grade, $p < 0.001$; (**D**) DTI, $p < 0.001$; (**E**) ELN count, $p < 0.001$; (**F**) Marital, $p < 0.001$; (**G**) Race, $p < 0.001$; (**H**) Surgery type, $p < 0.001$; (**I**) Histologic type, $p < 0.001$; (**J**) Radiotherapy, $p < 0.001$; (**K**) Income level, $p < 0.001$.

However, this finding might be explained by the fact that patients with late-stage lung cancer typically presented with more severe clinical symptoms, which lead to them receiving treatment sooner than those with early-stage lung cancer. Others report indicated that the shorter time for patients to wait the higher survival rate was [37–39].

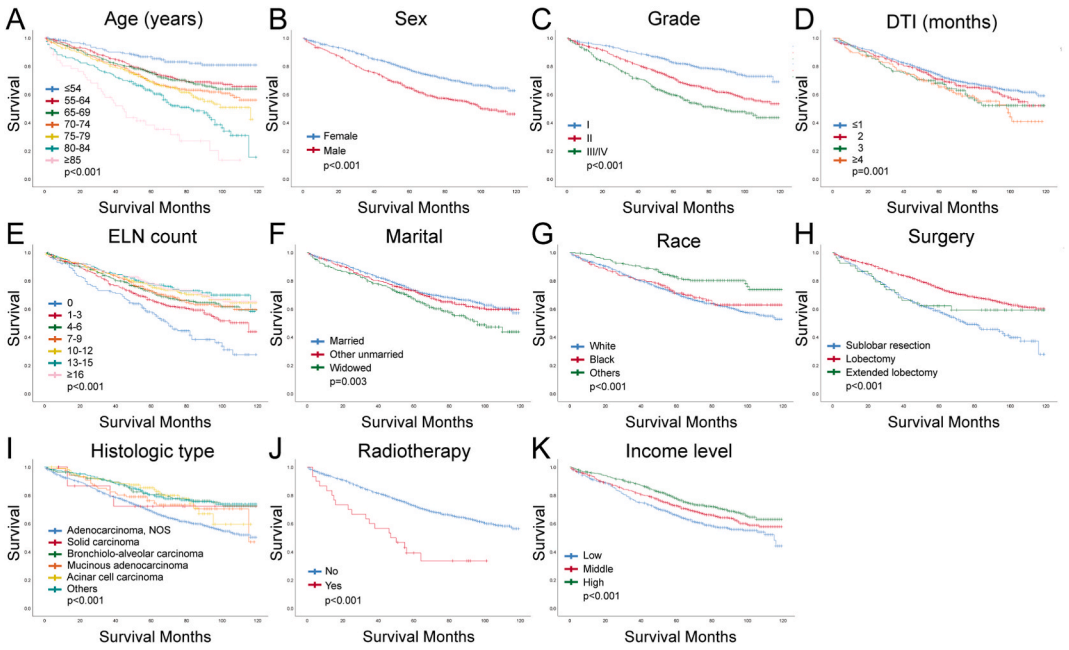

Fig. 8. Kaplan–Meier curves of OS for T1cN0M0 patients stratified by (**A**) Age, $p < 0.001$; (**B**) Sex, $p < 0.001$; (**C**) Differentiation grade, $p < 0.001$; (**D**) DTI, $p = 0.001$; (**E**) ELN count, $p < 0.001$; (**F**) Marital, $p = 0.003$; (**G**) Race, $p < 0.001$; (**H**) Surgery type, $p < 0.001$; (**I**) Histologic type, $p < 0.001$; (**J**) Radiotherapy, $p < 0.001$; (**K**) Income level, $p < 0.001$.

Our analysis also proved that, as an independent prognostic factor, DTI was inversely associated with the OS of Stage IA LUAD patients (Table 2). We suggested that for patients with early-stage lung cancer, the duration of DTI was not related to the severity of symptoms. Some studies showed that about half of the early patients were found by accident and had no relevant symptoms [40]. Patients with stage IA lung cancer generally did not have obvious symptoms, so it was unlikely to choose treatment as soon as possible due to the suffering of tumor, as patients with advanced stage lung cancer did. At the same time, the prolongation of DTI led to tumor progression in size and differentiation, which reduced the OS of patients undoubtedly [22]. Based on subgroup analysis, we found some distinctions among T1a, 1b and 1c patients. Our study showed patients with T1a LUAD were more likely those whose DTI was less than 1 month. As for T1c LUAD patients, most of them were with long wait time over than 1 month. Considering that the TNM stage we analyzed was after the surgy, our study also confirmed the relationship between DTI and tumor size. Among the patients of stage T1a, 1b and 1c, DTI less than 1 month was associated with the best OS.

Previous studies showed that sex was also one of the important independent factors which may affect the morbidity and mortality of lung cancer [41]. While overall lung cancer outcomes were more favorable in women compared to men even when adjusted for age and stage, the global rise in incidence of lung cancer in women was alarming and threatened to upend the current patterns in the next few years [41]. Recent studies showed that the prevalence of lung cancer in women had gradually increased [42,43]. It was unexpected to find that there were more female Stage IA LUAD patients in our study than male patients (Table 1). However, as in previous reports, our research showed that, compared with men, women with stage IA LUAD still had a better survival rate (Table 2). In recent years, some studies showed why the occurrence and prognosis of lung cancer was affected by gender. Some researchers suggested that the difference in sex hormones had a major impact on lung cancer [44,45]. Another possible explanation of this unexpected pattern in early stage LUAD was that women were more attentive to physical discomfort than men and they were more willing to get medical check-up and seek treatment [46], which can also explain why the proportion of female patients in Stage T1a was higher than it in T1b and 1c (Table 3).

How to choose the surgical method, whether to choose lobectomy or sublobectomy (such as segmentectomy and wedge resection), had puzzled doctors and patients for many years [31]. Some studies suggested that lobectomy was an overtreatment, which would affect the quality of life and even the prognosis of early-stage lung cancer patients, because of the disadvantages in terms of post-operative lung function [47,48]. Others believed that for patients with early lung cancer, sublobectomy might still lead to residual tumor cells which can cause recrudescence and affect the OS of patients [49]. However, our study indicated that the latter view was more convincing, especially for T1b and 1c patients. Among the stage IA patients, for the group with T1b and 1c LUAD, lobectomy was associated with the best OS, but for the patients of T1a, surgery type was not related to OS (Tables 4 and 5).

With the development of radiotherapy technology, radiation therapy has become an effective treatment for patients who are not suitable for surgery or refuse it [50]. However, our study showed that IA stage LUAD patients cannot significantly benefit from radiation therapy. According to relevant guidelines, radiation therapy is not recommended for Stage IA LUAD patient [51]. We suspected that patients might receive radiotherapy as a substitute for surgery temporarily due to being diagnosed with transient inoperable disease [52]. They might have poor prognosis because of prolonged DTI (Supplementary Table 2). Recent studies had shown that

Table 4
Univariate Cox analyses for three subtypes.

Characteristics	T1a		T1b		T1c	
	Univariate analysis		Univariate analysis		Univariate analysis	
	HR (95 % CI)	***p* value**	HR (95 % CI)	***p* value**	HR (95 % CI)	***p* value**
Age (years)		<0.001		<0.001		<0.001
≤54	Reference		Reference		Reference	
55-64	1.916 (0.998–3.681)	0.051	1.048 (0.818–1.341)	0.712	1.492 (1.075–2.071)	0.017
65-69	1.727 (0.863–3.458)	0.123	1.288 (0.999–1.661)	0.051	1.636 (1.173–2.282)	0.004
70-74	2.166 (1.095–4.286)	0.026	1.663 (1.296–2.135)	<0.001	1.865 (1.341–2.595)	<0.001
75-79	3.407 (1.707–6.800)	<0.001	2.228 (1.730–2.870)	<0.001	2.278 (1.637–3.170)	<0.001
80-84	5.412 (2.482–11.800)	<0.001	2.864 (2.171–3.778)	<0.001	3.141 (2.228–4.428)	<0.001
≥85	2.819 (0.624–12.725)	0.178	4.878 (3.406–6.986)	<0.001	5.733 (3.780–8.695)	<0.001
Sex		<0.001		<0.001		<0.001
Female	Reference		Reference		Reference	
Male	1.746 (1.290–2.362)		1.515 (1.340–1.713)		1.711 (1.490–1.965)	
Primary site		0.628		0.720		0.127
Upper	Reference		Reference		Reference	
Middle	0.704 (0.343–1.445)	0.339	0.895 (0.674–1.187)	0.440	1.080 (0.763–1.529)	0.663
Lower	0.955 (0.686–1.330)	0.786	0.976 (0.854–1.114)	0.716	1.165 (1.005–1.350)	0.042
Grade		0.001		<0.001		<0.001
I	Reference		Reference		Reference	
II	1.577 (1.110–2.242)	0.011	1.542 (1.326–1.794)	<0.001	1.756 (1.450–2.127)	<0.001
III/IV	2.133 (1.381–3.296)	<0.001	2.192 (1.833–2.621)	<0.001	2.657 (2.157–3.272)	<0.001
Lateral		0.094		0.462		0.249
Left	Reference		Reference		Reference	
Right	0.771 (0.569–1.045)		0.954 (0.843–1.081)		1.087 (0.943–1.254)	
Histologic type		0.038		<0.001		<0.001
AD, NOS	Reference		Reference		Reference	
Solid	2.767 (0.879–8.709)	0.082	1.796 (0.990–3.258)	0.054	1.090 (0.517–2.295)	0.821
BAC	0.557 (0.308–1.010)	0.054	0.698 (0.566–0.861)	0.001	0.507 (0.375–0.684)	<0.001
Mucinous	0.827 (0.434–1.576)	0.564	0.832 (0.620–1.117)	0.222	0.611 (0.421–0.887)	0.010
Acinar	1.056 (0.596–1.871)	0.851	0.474 (0.351–0.641)	<0.001	0.527 (0.363–0.764)	<0.001
Others	0.429 (0.200–0.919)	0.029	0.667 (0.526–0.846)	<0.001	0.568 (0.436–0.740)	<0.001
Surgery		0.511		<0.001		<0.001
Sublobar	Reference		Reference		Reference	
Lobectomy	0.835 (0.615–1.133)	0.247	0.633 (0.555–0.722)	<0.001	0.517 (0.435–0.614)	<0.001
Extended	0.869 (0.213–3.544)	0.845	1.195 (0.790–1.810)	0.399	0.946 (0.634–1.413)	0.787
Radiotherapy		0.064		<0.001		<0.001
No	Reference		Reference		Reference	
Yes	2.555 (0.948–6.890)		4.112 (2.984–5.665)		2.582 (1.746–3.818)	
DTI (months)		0.007		<0.001		<0.001
≤1	Reference		Reference		Reference	
2	1.239 (0.781–1.965)	0.362	1.125 (0.956–1.323)	0.156	1.207 (1.014–1.437)	0.034
3	0.838 (0.370–1.900)	0.672	1.561 (1.245–1.957)	<0.001	1.458 (1.141–1.864)	0.003
≥4	2.680 (1.513–4.745)	<0.001	1.475 (1.130–1.924)	0.004	1.505 (1.144–1.979)	0.003
ELN count		0.003		<0.001		<0.001
0	Reference		Reference		Reference	
1-3	0.605 (0.396–0.926)	0.021	0.641 (0.524–0.784)	<0.001	0.662 (0.511–0.856)	0.002
4-6	0.544 (0.341–0.869)	0.011	0.515 (0.420–0.633)	<0.001	0.526 (0.408–0.678)	<0.001
7-9	0.452 (0.256–0.798)	0.006	0.462 (0.369–0.579)	<0.001	0.503 (0.383–0.661)	<0.001
10-12	0.463 (0.251–0.857)	0.014	0.452 (0.350–0.584)	<0.001	0.414 (0.305–0.560)	<0.001
13-15	0.427 (0.182–0.998)	0.050	0.428 (0.318–0.577)	<0.001	0.407 (0.287–0.576)	<0.001
≥16	0.320 (0.170–0.604)	<0.001	0.405 (0.317–0.519)	<0.001	0.415 (0.312–0.553)	<0.001
Race		0.015		<0.001		<0.001
White	Reference		Reference		Reference	
Black	0.836 (0.454–1.542)	0.567	0.837 (0.662–1.058)	0.137	0.836 (0.648–1.078)	0.166
Others	0.189 (0.060–0.591)	0.004	0.431 (0.323–0.577)	<0.001	0.516 (0.390–0.683)	<0.001
Marital		0.009		<0.001		0.003
Married	Reference		Reference		Reference	
Widowed	1.352 (0.946–1.930)	0.097	1.276 (1.103–1.475)	0.001	1.088 (0.921–1.285)	0.321
Others	1.880 (1.240–2.850)	0.003	1.690 (1.434–1.992)	<0.001	1.383 (1.146–1.669)	<0.001
Income level		0.334		<0.001		<0.001
Low	Reference		Reference		Reference	
Middle	0.826 (0.564–1.209)	0.324	0.736 (0.635–0.853)	<0.001	0.799 (0.677–0.942)	0.008
High	0.764 (0.532–1.098)	0.146	0.605 (0.522–0.702)	<0.001	0.646 (0.545–0.767)	<0.001

household income level was closely related to cancer prognosis [53]. For cancer patients, high household income was a protective factor. In addition to the difference in diagnosis intensity, poorer patients were less likely to receive multidisciplinary assessment than richer patients, which might lead to higher all-cause and specific cause mortality of patients with early disease [54]. Our research also

Table 5
Multivariate Cox analyses for three subtypes.

Characteristics	T1a		T1b		T1c	
	Multivariate analysis		Multivariate analysis		Multivariate analysis	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age (years)						
≤54	Reference		Reference		Reference	
55-64	1.972 (0.941–4.133)	0.072	0.980 (0.745–1.288)	0.883	1.813 (1.236–2.660)	0.002
65-69	2.100 (0.954–4.622)	0.065	1.227 (0.924–1.629)	0.157	2.294 (1.554–3.387)	<0.001
70-74	2.780 (1.273–6.074)	0.010	1.662 (1.256–2.198)	<0.001	2.670 (1.818–3.922)	<0.001
75-79	4.496 (2.050–9.861)	<0.001	2.263 (1.698–3.016)	<0.001	3.173 (2.147–4.691)	<0.001
80-84	5.127 (2.137–12.302)	<0.001	2.910 (2.134–3.970)	<0.001	3.815 (2.525–5.765)	<0.001
≥85	7.392 (1.479–36.942)	0.015	3.997 (2.659–6.007)	<0.001	6.341 (3.881–10.362)	<0.001
Sex						
Female	Reference		Reference		Reference	
Male	1.897 (1.317–2.733)	<0.001	1.694 (1.474–1.947)	<0.001	1.617 (1.380–1.896)	<0.001
Grade						
I	Reference		Reference		Reference	
II	1.346 (0.908–1.996)	0.166	1.613 (1.361–1.912)	<0.001	1.774 (1.434–2.194)	<0.001
III/IV	1.492 (0.895–2.485)	0.160	2.015 (1.644–2.469)	<0.001	2.495 (1.964–3.170)	<0.001
Histologic type						
AD, NOS	Reference		Reference		Reference	
Solid	1.188 (0.262–5.387)	0.824	0.860 (0.379–1.947)	0.717	0.619 (0.229–1.670)	0.343
BAC	0.774 (0.398–1.504)	0.449	0.939 (0.732–1.205)	0.622	0.712 (0.508–0.998)	0.048
Mucinous	0.826 (0.392–1.741)	0.614	1.139 (0.817–1.589)	0.442	1.037 (0.686–1.566)	0.864
Acinar	1.152 (0.618–2.146)	0.656	0.63 (0.455–0.871)	0.005	0.599 (0.402–0.894)	0.012
Others	0.651 (0.261–1.622)	0.357	0.732 (0.564–0.950)	0.019	0.591 (0.429–0.813)	0.001
Surgery						
Sublobar			Reference		Reference	
Lobectomy			0.934 (0.784–1.112)	0.440	0.743 (0.600–0.920)	0.006
Extended			1.363 (0.846–2.194)	0.203	1.147 (0.713–1.843)	0.572
Radiotherapy						
No			Reference		Reference	
Yes			2.247 (1.549–3.258)	<0.001	2.115 (1.317–3.397)	0.002
DTI (months)						
≤1	Reference		Reference		Reference	
2	1.295 (0.781–2.148)	0.316	1.086 (0.908–1.298)	0.366	1.168 (0.963–1.418)	0.115
3	0.978 (0.425–2.250)	0.958	1.498 (1.171–1.918)	0.001	1.491 (1.131–1.967)	0.005
≥4	1.066 (0.451–2.520)	0.885	1.343 (0.996–1.811)	0.053	1.386 (1.026–1.873)	0.033
ELN count						
0	Reference		Reference		Reference	
1-3	0.608 (0.386–0.959)	0.033	0.741 (0.590–0.931)	0.010	0.751 (0.561–1.004)	0.054
4-6	0.574 (0.347–0.949)	0.030	0.622 (0.487–0.794)	<0.001	0.686 (0.510–0.922)	0.012
7-9	0.385 (0.209–0.708)	0.002	0.609 (0.467–0.796)	<0.001	0.692 (0.504–0.950)	0.023
10-12	0.342 (0.157–0.744)	0.007	0.630 (0.466–0.853)	0.003	0.583 (0.410–0.827)	0.003
13-15	0.266 (0.081–0.871)	0.029	0.540 (0.382–0.764)	<0.001	0.538 (0.363–0.797)	0.002
≥16	0.29 (0.143–0.585)	<0.001	0.487 (0.365–0.651)	<0.001	0.573 (0.410–0.801)	0.001
Race						
White	Reference		Reference		Reference	
Black	0.824 (0.410–1.657)	0.586	0.868 (0.669–1.125)	0.284	1.011 (0.766–1.333)	0.940
Others	0.241 (0.076–0.762)	0.015	0.527 (0.386–0.722)	<0.001	0.578 (0.422–0.792)	<0.001
Marital						
Married	Reference		Reference		Reference	
Widowed	1.620 (1.068–2.457)	0.023	1.392 (1.183–1.637)	<0.001	1.202 (0.997–1.449)	0.053
Others	1.443 (0.868–2.398)	0.157	1.370 (1.132–1.658)	0.001	1.317 (1.062–1.632)	0.012
Income level						
Low			Reference		Reference	
Middle			0.786 (0.667–0.926)	0.004	0.847 (0.705–1.017)	0.075
High			0.717 (0.608–0.846)	<0.001	0.710 (0.585–0.862)	<0.001

verified this point of view (Table 2).

For other characteristics such as Age (at diagnosis), Differentiation Grade, Histology Type, ELN, Tumor Size and Marital Status, our research showed similar results to previous studies. Clinically, age played an essential role in assessing the risk of surgery and the choice of surgical method, which had an important impact on the prognosis of patients [55]. Over two-thirds of all new cancers are diagnosed among adults aged ≥60 years [56] and our study also confirmed the above viewpoints (Tables 1 and 2). Previous studies showed that the differentiation grade and histology type play important roles in the prognosis of LUAD. Some studies suggested that the expression of the E-cadherin-catenin complex was related to the degree of differentiation and is an independent prognostic factor related to lung cancer [57]. Therefore, for accurately assessing the prognosis of LUAD patients, the differentiation grade is an indispensable factor. In our research, ELN was a protective factor (Table 2). The more lymph nodes detected, the lower the risk.

However, patients having 7–9 nodes examined had similar benefits as those who examined more lymph nodes. The relationship of overall survival with ELN presumably was due to the avoidance of mis-staging [57]. Therefore, appropriate lymph node examination remained an important part of surgery for lung cancer. Previous studies showed that marriage is protective in cancer care [58]. In this study, marital status played an important role. Unmarried patients had a higher risk compared with married patients. Our research also confirmed that tumor size was directly related to the prognosis of patients (Table 2).

To our knowledge, it was the first systematic review model to predict the prognosis of T1aN0M0 LUAD patients after surgery, taking new factors into account such as DTI and Income Level. However, there were some limitations. In the training and internal validation cohorts, the number of LUAD patients with tumor size$\leq$1 cm was relatively sufficient [59], and some factors such as previous diseases and smoking status were unknown. In the external validation cohort, the total number of cases was limited. Due to the privacy issues, some factors, such as household income level, are difficult to count and collect detailed information in application. Besides, Stereotactic Ablative Radiotherapy (SABR) was recommended as the first choice for early-stage lung cancer recently years [60], while relevant data was not given, and the comparation still remained to be explored. Therefore, there are still many works to do for all of us.

4. Conclusion

Based on SEER database, we summarized 12 factors that affect prognosis of Stage IA LUAD patients and constructed a novel nomogram to predict overall survival for them. We also summarized the factors that might affect prognosis, such as DTI, Sex, Surgery Type and Income Level. All these may be helpful in the selection of treatment methods for early-stage LUAD in the future.

5. Materials and methods

5.1. Patients and selection criteria

In the training and internal validation cohorts, the data was downloaded from the SEER database of National Cancer Institute using SEER*Stat software version 8.3.9 (www.seer.cancer.gov/seerstat). According to the 8th edition TNM staging system, a total of 5942 samples diagnosed as T1N0N0 LUAD were available in SEER database. The patients were selected according to the following criteria: 1) they were diagnosed as primary lung adenocarcinoma between 2010 and 2015. According to the 2015 WHO Classification of Lung Tumors [61], the following codes represented LUAD in the SEER database: (ICD-*O*-3: 8140 Adenocarcinoma, NOS, 8144 Adenocarcinoma, intestinal type, 8230 Solid carcinoma, NOS, 8250 Bronchiolo alveolar adenocarcinoma, NOS, 8251 Alveolar adenocarcinoma, 8252 Bronchiolo alveolar carcinoma, non-mucinous, 8253 Bronchiolo alveolar carcinoma, mucinous, 8254 Bronchiolo-alveolar carcinoma, mixed mucinous and non-mucinous, 8255 Adenocarcinoma with mixed subtypes, 8260 Papillary adenocarcinoma, NOS, 8310 Clear cell adenocarcinoma, NOS, 8323 Mixed cell adenocarcinoma, 8333 Fetal adenocarcinoma, 8480 Mucinous adenocarcinoma, 8481 Mucin producing adenocarcinoma, 8490 Signet ring cell carcinoma, 8550 Acinar cell carcinoma, 8551 Acinar cell cystadenocarcinoma); 2) based on the criteria of T1N0M0 LUAD, the diameter of tumor size was less than or equal to 3 cm; and 3) the tumor was not accompanied by lymph nodes or distant metastasis; 4) in order to explore the role of surgical type in survival, we selected patients who had undergone surgical treatment (in SEER database, Surgery Codes: 20–70); 5) patient's clinical and pathological data (Sex, Age, Race, Marital Status, Tumor Primary Site, Tumor Size, ELN, DTI, Therapy, Income Level, Overall Survival, Cause of Death, Differentiation Grade and Histology Type) were complete and available; 6) for each patient, the age at diagnosis should be more than or equal to 18 years and the survival month should be more than or equal to 1 month (Fig. 1). Afterwards, we collected all these eligible cases for further analysis. There was no requirement for ethical approval since all the data from the SEER database was obtained in a public method.

We also built an external validation cohort with 136 samples using the same standards as in the preceding paragraph. The patients were selected from the Thoracic Surgery Department of Shandong Provincial Hospital between 2012 and 2017. All patients had undergone surgery, and their clinicopathological information was available.

5.2. Survival analysis

Survival curves were produced using the Kaplan-Meier method and evaluated by log-rank test. To evaluate the effects of clinicopathological factors on prognosis, univariate and multivariate Cox proportional hazards regression was applied using SPSS 25.0 (IBM Corporation, Armonk, NY, USA), and results were presented as hazards ratio and 95 % CI.

5.3. Construction of nomogram

The 5942 LUAD patients included were randomly divided into a training group and an internal validation group, including 4754 and 1188 samples (the split ratio was 8:2), respectively. For the building of nomogram, the split ration of clinical cohort was usually 7:3 or 8:2 [62–64]. Random grouping, data inclusion and exclusion was performed by Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA).The nomogram model was built and tested as follow steps: **1)** in the training cohort, Kaplan–Meier curves and univariate Cox risk regression were performed to determine factors for multivariate regression analysis by SPSS 25.0; **2)** in the training cohort, factors with a $p < 0.05$ in univariate analysis were further analyzed in a multivariate regression analysis by SPSS 25.0; **3)** in the training cohort, independent prognostic factors ($p < 0.05$) were used to construct the nomogram and predict the 3- and 5-year OS by R4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). (R package: (rms) (foreign) (survival)).

5.4. Validation of nomogram

In the training cohort, internal and external validation cohorts, the accuracy of the nomogram was evaluated by the C index, calibration curve and the AUC by R4.1.3 (R package: (rms) (foreign) (survival) (regplot) (timeROC)). When the value of C index was greater than 0.7, the results demonstrated that the model has a reliable discriminant ability. The same was AUC. In a well-calibrated model, the calibration curve should be close to 45°.

DCA curves of this nomogram model were constructed by R4.1.3 (R package: (rmda) and "stdca.R″) to further assess the advantages of our novel nomogram and determine whether the nomogram was more accurate than other reported models and AJCC TNM staging system.

5.5. Grouping of income level

Specifically, the grouping criteria of Income Level in this article were as follows: **1)** in the training and internal validation cohorts, the Income Level of patient were directly related to 'family annual income' in the SEER database; **2)** in the external validation cohort, we were unable to obtain the patient's personal income level information. Considering the differences in economic levels between city and countryside in the local area, the urban patients were classified into the Low, Middle and High groups and the rural patients were grouped into the Low and Middle groups based on their annual per capita income level in their respective area.

5.6. Subgroup analysis

The subgroup analyses were performed as follow steps: **1)** the total cohort was divided into 3 subgroups by T stage (T1a, 1b, 1c), including 728, 3186 and 2028 samples; **2)** construct cross tables and perform chi square testing for 3 subgroups by using SPSS 25.0; **3)** Kaplan–Meier curves, univariate and multivariate Cox regression analyses were performed to compare the differences among three subgroups by SPSS 25.0. In the training and validation cohorts. **4)** Each of training and internal validation cohorts was divided into 3 subgroups by T stage, including 584, 2545, 1625 and 144, 641, 403 samples, respectively. The accuracy of our nomogram in each subgroup was evaluated by the C index and the AUC by R4.1.3 (R package: (rms) (foreign) (survival) (timeROC)).

5.7. Statistical analysis

R packages used in this article (rms, foreign, survival, timeROC, regplot, rmda) were from CRAN (cran.r-project.org/mirrors.html). 'stdca.R' was downloaded from Memorial Sloan Kettering Cancer Center (www.mskcc.org) to conduct DCA. All codes used in this study were provided in Supplementary Materials. Statistical significance was set at $p < 0.05$. In research using SEER database and nomogram, $p < 0.05$ was considered statistically significant normally [16,65].

Ethics statement

The ethical review was approved by the Ethics Committee of Shandong Provincial Hospital (SWYX: NO. 2023-352).

Data availability statement

Data of training and internal validation cohorts in this study were downloaded from SEER database (https://seer.cancer.gov/). Relative R codes were uploaded to supplementary material. Everyone can get the SEER data online.

The external validation cohort was provided in the supplementary material, and the data associated with this study has not been deposited into a publicly available repository. The data will be made available on request.

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CRediT authorship contribution statement

Jiahao Li: Writing - review & editing, Writing - original draft, Software, Formal analysis, Data curation. **Yadong Wang:** Writing - review & editing, Writing - original draft, Validation, Investigation, Formal analysis, Data curation. **Yong Liu:** Validation, Software, Investigation. **Qiang Liu:** Investigation, Formal analysis, Data curation. **Hongchang Shen:** Investigation, Funding acquisition, Data curation. **Xiaoyang Ren:** Funding acquisition, Data curation. **Jiajun Du:** Writing - review & editing, Writing - original draft, Supervision, Software, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23205.

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