Original Article

Establishment and validation of a clinicopathological prediction model for postoperative recurrence of stage IA lung adenocarcinoma

Xin Zhang[1], Jie Yang[1], Shining Li[1], Yong Ao[1], Leqi Zhong[1], Xinyu Liu[1], Kongjia Luo[1,2], Yi Hu[1,2]

[1]Department of Thoracic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China; [2]Guangdong Esophageal Cancer Research Institute, Guangzhou, China

Contributions: (I) Conception and design: Y Hu, K Luo; (II) Administrative support: L Zhong, X Liu; (III) Provision of study materials or patients: X Zhang, Y Ao; (IV) Collection and assembly of data: X Zhang, J Yang, S Li; (V) Data analysis and interpretation: X Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yi Hu, MD, PhD. Department of Thoracic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, 651 East Dongfeng Rd., Guangzhou 510080, China; Guangdong Esophageal Cancer Research Institute, Guangzhou, China. Email: huyisci@163.com.

Background: With the popularization of low-dose spiral computed tomography (CT), an increasing number of stage IA lung cancers have been discovered. Patients with stage IA lung adenocarcinoma who undergo radical surgical resection tend to have a favourable prognosis. However, A significant proportion of patients undergo postoperative recurrence and metastasis. The purpose of this study was to screen out the risk factors in patients with stage IA lung adenocarcinoma and establish a nomogram model to help clinicians identify high-risk patient groups.

Methods: A nomogram was conducted based on a retrospective study of 731 patients with stage IA lung adenocarcinoma. Concordance index (C-index), clinical decision analysis, receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the discrimination and calibration of the nomogram. Survival curves were drawn by Kaplan-Meier method, and significance was determined by log-rank test. According to nomogram scores, the patients were divided into low- and high-risk subgroups.

Results: The internal and external cohorts included 731 and 235 eligible patients. In univariate and multivariate analyses, the independent factors for recurrence-free survival (RFS) were all selected in the nomogram. C-indexes of the nomogram were 0.812 (95% confidence interval: 0.756–0.868) and 0.817 in the internal and external validation, respectively, showing that the prominent prediction performance was great. Nomogram scores showed that patients in the low-risk group (5-RFS rate, 0.797 to 0.99) had better RFS than patients in the high-risk group (5-RFS rate, 0.10 to 0.797) (P<0.001).

Conclusions: A nomogram model was established that can be beneficial to evaluate RFS in patients with stage IA lung adenocarcinoma after curative resection. It can be of value in helping clinicians develop treatment strategies to improve patient survival.

Keywords: Nomogram; lung adenocarcinoma; IA stage; recurrence-free survival (RFS)

Submitted Jan 19, 2024. Accepted for publication Apr 03, 2024. Published online May 21, 2024.
doi: 10.21037/jtd-24-116
View this article at: https://dx.doi.org/10.21037/jtd-24-116

Introduction

Lung cancer continues to be one of the most prevalent malignancies over the world and the primary cause of cancer deaths, leading to 18% of all cancer-related deaths (1). Non-small cell lung cancer (NSCLC) is diagnosed in approximately 85% of all lung cancer patients, with adenocarcinoma being its most common subtype (2). In recent years, more and more high-resolution computed tomography (HRCT) and low-dose CT have been used for lung cancer screening and diagnosis, helping to detect more lung cancer cases at an early stage and effectively reducing lung cancer mortality. Curative surgical resection remains the primary treatment for early-stage patients. Nevertheless, some patients still experience postoperative recurrence and metastasis. For stage IA lung cancer patients, the postoperative recurrence rate is 4.8–10% (3,4). There is a pressing need for a robust prediction model that integrates tumor factors and clinical characteristics to help clinicians screen out high-risk patients who are prone to recurrence of stage IA lung cancer after surgery. Nomogram has been proven a useful tool in facilitating risk evaluation by integrating critical pathological and clinical features for oncologic outcomes and have shown better predictive accuracy than traditional tumor-node-metastasis (TNM) classification systems across cancer types (5,6). In addition, most articles have provided verification that a single factor affects the prognosis of stage IA lung cancer leading to recurrence, but few scholars have established an intuitive nomogram model to quantify the recurrence risk of each patient and select high-risk patients with postoperative recurrence. Therefore, this study was designed to develop a nomogram that includes known clinicopathological variables to predict the long-term survival outcomes of patients with stage IA lung adenocarcinoma. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-116/rc).

Highlight box

Key findings

- We find that in addition to T stage, radiological ground glass components, lymphovascular invasion, tumor differentiation, and pathological subtypes also affect the prognosis of stage IA lung adenocarcinoma.

What is known and what is new?

- Stage IA lung adenocarcinoma patients are a heterogeneous population with varying risk of recurrence.
- We constructed a nomogram model for predicting postoperative recurrence-free survival in patients with stage IA lung adenocarcinoma. The model had good predictive performance with a C-index of 0.812 (95% confidence interval: 0.756–0.868).

What is the implication, and what should change now?

- The model can be used to classify stage IA lung adenocarcinoma patients into different prognostic categories and facilitate decision-making regarding appropriate postoperative management in high-risk patients.

Methods

Study population

The study included 731 patients who underwent surgical treatment at Sun Yat-sen University Cancer Center between January 2016 and December 2018. Patients with pathological stage IA lung adenocarcinoma were screened out through severe inclusion and exclusion criteria, and 235 patients who underwent surgical treatment at the Sun Yat-sen University Cancer Center between January 2019 and June 2019 were included as an external cohort. All patients underwent hematology routine examination, lung function, cardiac color Doppler ultrasound, CT plain scan and enhanced scan, electrocardiogram, craniocerebral magnetic resonance plain scan and enhanced scan for preoperative evaluation. Most of patients underwent video-assisted lobectomy and systemic lymphadenectomy, and some patients underwent sublobectomy (n=81). Study inclusion criteria were as follows: (I) postoperative pathological findings of stage IA invasive lung adenocarcinoma; (II) patients undergoing standard radical resection for lung cancer and the distance between incisal margin and tumor was >2 cm or > maximum diameter of tumor; (III) patients undergoing epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) diagnosis of surgical specimens. Study exclusion criteria were as follows: (I) pathologically confirmed adenocarcinoma *in situ* or minimally invasive adenocarcinoma; (II) death during the first hospitalization or within 30 days after the operation; (III) patients receiving neoadjuvant therapy before surgery or receiving adjuvant therapy after surgery; (IV) postoperative pathological findings of other types of primary or secondary lung cancer; (V) malignant tumors related to other organs; and (VI) a diagnosis of multiple primary carcinomas. Basic information and

clinicopathological data of patients were obtained from the hospital's electronic medical record system. They included sex, age, family history, smoking status, surgical method, surgical intervention, nodule imaging features (ground glass nodules, mixed-density nodules, and solid nodules), pleural retraction, spicule sign, tumor size, tumor differentiation, proportion of solid and micropapillary components (S + MP), adenocarcinoma histological subtype, lymphovascular invasion (LVI), perineural invasion, preoperative carcinoembryonic antigen (CEA) level, cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) level, neuron-specific enolase (NSE) level, EGFR, and ALK. The stage of tumor was performed based on TNM Staging of Lung Cancer (8th edition). In general, follow-up was conducted every six months for the first two years after surgery and once a year after the first two years. At each follow-up, we routinely included physical examination, lung cancer tumor markers such as CEA, lung CT, and head magnetic resonance imaging (MRI). Once imaging or pathology confirmed tumor recurrence and metastasis, regardless of whether tumor markers were elevated, the time of first detection was recorded. The study was conducted in accordance with the Declaration of Helsinki (as amended in 2013). This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (No. SL-B2023-334), and informed consent was taken from all individual participants.

Histopathological judgment

Tissue types of surgical specimens were implemented from two senior pathologists of our hospital in accordance with the World Health Organization (WHO) 2015 lung tumor tissue typing standards and the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Association Lung adenocarcinoma typing standards. LVI is defined as the identification of tumor cells in the lymphatic or vascular lumen. Perineural invasion is defined as the infiltration of cancer cells into the nerve tissue surrounding the lesion, at which time cancer cells can spread along the nerve sheath for distant dissemination. Invasive lung adenocarcinoma can be divided into lepidic type, acinar type, papillary type, solid type and micropapillary pathological subtypes. The proportion of each subtype of lung adenocarcinoma was calculated in 5% increments. When the proportion of a subtype in the tumor was greater than 5%, its existence was considered. According to the 2015 WHO classification of lung adenocarcinoma, tumor differentiation was divided into three grades as follows: grade 1: lepidic predominant; grade 2: acinar or papillary predominant; grade 3: solid or micropapillary predominant; these grades correspond to well, moderately, and poorly differentiated tumors, respectively. The amplification refractory mutation system (ARMS) method was employed to assess the status and types of *EGFR* mutation. The human *EGFR* gene mutation fluorescence polymerase chain reaction (PCR) diagnostic kit was utilized for the identification of the most common *EGFR* mutations. Fluorescence in situ hybridization (FISH) was used to examine the status of the *ALK* gene.

Evaluation of radiological features

The imaging features were independently assessed by two experienced chest radiologists (with 6 and 13 years of experience interpreting chest CT) who were unaware of the pathological findings. Differences in interpretation among the observers were resolved by consensus. Imaging features of each nodule were analyzed, including (I) margin (clear, blurred), (II) spiculation (absent, present), and (III) pleural attachment (absent, present). All CT findings were evaluated based on HRCT images.

Definition of recurrence and metastasis

Local recurrence refers to the recurrence of the ipsilateral lobe, bronchial stump, or local lymph nodes (subcarinal, paraesophageal, supraclavicular, or hilar lymph nodes) as confirmed by imaging or pathology. Distal metastasis refers to the recurrence and metastasis of distal organs, such as the lung, brain, liver, adrenal gland, and bone, confirmed by imaging or pathology. Distant metastasis was defined when both local recurrence and distant metastasis occur. Recurrence-free survival (RFS) was defined as the time interval from the day of surgery to the last day of follow-up when the tumor recurred and metastasized as confirmed by radiography and pathology.

Statistical analysis

Continuous variables were subjected to normality tests. For data conforming to a normal distribution, mean ± standard deviation was used for representation, and intergroup differences were analyzed using independent *t*-tests. Data not following a normal distribution were represented by median and interquartile range (IQR), and

intergroup differences were analyzed using Mann-Whitney *U* tests. Classified variables were summarized in terms of frequencies and percentages, and differences between groups were analyzed using the Chi-square test. The end point of the follow-up period was RFS. Survival curves were plotted by the Kaplan-Meier method, and survival differences between groups were tested by the log-rank test. Significance tests were all two-sided. We conducted both univariate and multivariate analyses using COX regression. Risk factors identified in the univariate analysis were included in the multivariate analysis. In the multivariate analysis, a significance level of P<0.05 was considered statistically significant, helping to identify independent risk factors affecting postoperative RFS. Hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI) were calculated for each variable. Statistical analysis was performed using r4.2.2 software.

Nomogram construction

Using the "rms", "foreign", and "survival" packages in R studio, we created nomograms based on the risk factors identified from the multivariate analysis. The concordance index (C-index) and correction curve were used to measure the performance of the model. The larger the C-index is, the more accurate the prognosis. We used the "prediction" function in the "Survival" R package to calculate the risk score of the sample in the training cohort. According to the risk score, the samples were classified into a high-risk group and a low-risk group. Survival curves were drawn by the Kaplan-Meier method and compared by the log-rank test.

Nomogram verification

To reduce the overfitting bias, self-sampling (number of self-sampling B =1,000) was used for internal verification, and the C-index was used to evaluate the accuracy of nomogram prediction. In general, the closer the C-index is to 1, the better the model's prediction. If the C-index = 1, the model's prediction results perfectly match the real results. To assess the association between the event rates predicted by the nomogram model and the observed reality, we constructed a calibration curve. From January 2019 to June 2019, external validation of the nomogram was conducted in an external cohort of patients with stage IA lung adenocarcinoma (n=235) at Sun Yat-sen University Cancer Center. Decision curve analysis (DCA) was employed to assess the clinical utility of the model.

Results

Basic characteristics of the study population

This study included 731 patients diagnosed with stage IA invasive lung adenocarcinoma who underwent surgical treatment, and their clinical, imaging, and pathological characteristics are shown in *Table 1*. The median age of the patients was 60 years (IQR: 53–66 years), with 343 males (46.9%) and 388 females (53.1%). A total of 514 patients (70.3%) were never smoking. Lobectomy was performed in 650 patients (88.9%), and a minimally invasive rate of 83.7% was achieved. There were 486 patients (66.5%) with mixed-density nodules on chest CT, but only 75 patients (10.3%) had solid nodules. The postoperative pathology showed that the tumor size was T1b in 447 cases (61.1%), and there was moderate differentiation in 533 cases (72.9%). The numbers of patients with LVI and perineural invasion were 32 (4.4%) and 10 (1.4%), respectively. S + MP accounted for ≥5% in 109 patients (14.9%). A total of 70 recurrences were observed, including 14 local recurrences and 56 distant metastases. The mean recurrence time was 26.7 months, and the median follow-up time was 51.0 months.

Univariate and multifactorial analyses of RFS

We utilized a Cox regression model to identify the independent risk factors associated with RFS. Univariate analysis identified the following: gender (HR: 0.46, 95% CI: 0.28–0.75, P=0.002), smoking status (HR: 2.3, 95% CI: 1.4–3.6, P<0.001), imaging characteristics of nodules (HR: 5.0, 95% CI: 3.1–8.2, P<0.001), pleural traction (HR: 1.7, 95% CI: 1.1–2.7, P=0.03), spiculation (HR: 2.5, 95% CI: 1.6–4.2, P<0.001) and tumor size (HR: 3.7, 95% CI: 2.3–6.0, P<0.001), degree of tumor differentiation (HR: 5.9, 95% CI: 3.7–9.4, P<0.001), LVI (HR: 5.9, 95% CI: 3.2–11, P<0.001), perineural invasion (HR: 6.5, 95% CI: 2.6–16, P<0.001), CEA level (HR: 2.8, 95% CI: 1.7–4.6, P<0.001), NSE level (HR: 2.6, 95% CI: 1.2–5.5, P=0.01) and S + MP ≥5% (HR: 6.9, 95% CI: 4.3–11, P<0.001) were risk factors for postoperative recurrence and metastasis in patients with stage IA lung adenocarcinoma. The aforementioned risk factors were incorporated into the multivariate analysis, and the results showed that solid nodules (HR: 2.36, 95% CI: 1.33–4.19, P=0.003), T1c stage (HR: 1.84, 95% CI: 1.06–3.17, P=0.03), poor differentiation (HR: 2.27, 95% CI: 1.24–4.17, P=0.008), LVI (HR: 2.09, 95% CI: 1.06–4.14, P=0.03) and S + MP ≥5% (HR: 3.02, 95% CI: 1.55–5.87,

Table 1 Clinicopathological characteristics of patients with stage IA lung adenocarcinoma (n=731)

Variables	N (%)
Age (years), median [IQR]	60 [53, 66]
<60	365 (49.9)
≥60	366 (50.1)
Sex	
Male	343 (46.9)
Female	388 (53.1)
Smoking	
No	514 (70.3)
Yes	217 (29.7)
Family history	
No	567 (77.6)
Yes	164 (22.4)
Surgical method	
Sublobectomy	81 (11.1)
Lobectomy	650 (88.9)
Surgical intervention	
Thoracotomy	119 (16.3)
Video-assisted thoracoscopic surgery	612 (83.7)
Imaging features	
GGO	170 (23.3)
Mixed density nodules	486 (66.5)
Solid nodules	75 (10.3)
Pleural retraction	
No	436 (59.6)
Yes	295 (40.4)
Spicule sign	
No	413 (56.5)
Yes	318 (43.5)
Tumor size (8th AJCC)	
1a	145 (19.8)
1b	447 (61.1)
1c	139 (19.0)
Tumor differentiation	
Well	83 (11.4)
Moderate	533 (72.9)
Poor	115 (15.7)
Histological subtype	
Lepidic	118 (16.1)
Acinar	450 (61.6)
Papillary	118 (16.1)
Micropapillary	8 (1.1)
Solid	37 (5.1)
Lymphovascular invasion	
No	699 (95.6)
Yes	32 (4.4)
Perineural invasion	
No	721 (98.6)
Yes	10 (1.4)
CEA (ng/mL)	
<5	599 (81.9)
≥5	132 (18.1)
CYFRA21-1 (ng/mL)	
<3.3	516 (70.6)
≥3.3	215 (29.4)
NSE (ng/mL)	
<16.3	692 (94.7)
≥16.3	39 (5.3)
EGFR mutation	
No	278 (38.0)
Yes	453 (62.0)
ALK mutation	
No	711 (97.3)
Yes	20 (2.7)
S + MP ≥5%	
No	622 (85.1)
Yes	109 (14.9)
Recurrence and metastasis	
No	661 (90.4)
Local recurrence	14 (1.9)
Distant metastasis	56 (7.7)

IQR, interquartile range; GGO, ground-glass opacity; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; NSE, neuron-specific enolase; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; S + MP, solid and micropapillary component.

Table 2 Univariate and multivariate analysis of RFS

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age (years)		0.36		
<60	Ref			
≥60	1.20 (0.78–2)			
Sex		0.002		0.059
Male	Ref		Ref	
Female	0.46 (0.28–0.75)		0.52 (0.26–1.02)	
Smoking		<0.001		0.72
No	Ref		Ref	
Yes	2.30 (1.40–3.60)		0.88 (0.44–1.75)	
Family history		0.84		
No	Ref			
Yes	1.10 (0.61–1.80)			
Surgical method		0.38		
Sublobectomy	Ref			
Lobectomy	1.5 (0.61–3.7)			
Surgical intervention		0.46		
Thoracotomy	Ref			
Video-assisted thoracoscopic surgery	0.80 (0.45–1.40)			
Imaging features		<0.001		0.003
Non-solid nodules	Ref		Ref	
Solid nodules	5.00 (3.10–8.20)		2.36 (1.33–4.19)	
Pleural retraction		0.03		0.81
No	Ref		Ref	
Yes	1.70 (1.10–2.70)		1.07 (0.63–1.79)	
Spicule sign		<0.001		0.37
No	Ref		Ref	
Yes	2.50 (1.60–4.20)		1.29 (0.74–2.24)	
Tumor size (8th AJCC)		<0.001		0.03
1a/1b	Ref		Ref	
1c	3.70 (2.30–6.00)		1.84 (1.06–3.17)	
Tumor differentiation		<0.001		0.008
Well or moderate	Ref		Ref	
Poor	5.90 (3.70–9.40)		2.27 (1.24–4.17)	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Histological subtype		<0.001		
Lepidic	Ref		Ref	
Acinar	2.80 (1.00–7.90)		1.28 (0.44–3.78)	0.65
Papillary	3.30 (1.10–10.00)		1.54 (0.48–4.91)	0.47
Micropapillary	21.00 (5.30–85.00)		1.67 (0.34–8.22)	0.53
Solid	8.4 (2.60–27.00)		0.90 (0.24–3.42)	0.88
Lymphovascular invasion		<0.001		0.03
No	Ref		Ref	
Yes	5.90 (3.20–11.00)		2.09 (1.06–4.14)	
Perineural invasion		<0.001		0.57
No	Ref		Ref	
Yes	6.50 (2.60–16.00)		1.35 (0.48–3.85)	
CEA (ng/mL)		<0.001		0.18
<5	Ref		Ref	
≥5	2.80 (1.70–4.60)		1.47 (0.84–2.58)	
CYFRA21-1 (ng/mL)		0.92		
<3.3	Ref			
≥3.3	0.97 (0.58–1.60)			
NSE (ng/mL)		0.01		0.06
<16.3	Ref		Ref	
≥16.3	2.60 (1.20–5.50)		2.15 (0.96–4.79)	
EGFR mutation		0.045		0.97
No	Ref		Ref	
Yes	0.62 (0.39–0.99)		1.01 (0.61–1.67)	
ALK mutation		0.33		
No	Ref			
Yes	1.80 (0.56–5.60)			
S + MP ≥5%		<0.001		0.001
No	Ref		Ref	
Yes	6.90 (4.30–11.00)		3.02 (1.55–5.87)	

RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; NSE, neuron-specific enolase; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; S + MP, solid and micropapillary component.

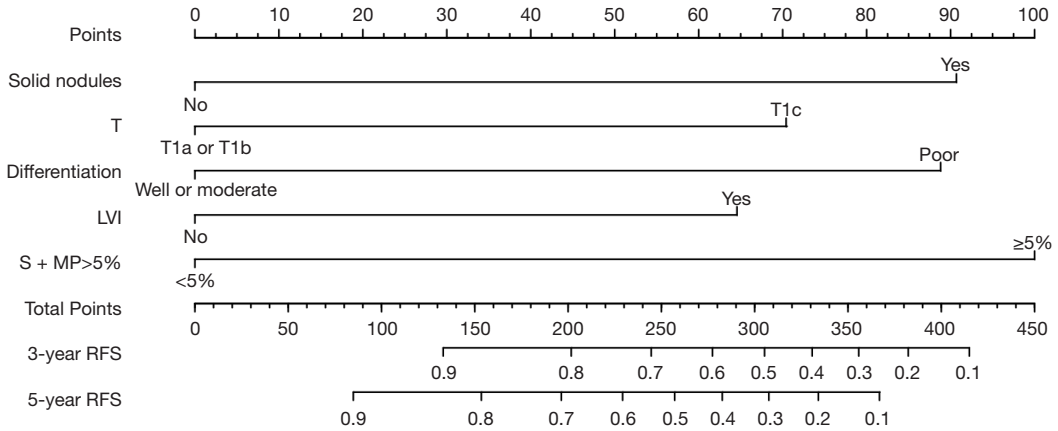

Figure 1 Nomogram for predicting RFS in patients with stage IA lung adenocarcinoma. The nomogram is composed of five variables. Each variable has a corresponding axis, and each sub-variable has a corresponding score on the axis. The total score of the patient can be obtained by adding the scores corresponding to each sub-variable to obtain the predicted probability of RFS at 3 and 5 years after surgery. T, tumor size; LVI, lymphovascular invasion; S + MP, solid + micropapillary component; RFS, recurrence-free survival.

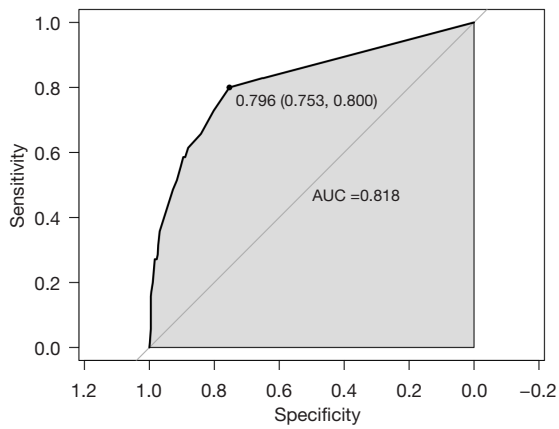

Figure 2 The receiver operating characteristic curve for the RFS prediction model. RFS, recurrence-free survival; AUC, area under the curve.

P=0.001) were independent risk factors for postoperative RFS in patients with stage IA lung adenocarcinoma (*Table 2*).

Nomogram construction

The results of the multivariate Cox regression analysis revealed that solid nodules, T1c stage, poor differentiation, LVI, and micropapillary consolidation ≥5% were independent risk factors for postoperative RFS in patients with stage IA lung adenocarcinoma. We then established 3-year and 5-year nomogram prediction models of RFS based on these results (*Figure 1*). The nomogram comprised five variables, with each variable represented by an axis, and each sub-variable associated with a corresponding score along the axis. The score corresponding to each subvariable was added to obtain the total score of the patient, and the predicted probability of RFS at 3 and 5 years after surgery was obtained. For example, in patients with stage T1c, poor differentiation, imaging evidence of solid pulmonary nodules, postoperative pathology of lung adenocarcinoma with S + MP ≥5%, and postoperative pathology without LVI, the total score was 344.7, and the predicted 5-year RFS was 14.8%.

Nomogram validation

In the internal cohort, the RFS prediction model had a C-index of 0.812 (95% CI: 0.756–0.868) and an area under the receiver operating characteristic curve of 0.818 (*Figure 2*), while the calibration curve showed that the predicted values of the 3- and 5-year RFS were consistent with the actual values (*Figure 3*). The clinical, pathological and image characteristics of the nomogram validation in an external cohort are shown in *Table 3*. The median age of all patients was 59 [IQR: 51–65] years; 107 (45.5%) were male, 128 (54.5%) were female, 64 (27.2%) were smokers, and 6 (2.6%) had solid nodules on chest CT. The postoperative pathology showed that the tumor size was T1c in 52 cases (22.1%) and low differentiation in 32 cases (13.6%). There were 16 patients (6.8%) with LVI and 28 patients (11.9%) with a S + MP ≥5%. During

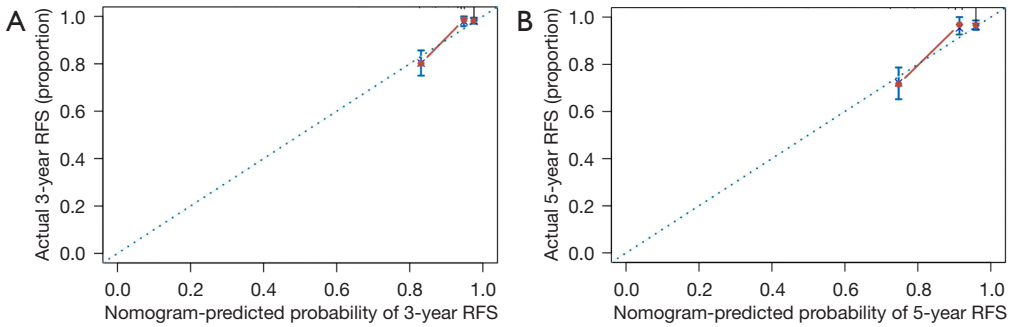

Figure 3 Calibration plots for RFS of internal data. (A) 3-year RFS of calibration plots; (B) 5-year RFS of calibration plots. RFS, recurrence-free survival.

the study period, 14 patients (14/235, 6.0%) had tumor recurrence, all of which were distant metastases. The RFS nomogram model was used to score each patient in the cohort, and the C-index was 0.817. *Figure 4* illustrates the calibration curve for RFS in the external cohort. Based on the established nomogram model, we generated a clinical decision analysis curve (*Figure 5*), and the results demonstrated that this nomogram had favorable clinical utility to predict postoperative RFS in patients with stage IA lung adenocarcinoma. In addition, the net benefit of the corresponding treatment was higher than that of "all treatment" or "no treatment".

Risk grouping based on nomogram model

We use the "surv_cutpoint" function in the "survminer" R package to get the cutoff value according to the nomogram score for each patient in the internal cohort, and the cutoff value was 155.3. Besides, the overall 5-year RFS ratio corresponding to the cutoff value is 0.797. According to the cutoff value, we stratified the cohort of patients into two groups: a low-risk group and a high-risk group. *Figure 6* shows that according to the fitted survival curve, the RFS of the low-risk group IA was better than that of the high-risk group IA (Chi-square value 368.9254, P<0.001).

Discussion

The National Comprehensive Cancer Network (NCCN) guidelines do not recommend postoperative adjuvant therapy for stage IA lung adenocarcinoma, possibly because they do not accurately distinguish the specific groups at high risk of recurrence. In our study, we established a new nomogram model that is good at predicting RFS in patients with stage IA disease and has a dramatically higher C-index of 0.812 (95% CI: 0.756–0.868). We divided the cohort of patients into a high-risk group and a low-risk group based on the 5-year RFS risk ratio of the nomogram, which helps clinicians identify high-risk groups and develop individualized follow-up strategies. This may result in a more rational distribution of healthcare resources and improve outcomes for patients with stage IA lung adenocarcinoma.

According to the current TNM staging system, the only variable available for subdivision in patients with stage IA NSCLC is the T stage (T1a/T1b/T1c), which has a dramatically lower C-index of 0.598 (95% CI: 0.486–0.711) (7). We found that in addition to T stage, radiological ground glass components, LVI, tumor differentiation, and pathological subtypes also affect the prognosis of stage IA lung adenocarcinoma.

Our findings are largely in agreement with previous studies and show that in patients with stage IA lung adenocarcinoma, radiologically pure-solid nodules are an important prognostic factor that should be accounted for. Pure solid lung cancers with no radiologic ground-glass opacity (GGO) component show more malignant behavior both clinically and pathologically (8). This finding is associated with nodal involvement, vessel invasion, and pleural invasion and is associated with poor prognosis (9). JCOG0201 found that the 5-year survival rate of patients with GGO components was higher than that of patients with solid nodules in all substages of stage IA regardless of the proportion of solid components in mixed nodules (10). In the eighth edition staging system, if both show the same solid component size, clinicians will assign them to the same clinical T category, which will result in stage migration and misjudgment of patient prognosis. Therefore, the presence

Table 3 Clinicopathological characteristics of patients with stage IA lung adenocarcinoma (data of external validation)

Variables	N (%)
Age (years), median [IQR]	59 [51, 65]
<60	124 (52.8)
≥60	111 (47.2)
Sex	
Male	107 (45.5)
Female	128 (54.5)
Smoking	
No	171 (72.8)
Yes	64 (27.2)
Family history	
No	185 (78.7)
Yes	50 (21.3)
Surgical method	
Sublobectomy	33 (14.0)
Lobectomy	202 (86.0)
Surgical intervention	
Thoracotomy	42 (17.9)
Video-assisted thoracoscopic surgery	193 (82.1)
Imaging features	
GGO	69 (29.4)
Mixed density nodules	160 (68.1)
Solid nodules	6 (2.6)
Pleural retraction	
No	141 (60.0)
Yes	94 (40.0)
Spicule sign	
No	145 (61.7)
Yes	90 (38.3)
Tumor size (8th AJCC)	
1a	45 (19.1)
1b	138 (58.7)
1c	52 (22.1)
Tumor differentiation	
Well	19 (8.1)
Moderate	184 (78.3)
Poor	32 (13.6)
Histological subtype	
Lepidic	21 (8.9)
Acinar	174 (74.0)
Papillary	33 (14.0)
Micropapillary	4 (1.7)
Solid	3 (1.3)
Lymphovascular invasion	
No	219 (93.2)
Yes	16 (6.8)
Perineural invasion	
No	232 (98.7)
Yes	3 (1.3)
CEA (ng/mL)	
<5	209 (88.9)
≥5	26 (11.1)
CYFRA21-1 (ng/mL)	
<3.3	181 (77.0)
≥3.3	54 (23.0)
NSE (ng/mL)	
<16.3	222 (94.5)
≥16.3	13 (5.5)
EGFR mutation	
No	57 (24.3)
Yes	178 (75.7)
ALK mutation	
No	234 (99.6)
Yes	1 (0.4)
S + MP ≥5%	
No	207 (88.1)
Yes	28 (11.9)
Recurrence and metastasis	
No	221 (94.0)
Local recurrence	0 (0.0)
Distant metastasis	14 (6.0)

IQR, interquartile range; GGO, ground-glass opacity; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; NSE, neuron-specific enolase; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; S + MP, solid and micropapillary component.

or absence of GGOs will be considered an important indicator of the next clinical T classification.

The results of our research have shown that LVI is also considered an independent risk factor for the recurrence of early lung cancer and that the risk exceeds that of tumor size. LVI, which includes lymphatic and vascular infiltration, is believed to indicate tumor aggressiveness and is crucial in the initial step of tumor metastasis in numerous types of human cancers (11). The 5-year survival of stage IA patients with or without LVI was 79% and 91%, respectively (12). Numerous previous studies have suggested that LVI should be considered in the staging criteria and indications of adjuvant chemotherapy (13,14). In our study, we also found that poorly differentiated lung adenocarcinoma is an important independent risk factor for the prognosis of stage IA lung adenocarcinoma. Several studies have shown that patients with poorly differentiated cancer are at higher risk of recurrence and death after resection for stage IA NSCLC and suggested that the biological aggressiveness of cancer cells may be related to the degree of differentiation and thus to tumor recurrence (15,16).

Our results show that a ratio of S + MP ≥5% is an

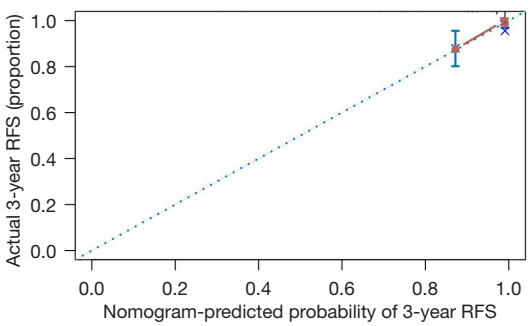

Figure 4 Calibration plots for 3-year RFS of external data. RFS, recurrence-free survival.

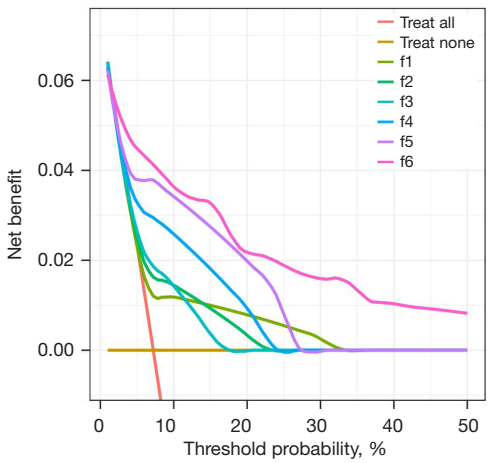

Figure 5 DCA of RFS nomogram model after surgical treatment of IA lung adenocarcinoma was predicted. "All" assumes all patients with stage IA lung adenocarcinoma are treated. "None" indicates all patients with stage IA lung adenocarcinoma are not treated (f1 = T, f2 = solid nodules, f3 = differentiation, f4 = LVI, f5 = S + MP ≥5%, f6 = f1 + f2 + f3+ f4 + f5). DCA, decision curve analysis; RFS, recurrence-free survival; T, tumor stage; LVI, lymphovascular invasion; S + MP, solid + micropapillary component.

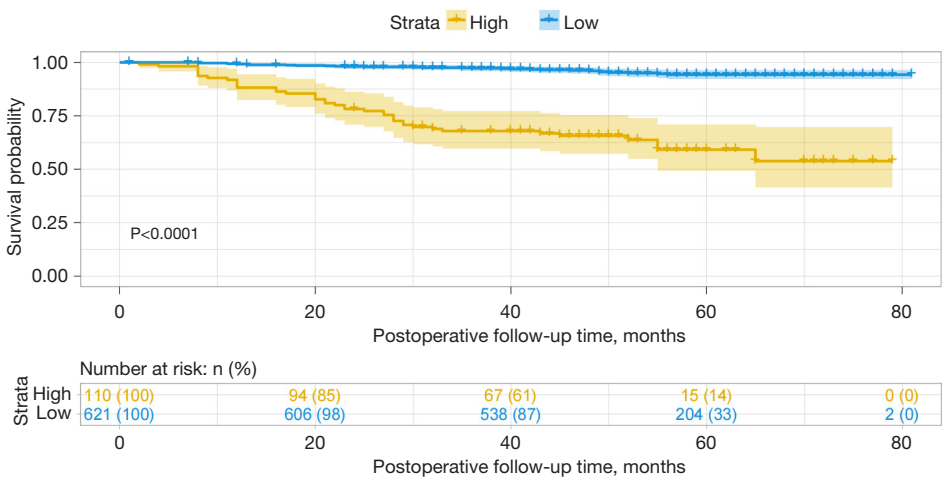

Figure 6 Survival curves of risk group. Kaplan-Meier recurrence-free survival for high-risk (155.3 > total nomogram score) versus low-risk patients with pathologic stage IA lung adenocarcinoma.

independent risk factor for postoperative RFS in stage IA lung adenocarcinoma. Therefore, we included the ratio of S + MP ≥5% into the nomogram model and obtained a good predictive effect. Following the introduction of the new lung adenocarcinoma classification in 2011, numerous authors reported important associations between major histopathological patterns and prognosis (17,18). The histological classification of lung adenocarcinoma includes adherent, acinar, papillary, solid and micropapillary subtypes. Over 80% of lung adenocarcinomas consist of multiple subtypes, and extensive studies have explored the correlation between these subtypes and prognosis (19,20). Patients with a predominant solid or micropapillary type have a worse prognosis than those with the other major subtypes in phase IA, so they are often combined for analysis (21,22). Data from Ito *et al.* showed that the 5-year RFS of stage IA S/MP patients was significantly lower than that of patients with other major subtypes (83.3% *vs.* 95%, P<0.05) (23). Some studies suggested that the 5-year RFS of patients with 5% S + MP at stage IA was significantly worse than that of patients without S + MP (73% *vs.* 93%, P<0.001), and a continued increase in the percentage of S + MP after reaching a certain value may not increase the difference in survival between subsequent groups (24,25). Therefore, we performed univariate and multivariate analyses with a micropapillary + consolidation ratio ≥5%, and the results showed that the high malignant potential of the S and MP modes influenced the prognosis of stage IA lung adenocarcinoma.

In addition, we did not find *EGFR* mutation to be an independent risk factor for postoperative recurrence of stage IA lung adenocarcinoma. Similar to our study, some studies have indicated that while *EGFR* mutation appeared as a prognostic factor in univariate analysis, it did not maintain significance in multivariate analysis (26,27). The reason may be that the relationship between *EGFR* gene mutation and prognosis is affected by the age or ethnicity of the patient (28). It is worth noting that in our study, there was no potential association between the resection method and recurrence, possibly due to the large proportion of patients in this study who underwent lobectomy. In our study, there were many people who had never smoked, and smoking was associated with RFS in the univariate analysis, but there was no such association in the multivariate analysis. The possible reason is that we did not count the duration of smoking because studies have shown that long-term smoking can be used as a clinical indicator for poor postoperative prognosis (29,30).

The study was subject to certain limitations, such as its retrospective design and the potential for selection bias. First, the case selection time span of our study was 5 years, and the external validation time span was 3 years, which may have led to the failure to observe the RFS of some patients. Then, the cohort was only extracted from a single-center database and included Chinese patients only. Therefore, future prospective multicenter studies from other countries with more variables and external validation of the results are necessary. Finally, while we can estimate the probability of recurrence using this nomogram, we cannot determine precisely at what risk threshold adjuvant chemotherapy should be initiated.

Conclusions

In summary, we constructed a nomogram model for predicting postoperative RFS in patients with stage IA lung adenocarcinoma. Patients with stage IA lung adenocarcinoma are a heterogeneous population with varying risks of recurrence. The model can be used to classify these patients into different prognostic categories and facilitate decision-making regarding appropriate postoperative management in high-risk patients.

Acknowledgments

The authors thank all patients included in this study for their participation.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-116/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-116/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-116/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-116/coif). The authors

have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as amended in 2013). This study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (No. SL-B2023-334), and informed consent was taken from all individual participants.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018;553:446-54.
3. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
4. Detterbeck FC, Boffa DJ, Kim AW, et al. The Eighth Edition Lung Cancer Stage Classification. Chest 2017;151:193-203.
5. Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011;29:3163-72.
6. Han DS, Suh YS, Kong SH, et al. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. J Clin Oncol 2012;30:3834-40.
7. Abdel-Rahman O. Validation of the prognostic value of new sub-stages within the AJCC 8th edition of non-small cell lung cancer. Clin Transl Oncol 2017;19:1414-20.
8. Hattori A, Matsunaga T, Takamochi K, et al. Indications for sublobar resection of clinical stage IA radiologic pure-solid lung adenocarcinoma. J Thorac Cardiovasc Surg 2017;154:1100-8.
9. Russell PA, Wainer Z, Wright GM, et al. Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification. J Thorac Oncol 2011;6:1496-504.
10. Hattori A, Suzuki K, Takamochi K, et al. Prognostic impact of a ground-glass opacity component in clinical stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg 2021;161:1469-80.
11. Kopfstein L, Christofori G. Metastasis: cell-autonomous mechanisms versus contributions by the tumor microenvironment. Cell Mol Life Sci 2006;63:449-68.
12. Shimada Y, Saji H, Yoshida K, et al. Pathological vascular invasion and tumor differentiation predict cancer recurrence in stage IA non-small-cell lung cancer after complete surgical resection. J Thorac Oncol 2012;7:1263-70.
13. Harada M, Hato T, Horio H. Intratumoral lymphatic vessel involvement is an invasive indicator of completely resected pathologic stage I non-small cell lung cancer. J Thorac Oncol 2011;6:48-54.
14. Maeda R, Yoshida J, Ishii G, et al. Prognostic impact of intratumoral vascular invasion in non-small cell lung cancer patients. Thorax 2010;65:1092-8.
15. Kuo SW, Chen JS, Huang PM, et al. Prognostic significance of histologic differentiation, carcinoembryonic antigen value, and lymphovascular invasion in stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2014;148:1200-1207.e3.
16. Zhang Y, Sun Y, Xiang J, et al. A clinicopathologic prediction model for postoperative recurrence in stage Ia non-small cell lung cancer. J Thorac Cardiovasc Surg 2014;148:1193-9.
17. Ujiie H, Kadota K, Chaft JE, et al. Solid Predominant Histologic Subtype in Resected Stage I Lung Adenocarcinoma Is an Independent Predictor of Early, Extrathoracic, Multisite Recurrence and of Poor Postrecurrence Survival. J Clin Oncol 2015;33:2877-84.
18. Yanagawa N, Shiono S, Abiko M, et al. The Clinical Impact of Solid and Micropapillary Patterns in Resected Lung Adenocarcinoma. J Thorac Oncol 2016;11:1976-83.

19. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
20. Kim M, Chung YS, Kim KA, et al. Prognostic factors of acinar- or papillary-predominant adenocarcinoma of the lung. Lung Cancer 2019;137:129-35.
21. Zhang J, Wu J, Tan Q, et al. Why do pathological stage IA lung adenocarcinomas vary from prognosis?: a clinicopathologic study of 176 patients with pathological stage IA lung adenocarcinoma based on the IASLC/ATS/ERS classification. J Thorac Oncol 2013;8:1196-202.
22. Huang W, Zhang H, Zhang Z, et al. A prognostic nomogram based on a new classification of combined micropapillary and solid components for stage IA invasive lung adenocarcinoma. J Surg Oncol 2022;125:796-808.
23. Ito H, Nakayama H, Murakami S, et al. Does the histologic predominance of pathological stage IA lung adenocarcinoma influence the extent of resection? Gen Thorac Cardiovasc Surg 2017;65:512-8.
24. Choi SH, Jeong JY, Lee SY, et al. Clinical implication of minimal presence of solid or micropapillary subtype in early-stage lung adenocarcinoma. Thorac Cancer 2021;12:235-44.
25. Peng B, Li G, Guo Y. Prognostic significance of micropapillary and solid patterns in stage IA lung adenocarcinoma. Am J Transl Res 2021;13:10562-9.
26. Kosaka T, Yatabe Y, Onozato R, et al. Prognostic implication of EGFR, KRAS, and TP53 gene mutations in a large cohort of Japanese patients with surgically treated lung adenocarcinoma. J Thorac Oncol 2009;4:22-9.
27. Matsumura Y, Owada Y, Yamaura T, et al. Epidermal growth factor receptor gene mutation as risk factor for recurrence in patients with surgically resected lung adenocarcinoma: a matched-pair analysis. Interact Cardiovasc Thorac Surg 2016;23:216-22.
28. Nishii T, Yokose T, Miyagi Y, et al. Clinicopathological features and EGFR gene mutation status in elderly patients with resected non-small-cell lung cancer. BMC Cancer 2014;14:610.
29. Maeda R, Yoshida J, Ishii G, et al. Influence of cigarette smoking on survival and tumor invasiveness in clinical stage IA lung adenocarcinoma. Ann Thorac Surg 2012;93:1626-32.
30. Nordquist LT, Simon GR, Cantor A, et al. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. Chest 2004;126:347-51.

Cite this article as: Zhang X, Yang J, Li S, Ao Y, Zhong L, Liu X, Luo K, Hu Y. Establishment and validation of a clinicopathological prediction model for postoperative recurrence of stage IA lung adenocarcinoma. J Thorac Dis 2024;16(5):3061-3074. doi: 10.21037/jtd-24-116