Original Article

Establishment and validation of a nomogram model for predicting postoperative recurrence-free survival in stage IA3 lung adenocarcinoma: a retrospective cohort study

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Background: The increased use of computed tomography has brought a corresponding increase in the numbers of early-stage lung cancer patients receiving treatment. However, even for stage IA3 lung adenocarcinoma, many patients experience postoperative recurrence and metastasis. The existing TNM staging system for lung cancer does not take many clinical and pathological factors into consideration, resulting in the failure to detect and intervene as soon as possible in those with high recurrence risk. The purpose of this study was to explore the risk factors for postoperative recurrence-free survival (RFS) in patients with stage IA3 lung adenocarcinoma, and to construct and verify a nomogram model for predicting RFS in patients with the disease.

Methods: This study analyzed patients with stage IA3 lung adenocarcinoma who underwent surgical treatment. Univariate and multivariate analysis were used to analyze the independent risk factors for postoperative RFS and establish a nomogram model. Concordance index (C-index), receiver operating characteristic curve, clinical decision analysis, and calibration curve were used to evaluate the discrimination and calibration of the nomogram model. Data from two other institutions were used for external validation, and the nomogram scores were combined with X-tile software to screen high-risk groups of recurrence.

Results: The internal cohort included 235 eligible patients with stage IA3 lung adenocarcinoma from 7,235 lung cancer. Multivariate analysis showed smoking, solid nodules, mucinous lung adenocarcinoma, and micropapillary component ≥5% were independent risk factors for RFS. A nomogram model was constructed based on the above results and the bootstrap method was used for internal validation. The internal and external validation C-indexes of the nomogram were 0.822 (95% CI: 0.751–0.891) and 0.812, respectively, indicating the obvious prediction performance was good. The X-tile software combined with nomogram scores showed the low-risk group (5-RFS rate, 0.65–0.99) had better RFS than the high-risk group (5-RFS rate, 0.20–0.65) (P<0.0001).

Conclusions: We constructed a nomogram model for predicting postoperative RFS in patients with stage IA3 lung adenocarcinoma which can individually evaluate the risk of postoperative recurrence, screen high-risk groups, and develop individualized follow-up and intervention strategies to improve the survival rate of the patients.

Keywords: Nomogram; lung adenocarcinoma; IA3 stage; recurrence-free survival (RFS)

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Introduction

Lung cancer remains one of the most common malignancies worldwide and the leading cause of cancer deaths, accounting for 18% of all cancer deaths (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer, of which adenocarcinoma is the most common pathological subtype. With the popularization of computed tomography (CT) and the strengthening of public health awareness, early-stage lung cancers are increasingly detected in screening. Although most early-stage patients have a good prognosis, there are still some with postoperative recurrence and metastasis. The risk of recurrence varies among individuals and depends on multiple clinical and pathological factors, and studies have confirmed pleural invasion, tumor larger than 4 cm, and vascular tumor thrombus are independent risk factors affecting the prognosis of patients with stage IB NSCLC. As these patients can benefit from adjuvant chemotherapy, current guidelines recommend postoperative adjuvant chemotherapy for stage IB patients with high-risk factors. However, some patients with stage IA3 have an unsatisfactory prognosis, and the guidelines only recommend regular follow-up after surgery. Therefore, how to screen the high-risk population for postoperative recurrence and carry out early intervention is the key to improving the prognosis of stage IA3 lung adenocarcinoma.

It is insufficient to rely only on existing TNM staging to guide the postoperative follow-up of patients with stage IA3 lung adenocarcinoma. Patients with high risk of recurrence have not been detected and undergone treatment early, which is the main reason their survival is still not ideal. In fact, the postoperative recurrence rate of stage IA NSCLC patients is 4.8–10% with a 5-year overall survival rate of 80–90%, and for patients with stage IA3 disease, the postoperative recurrence rate is as high as 10%, and the 5-year overall survival rate is about 78–80% (2,3). Previous studies have shown that in addition to tumor size, there are many factors affecting the prognosis of patients with stage IA3 lung adenocarcinoma, such as age, gender, smoking status, degree of tumor differentiation, tumor volume, lymph node dissection, tumor histological type, and vascular invasion (4-6).

Nomogram models for lung adenocarcinoma have been developed in various centers (7). Although there are several nomogram models for early stage lung cancer, there are none for patients with stage IA3 lung adenocarcinoma after surgery. At present, there are no reports on the risk of postoperative recurrence of stage IA3 lung adenocarcinoma, but its recurrence rate in stage IA3 is significantly higher than that of stage IA1 and IA2. As a statistical prediction model, nomograms have been widely used in the prognosis prediction of gastric, breast, esophageal, liver, and other cancers (8,9). Therefore, in this study, we attempted to explore the independent risk factors for postoperative recurrence of stage IA3 lung adenocarcinoma and develop a new nomogram model which could individually and predict its postoperative recurrence risk and identify high-risk groups according to its score combined with X-tile software. This model could help clinicians formulate more scientific and effective postoperative follow-up and treatment plans to improve prognosis. We present the following article in accordance with the TRIPOD reporting checklist (available

Highlight box

Key findings

- We constructed a nomogram model for predicting postoperative RFS in patients with stage IA3 lung adenocarcinoma.

What is known and what is new?

- The existing TNM staging system for lung cancer could not predict the risk of postoperative recurrence of stage IA3 lung adenocarcinoma and there are also no reports about it.
- We explore the independent risk factors for postoperative recurrence of stage IA3 lung adenocarcinoma and develop a new nomogram model which could predict its postoperative recurrence risk.

What is the implication, and what should change now?

- This model can help clinicians identify individuals at high risk of recurrence, so as to develop earlier and more rational postoperative follow-up and intervention plans, improve prognosis, and save medical resources. The model can also be used as a screening tool for clinical trials of postoperative adjuvant therapy for $IA3_{H}$.

at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-776/rc).

Methods

Study population

This study included 7,235 patients who received treatment in the Department of Thoracic Surgery of Fujian Medical University Union Hospital from July 2012 to July 2020. A total of 235 patients with pathological stage IA3 lung adenocarcinoma were selected through strict inclusion and exclusion criteria, while a further 67 patients who underwent surgical treatment in the Department of Thoracic Surgery of Nanping First Hospital and Ningde Municipal Hospital from February 2016 to July 2020 were included as an external cohort. All patients received pre-treatment evaluation including routine hematology examination, electrocardiogram, cardiac color doppler ultrasound, lung function, lung CT plain + enhanced, cranial magnetic resonance imaging (MRI) plain + enhanced, whole abdominal color doppler ultrasound, and whole-body bone imaging. Patients generally underwent video-assisted lobectomy and complete systematic lymphadenectomy, a part of patients received anatomical segmentectomy (n=6) or wedge resection (n=5) because of poor lung function. The inclusion criteria were as follows: (I) postoperative pathology showed stage IA3 lung invasive adenocarcinoma; (II) patients received standard lung cancer radical resection; and (III) the malignant tumor was not associated with other organs. The exclusion criteria were as follows: (I) pathologically confirmed *in situ* or microinvasive adenocarcinoma; (II) patients who died during the first hospitalization or within 30 days after surgery; (III) patients who received preoperative neoadjuvant therapy or postoperative adjuvant therapy; (IV) postoperative pathology showed other types of primary lung cancer or secondary lung cancer; and (V) the malignant tumor was associated with other organs.

The basic information and clinicopathological data of patients were obtained from the electronic medical record system of each hospital and included gender, age, body mass index (BMI), family history, smoking status, clinical symptoms, tumor location, preoperative carcinoembryonic antigen (CEA) level, nodules imaging features (ground glass nodules, mixed density nodules, and solid nodules), surgical method, tumor volume, tumor pathological type, proportion of micropapillary components, and number of dissected lymph nodes. Tumor staging was re-staged according to the TNM Staging of Lung Cancer (8th Edition). The case screening process is shown in *Figure 1*.

In general, patients were followed up every 6 months for the first 2 years after surgery and annually thereafter. Postoperative follow-up included physical examination, tumor markers of lung cancer such as CEA, lung CT, cranial MRI, whole-abdominal color doppler ultrasound, and whole-body bone imaging or positron emission tomography (PET)-CT. Once tumor recurrence and metastasis were confirmed by imaging or pathology, the time of first discovery was recorded regardless of whether tumor markers were elevated.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Fujian Medical University Union Hospital (No. 2018KY033), and informed consent was taken from all individual participants.

Histopathological judgment

The histological typing of surgical specimens was performed by two senior pathologists in our hospital according to the 2015 version of the World Health Organization (WHO) lung tumor histological classification standard and the 2011 version of the International Association for the Study of Lung Cancer/American Thoracic Association/European Respiratory Association lung adenocarcinoma classification standard (10,11). Invasive lung adenocarcinomas can be classified into adherent, acinar, papillary, solid, and micropapillary pathological subtypes. The proportion of each subtype of lung adenocarcinoma was calculated in increments of 5%, and when the proportion of a certain subtype in the tumor was ≥5%, its existence was considered. In addition, according to whether the tumor contained mucinous components, it was divided into non-mucinous invasive lung adenocarcinoma and mucinous invasive lung adenocarcinoma. Since data from several studies have shown the 5-year recurrence-free survival (RFS) of patients with carcinoma *in situ* or microinvasive adenocarcinoma could reach 100% after radical pneumonectomy, such patients were not included in this study (12).

Definition of recurrence and metastasis

Local recurrence referred to recurrence in the ipsilateral lobe, bronchial stump, or regional lymph nodes (subcarinal, paraesophageal, supraclavicular, or hilar lymph nodes)

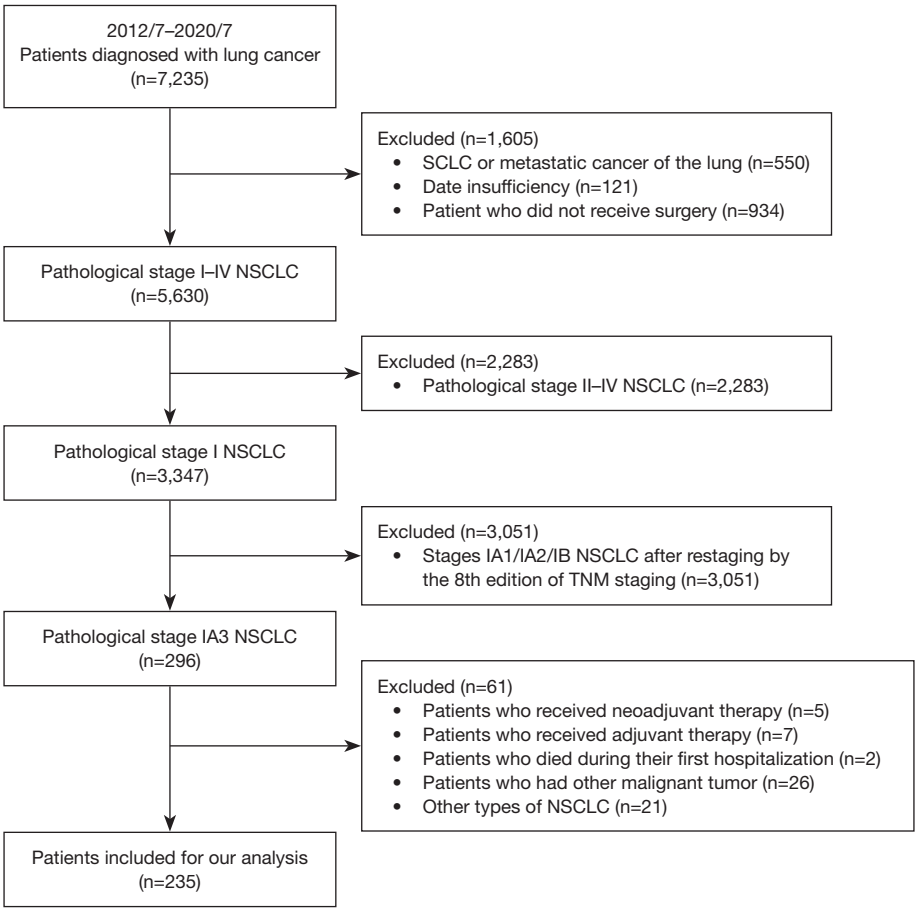

Figure 1 Data filtering process. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

confirmed by imaging or pathology. Distant metastasis referred to recurrent metastasis to the contralateral lung, brain, liver, adrenal gland, bone, and other remote organs confirmed by imaging or pathology. If both local recurrence and distant metastasis occurred, they were classified as distant metastasis (13). RFS was defined as the interval from the date of surgery to that of radiographic and pathological confirmation of tumor recurrence and metastasis or the last day of follow-up.

Statistical analysis

Normality tests were performed on continuous variables. The data conforming to the normal distribution were expressed as mean ± standard deviation, and differences between groups were analyzed by independent *t*-test. Non-normally distributed data were expressed as median and interquartile range (IQR), and differences between groups were analyzed by Mann-Whitney U test. Categorical variables were summarized as frequency and percentage, and differences between groups were analyzed by Chi-square test. The end point of follow-up was the RFS. Kaplan-Meier method was used to draw survival curves, and log-rank test was used to test survival differences between groups. Significance tests were all two-sided. Univariate and multivariate analyses were performed using COX regression analysis, and risk factors screened in the univariate analysis were included in the multivariate analysis. In the multivariate analysis, $P<0.05$ was considered to be statistically significant to determine the independent risk factors affecting postoperative RFS, and the hazard ratio (HR) and 95% confidence interval (95% CI) of each variable were calculated. All statistical analyses were conducted using SPSS 26.0 software.

Nomogram construction

Multivariate COX risk regression results were analyzed using R language software to construct nomogram prediction models of 3- and 5-year RFS in postoperative patients with stage IA3 lung adenocarcinoma. R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) was used to perform analyses via R Studio software (version 1.4.1106). According to the score of the nomogram, we used X-tile software to divide the patients into a high-risk group ($IA3_H$) and low-risk group ($IA3_L$) and drew the survival competitive risk curves of RFS in both groups.

Nomogram validation

The bootstrap self-sampling method (the number of self-sampling times B=1,000) was used for internal validation to reduce over-fitting deviation, and concordance index (C-index) and receiver operating characteristic (ROC) curve were used to evaluate the prediction accuracy of the nomogram (14). Generally speaking, the closer the C-index is to 1, the better the prediction result of the model. If the C-index is equal to 1, it means that the prediction result of the model is exactly the same as the actual result. To verify the relationship between the event rate predicted by the nomogram model and the actual situation, we drew a calibration curve. External validation of the nomogram was performed in an external cohort of patients with stage IA3 lung adenocarcinoma (n=67) from Nanping First Hospital and Ningde Municipal Hospital. In addition, we applied decision curve analysis (DCA) to evaluate the clinical value of the model.

Results

Basic characteristics of the study population

In the study, a total of 296 patients underwent surgical treatment with definitive pathological stage IA3 NSCLC in the Thoracic Surgery Department of Fujian Medical University Union Hospital. Among them, 61 cases (13.5%) were excluded because of death within 30 days after operation (n=2), complicating malignancy of other organs (n=26), receiving preoperative neoadjuvant therapy (n=5), receiving postoperative adjuvant therapy (n=7), and having other types of primary lung cancer (n=21). Finally, 235 patients with stage IA3 invasive lung adenocarcinoma were included in the study, and their clinical and pathological features are shown in *Table 1*. The median age of all patients was 62 [37–83] years, there were 113 (48.1%) males and 122 (51.9%) females, and 72 (30.6%) of patients were smokers. A preoperative CEA level ≥5 ng/mL was seen in 37 (15.7%) of patients, and 198 (84.3%) had a CEA level <5 ng/mL. Pulmonary nodules that were solid masses on chest CT were seen in 124 (52.7%) of cases, and 73 (31.1%) were mixed density shadow. There were 38 (16.2%) patients with ground-glass opacity (GGO) on imaging and 10 (4.3%) patients with mucinous lung adenocarcinoma. The median number of lymph node dissection in the whole group was 15, and 46 (19.6%) had micropapillary components accounting for ≥5%. During the study, we observed 23 cases of recurrence, including five of local recurrence and 18 of distant metastasis. The mean time of recurrence was 25.4 months (4–65 months), and the median follow-up time was 40.5 months (10–107 months).

Univariate and multivariate analysis of RFS

A COX regression model was used to identify independent risk factors for RFS. Univariate analysis showed smoking status (HR =3.792, 95% CI: 1.657–8.678, P=0.002), imaging features of nodules (HR =8.800, 95% CI: 2.061–37.571, P=0.003), tumor volume (HR =1.275, 95% CI: 1.071–1.519, P=0.006), pathological type of tumor (HR =3.878, 95% CI: 1.313–11.450, P=0.014), and proportion of micropapillary components (HR =2.606, 95% CI: 1.140–5.959, P=0.023) were risk factors for postoperative recurrence and metastasis in patients with stage IA3 lung adenocarcinoma (P<0.05). The above risk factors were then included in multivariate analysis, and showed smoking (HR =6.779, 95% CI: 2.521–18.228, P<0.001), solid nodules (HR =9.474, 95% CI: 2.194–40.902, P=0.003), mucinous lung adenocarcinoma (HR =4.909, 95% CI: 1.438–16.764, P=0.011), and micropapillary component ≥5% (HR =3.757, 95% CI: 1.524–9.263, P=0.004) were independent risk factors for postoperative RFS in patients with stage IA3 lung adenocarcinoma (*Table 2*).

Nomogram construction

Results of multivariate COX regression analysis showed smoking, solid nodules, mucus composition, and micropapillary composition ≥5% were independent risk factors for postoperative RFS in patients with stage IA3 lung adenocarcinoma. We then constructed 3- and 5-year postoperative RFS nomogram prediction models according

Table 1 Clinicopathological characteristics of patients with stage IA3 lung adenocarcinoma

Variables	Numbers (n=235)	Constituent ratio (%)
Sex		
Male	113	48.1
Female	122	51.9
Age (years), median [range]	62 [37–83]	
<60	93	39.6
≥60	142	60.4
BMI (kg/m^2)		
<24	141	60.0
≥24	94	40.0
Family history		
No	221	94.0
Yes	14	6.0
Smoking		
No	163	69.4
Yes	72	30.6
Clinical symptoms		
No	142	60.4
Yes	93	39.6
Central lung cancer		
No	230	97.9
Yes	5	2.1
CEA (ng/mL)		
<5	198	84.3
≥5	37	15.7
Imaging features		
GGO	38	16.2
Mixed density nodules	73	31.1
Solid nodules	124	52.7
Surgical method		
Lobectomy	224	95.3
Segmentectomy	6	2.6
Wedge resection	5	2.1
Tumor volume (cm^3), median (IQR)	2.63 (1.92–4.49)	
Tumor pathological type		
Non-mucinous adenocarcinoma	225	95.7
Mucinous adenocarcinoma	10	4.3
Tumor location		
Right upper lung	89	37.9
Right middle lung	16	6.8
Right lower lung	46	19.6
Left superior lung	47	20.0
Left inferior lung	37	15.7
Micropapillary components ≥5%	46	19.6
Number of dissected lymph nodes, median [IQR]	15 [11–20]	
Recurrence and metastasis		
Local recurrence	5	21.7
Distant metastasis	18	78.3

BMI, body mass index; CEA, carcinoembryonic antigen; GGO, ground-glass opacity; IQR, interquartile range.

to these results (*Figure 2*). The nomogram was composed of four variables, each of which had a corresponding axis, and each sub-variable had a corresponding score on the axis. The total score of the patient could 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. For example, a patient with a long history of smoking, imaging evidence of solid pulmonary nodules, and postoperative pathology of lung adenocarcinoma without micropapillary and mucous components would have a total score of 185 and a predicted 5-year RFS of 65%.

Nomogram validation

In the internal cohort, the C-index of the RFS prediction model was 0.822 (95% CI: 0.751–0.891) and the area under the ROC curve was 0.791, while the calibration curve showed the predicted and actual values of 3- and 5-year RFS were consistent (*Figure 3*). External validation of the nomogram was performed on an external cohort whose

Table 2 Univariate and multivariate analysis of RFS

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Sex		0.052		
Male	Ref			
Female	0.426 (0.180–1.007)			
Age (years)		0.681		
<60	Ref			
≥60	1.197 (0.507–2.826)			
BMI (kg/m^2)		0.229		
<24	Ref			
≥24	0.564 (0.222–1.432)			
Family history		0.453		
No	Ref			
Yes	0.046 (0.001–143.632)			
Smoking		0.002		<0.001
No	Ref		Ref	
Yes	3.792 (1.657–8.678)		6.779 (2.521–18.228)	
Clinical symptoms		0.811		
No	Ref			
Yes	0.903 (0.390–2.088)			
Central lung cancer		0.538		
No	Ref			
Yes	0.046 (0.001–807.904)			
CEA (ng/mL)		0.252		
<5	Ref			
≥5	1.723 (0.679–4.373)			
Imaging features		0.003		0.003
Non-solid nodules	Ref		Ref	
Solid nodules	8.800 (2.061–37.571)		9.474 (2.194–40.902)	
Surgical method		0.822		
Lobectomy	Ref			
Sublobectomy	1.261 (0.167–9.502)			
Tumor volume (cm^3)	1.275 (1.071–1.519)	0.006	–	0.201
Tumor pathological type		0.014		0.011
Non-mucinous adenocarcinoma	Ref		Ref	
Mucinous adenocarcinoma	3.878 (1.313–11.450)		4.909 (1.438–16.764)	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Tumor location		0.202		
Right upper lung	Ref			
Right middle lung	0.479 (0.146–1.572)			
Right lower lung	1.442 (0.344–6.044)			
Left superior lung	0.304 (0.059–1.568)			
Left inferior lung	1.059 (0.336–3.340)			
Micropapillary components ≥5%		0.023		0.004
<5%	Ref		Ref	
≥5%	2.606 (1.140–5.959)		3.757 (1.524–9.263)	
Number of dissected lymph nodes	0.995 (0.941–1.051)	0.848		

RFS, recurrence-free survival; BMI, body mass index; CEA, carcinoembryonic antigen, HR, hazard ratio; CI, confidence interval.

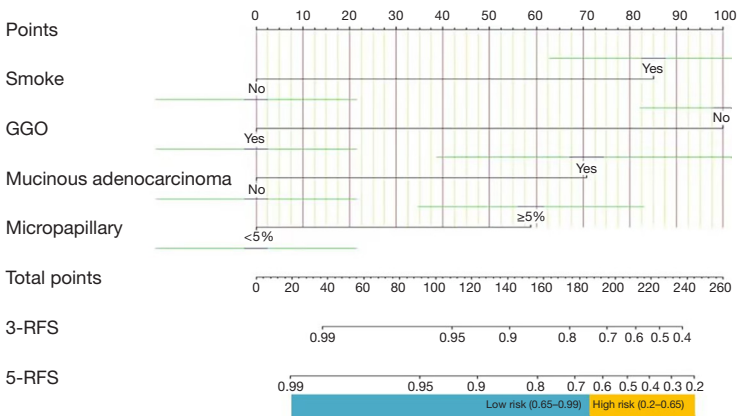

Figure 2 Nomogram for predicting RFS in patients with stage IA3 lung adenocarcinoma. The nomogram is composed of four variables. Each variable has a corresponding axis, and each sub-variable has a corresponding score on the axis. The total score of the patient can be obtained by adding the scores corresponding to each sub-variable to obtain the predicted probability of RFS at 3 and 5 years after surgery. GGO, ground-glass opacity; RFS, recurrence-free survival.

clinical and pathological features are shown in *Table 3*. The median age of all patients was 60 [46–77] years; 33 (49.3%) were male and 34 (50.7%) patients were female; 26 (38.8%) were smokers; and 38 (56.7%) patients showed solid nodules on chest CT. There were 13 (19.4%) patients with mucinous lung adenocarcinoma and 11 (16.4%) with micropapillary components accounting for ≥5%. The median number of lymph nodes dissected in the whole group was 18. During the study, eight patients (8/67, 11.9%) experienced tumor recurrence, including three with local recurrence and five with distant metastasis. Each patient in the cohort was scored using the nomogram model of RFS with a C-index of 0.812, and the RFS calibration curve for the external cohort is shown in *Figure 4*.

According to the constructed nomogram model, we drew the clinical decision analysis curve (*Figure 5*), and the analysis results showed the nomogram had good clinical applicability in predicting postoperative RFS in patients with stage IA3 lung adenocarcinoma. In addition, the corresponding treatment had higher net benefits compared

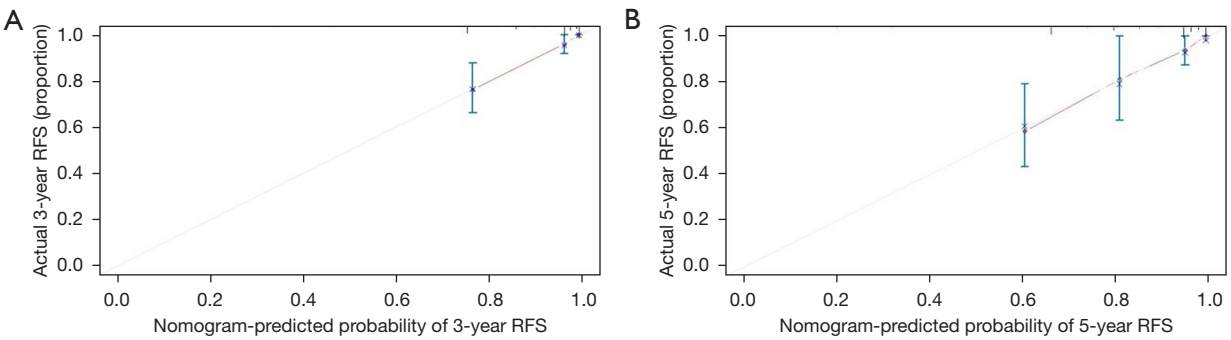

Figure 3 Calibration plots for RFS of internal data. (A) 3-year RFS of calibration plots; (B) 5-year RFS of calibration plots. RFS, recurrence-free survival.

Table 3 Clinicopathological characteristics of patients with stage IA3 lung adenocarcinoma (data of external validation)

Variables	Numbers (n=67)	Constituent ratio (%)
Sex, n (%)		
Male	33	49.3
Female	34	50.7
Age (years), median [range]	60 [46–77]	
<60	31	46.3
≥60	36	53.7
BMI (kg/m^2)		
<24	37	55.2
≥24	30	44.8
Family history		
No	65	97.0
Yes	2	3.0
Smoking		
No	41	61.2
Yes	26	38.8
Clinical symptoms		
No	67	100
Yes	0	0
Central lung cancer		
No	66	98.5
Yes	1	1.5
CEA (ng/mL)		
<5	50	74.6
≥5	17	25.4
Imaging features		
Non-solid nodules	29	43.3
Solid nodules	38	56.7
Surgical method		
Lobectomy	67	100
Sublobectomy	0	0
Tumor pathological type		
Non-mucinous adenocarcinoma	54	80.6
Mucinous adenocarcinoma	13	19.4
Micropapillary components ≥5%	11	16.4
Number of dissected lymph nodes, median [IQR]	18 [14–23]	
Recurrence and metastasis		
Local recurrence	3	37.5
Distant metastasis	5	62.5

BMI, body mass index; CEA, carcinoembryonic antigen; IQR, interquartile range.

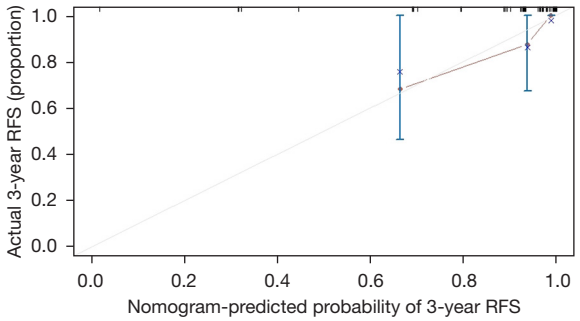

Figure 4 Calibration plots for 3-year RFS of external data. RFS, recurrence-free survival.

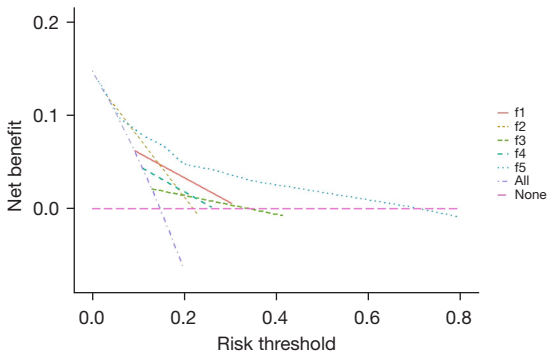

Figure 5 DCA of RFS nomogram model after surgical treatment of IA3 lung adenocarcinoma was predicted. "All" assumes all patients with stage IA3 lung adenocarcinoma are treated and "None" that all patients with stage IA3 lung adenocarcinoma are not treated. (f1= smoke, f2= GGO, f3= mucus, f4= micro, f5= smoke + GGO + mucus + micro). DCA, decision curve analysis; RFS, recurrence-free survival; GGO, ground-glass opacity.

with "all treatment" or "no treatment at all".

Risk grouping based on the nomogram model

We calculated the overall 5-year RFS ratio based on the nomogram score of each patient in the internal cohort, and a truncation value of 0.65 was obtained when combined with the X-tile software. Based on the truncation value, we divided patients into two groups: a 5-year-RFS, low-risk group, 0.65–0.99 and a high-risk group, 0.20–0.65. *Figure 6* shows that $IA3_L$ in the low-risk group had better RFS than $IA3_H$ in the high-risk group according to the fitted survival curve (Chi-square value 44.009, P<0.0001).

Discussion

The prognosis of patients with stage IA3 lung adenocarcinoma after surgery is unsatisfactory, but current guidelines do not recommend postoperative adjuvant therapy. Therefore, we collected multi-center clinical data, identified the risk factors for postoperative RFS of stage IA3 lung adenocarcinoma through statistical methods, and established intuitive nomogram models to quantify the recurrence risk of each patient and to screen out those at high risk for postoperative recurrence. Multi-center data were used to internally and externally validate the performance of the nomogram models. Nomogram models can help clinicians provide more refined follow-up strategies or interventions for patients as a means of improving the prognosis of patients with stage IA3 lung adenocarcinoma. In addition, they can be used as a screening tool for further prospective clinical trials in patients with a high risk of recurrence.

Guidelines do not recommend postoperative adjuvant therapy for stage IA3 lung adenocarcinoma because in early-stage lung cancer it is difficult to obtain positive results if clinical drug trials for postoperative adjuvant therapy are not designed for specific high-risk populations of recurrence. There is an urgent need for a tool to screen people at high risk of recurrence and to conduct prospective clinical drug trials for high-risk populations which can easily lead to a better expected outcome with fewer resources. Nomograms can express complex logical mathematical formulas through simple models and have been widely used in the prognosis prediction of many tumors. Although there are several nomogram models for lung cancer (7,15-17), there are none for patients with stage IA3 lung adenocarcinoma after surgery. Therefore, we innovatively constructed a nomogram model to predict postoperative recurrence in these patients.

According to the results of univariate and multivariate analysis in our study, smoking status, imaging features of nodules, histopathological types, and proportion of micropapillary components were independent risk factors for predicting RFS. In the evaluation of the model, the C-index, ROC curve, and calibration curve of the 3- and 5-year RFS all showed the nomogram models performed well in predicting RFS in patients with stage IA3 disease. We also divided patients into a high-risk group $IA3_H$ and low-risk group $IA3_L$ according to the 5-year RFS risk ratio of the nomogram combined with X-tile software, and there

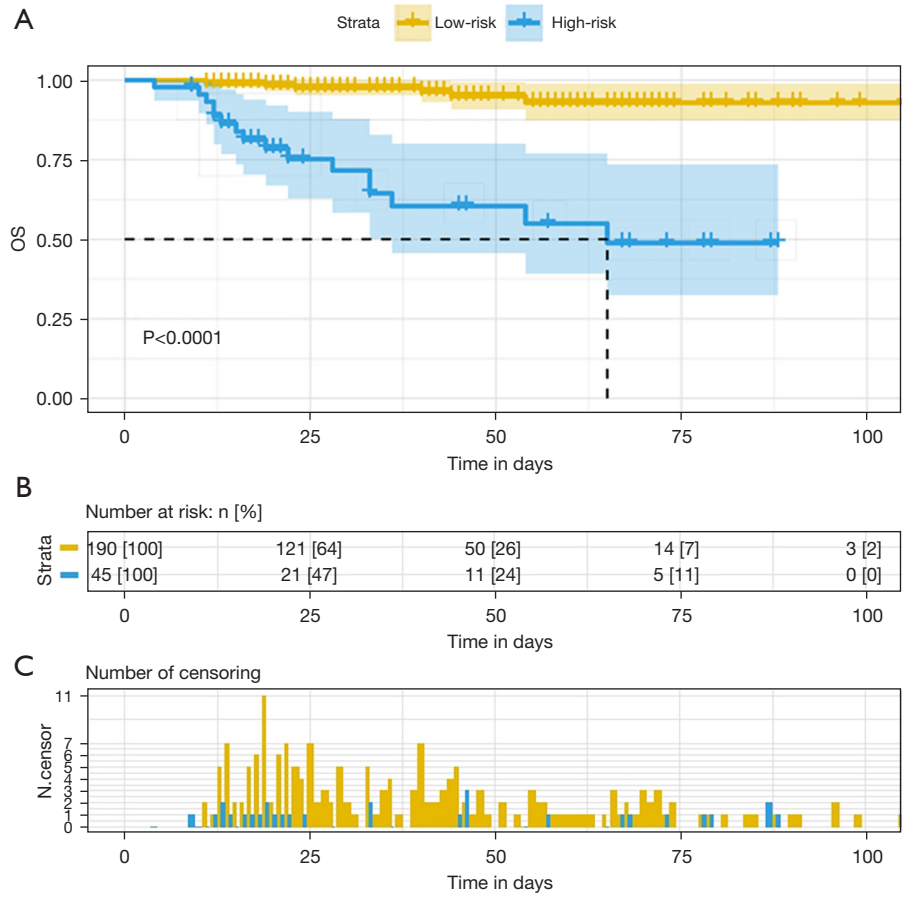

Figure 6 Survival curves of risk group. This picture consists of three parts, which are the lower, middle, and upper parts. The lower, middle and upper parts of the X-axis represent the postoperative follow-up time. The lower, middle and upper parts of the Y-axis represent the population density of recurrence, the number of cases without recurrence, the probability of no recurrence, respectively. OS, overall survival.

was a statistically significant difference in the survival rate between the two groups, which is helpful for clinicians to identify high-risk groups and formulate individualized follow-up strategies. This may lead to more rational allocation of medical resources and improved prognosis of patients with stage IA3 lung adenocarcinoma.

It is generally believed that smoking status is related to the prognosis of early-stage lung adenocarcinoma, and the risk of recurrence is significantly increased in patients with early lung adenocarcinoma who continue to smoke (18,19). A consistent conclusion was also obtained in our study. Previous reports have shown mucinous lung adenocarcinoma has a higher postoperative recurrence rate and worse prognosis than non-mucinous lung adenocarcinoma (20), and multivariate Cox regression confirmed it to be an independent risk factor for RFS and should be considered as a subtype with high recurrence risk. Therefore, in this study we included smoking status and histopathological type in the prediction model of RFS.

The histological classification of lung adenocarcinoma includes several subtypes including adherent, acinar, papillary, solid, and micropapillary. More than 80% of lung adenocarcinomas are composed of multiple subtypes (11,21), and many studies have investigated the relationship between these and prognosis. Micropapillary components refer to papillary and tufted tumor cells lacking a fibrous vascular axis, and micropapillary structures can be separated from or linked to the alveolar wall (22). Previous studies have shown the presence of micropapillary components is associated with lymph node metastasis and vascular invasion predicting poorer RFS. Peng *et al.* (23) believed a micropapillary component to be a risk factor for the recurrence of early lung adenocarcinoma, while Watanabe *et al.* (24) found it was associated with poorer RFS in stage

I lung adenocarcinoma and produced a high risk of early postoperative recurrence and poor prognosis. For stage IA lung adenocarcinoma mainly composed of micropapillary components, T stage and postoperative adjuvant chemotherapy are considered important predictors of RFS, while stage IA3 patients may benefit from postoperative adjuvant chemotherapy (25). As our results show the proportion of micropapillary components ≥5% was an independent risk factor for RFS in patients with stage IA3 lung adenocarcinoma after surgery, we believe postoperative adjuvant chemotherapy may be reasonable and urgently required. In addition, we included the proportion of micropapillary into the nomogram model and showed a good predictive effect.

Increasingly, studies have shown that ground-glass components are associated with a better prognosis in stage I patients and should play a role in the TNM staging of lung cancer. Hattori *et al.* (26) analyzed 671 patients with stage IA NSCLC registered in JCOG0201 and found that among patients with various substages of stage IA, the 5-year survival rate of those with a GGO component was higher than that of patients with solid nodules, regardless of the proportion of solid components in the mixed nodules. In addition, solid nodules showed poorer biological behavior than nodules containing GGO components. Aokage *et al.* (27) reported that among patients with stage IA3 NSCLC, the prognosis of patients with lung adenocarcinoma containing GGO components was significantly better than those of the same stage, and in patients with stage IA lung adenocarcinoma containing GGO components, low-grade lung adenocarcinoma (adenocarcinoma *in situ*, minimally invasive adenocarcinoma and adherent type) accounted for 50%. Even in lung adenocarcinoma patients with high metabolic activity (SUV ≥3.0 mg/dL), the presence of GGO components also predicted a better prognosis (28). Several clinical studies have reported an absence of reoccurrence during follow up in patients with stage I lung adenocarcinoma with pure ground glass nodules (29). Further, whether lobectomy or sublobectomy were performed, disease free survival reached 100% five years after surgery (30). Our findings are generally consistent with previous reports, and show that in patients with stage IA3 NSCLC, the presence of GGO component is an important prognostic factor, which should be paid attention to.

The advantages of this study are strong pertinence, sufficient sample size, and data from multiple centers. In addition, each prediction model only includes four variables, which are easily obtained in clinical case data, making it convenient for clinicians to use. However, the study also has some limitations, including its retrospective nature with associated selection bias. In addition, because the time span of case selection in our study was 8 years, our hospital lacked the equipment to conduct molecular residual disease (MRD) detection and genetic detection for NSCLC in the early years, and we did not include such variables in the study. We hope to include more variables in the future to further improve the prediction efficiency of the nomogram model. Furthermore, the external validation sample is relatively small, more data are needed to further refine our model in the future.

Conclusions

In conclusion, we constructed a nomogram model to predict postoperative RFS in patients with stage IA3 lung adenocarcinoma, which can individually assess the risk of postoperative recurrence in patients with the disease. This model can help clinicians identify individuals at high risk of recurrence, so as to develop earlier and more rational postoperative follow-up and intervention plans, improve prognosis, and save medical resources. In addition, patients in the high-risk group may be the potentially beneficial population for receiving postoperative adjuvant chemotherapy. The model can also be used as a screening tool for clinical trials of postoperative adjuvant therapy for $IA3_H$.

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Footnote

Reporting Checklist: The authors have completed the

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-776/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 revised in 2013). This study has been approved by the Ethics Committee of Fujian Medical University Union Hospital (No. 2018KY033) and informed consent was taken from all individual participants.

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