

Tumor Differentiation and *EGFR* Mutation Associated with Disease-Free Survival in Stage IA Lung Adenocarcinoma Patients with Curative Surgery

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Background: Nearly 30% of stage IA non-small-cell lung cancer patients eventually die of recurrence or metastasis. This study aimed to predict stage IA lung adenocarcinoma (LADC) patients who underwent radical resection with a high risk of recurrence or metastasis.

Methods: Information on clinicopathological, genetic and therapeutic features and recurrence status was collected in this retrospective and two-center study. A nomogram based on multivariate analysis was established to predict disease-free survival. Further stratification was performed to identify populations with a high risk of relapse.

Results: A total of 1584 patients with pathological stage IA LADC who underwent radical surgery between 2011 and 2015 were enrolled from two medical institutions in this study. The nomogram including tumor differentiation and *EGFR* mutation had a higher C-index of 0.880 (95% CI 0.833–0.926) compared to 0.598 (95% CI 0.486–0.711) for the AJCC 8th TNM staging system. Furthermore, the C-index for the validation cohort was 0.798 (95% CI 0.738–0.857). In addition, the 3-year cumulative nonrecurrence rate in the high-risk group stratified by this model was 21.8% compared to 98.1% in the low-risk group.

Conclusion: This study proposed a new nomogram including tumor differentiation and *EGFR* mutation to predict recurrence or metastatic probability in stage IA LADC patients who underwent radical surgery. This nomogram could identify patients in the high-risk group and help guide adjuvant treatment in the future.

Keywords: nomogram, stage IA, lung adenocarcinoma, disease-free survival

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of lung cancer cases and remains the leading cause of cancer death worldwide.^{1,2} Currently, an increasing number of patients are diagnosed with early-stage NSCLC resulting from the prevalence of low-dose computed tomography (CT) for screening.^{3,4} However, the predicted 5-year survival rates of completely resected patients with stage IA NSCLC has reached a plateau, with only a 67–82% 5-year survival rate without adjuvant therapy.^{5,6} In other words, nearly 30% of patients eventually die of recurrence or metastasis, although they are predicted to have good outcomes.⁷

Although each centimeter from ≤ 1 cm to 3 cm has been verified as a significant prognostic factor in the 8th edition of the American Joint Committee on Cancer Tumor Node Metastasis (AJCC TNM) staging system, the predictive accuracy of

this system has been shown to be limited.⁸ The treatment of stage IA patients with different prognoses has not changed because of the current TNM staging system.

The anatomic extent of the tumor is only a single snapshot of tumor burden, which is mainly described in TNM staging. Parameters beyond the TNM system that affect prognosis include clinicopathological information⁹ and surgical procedure.¹⁰ In addition, lung adenocarcinoma (LADC) carries significantly different clonal mutations than squamous lung carcinoma.¹¹ Genetic characterizations should not be ignored as one of numerous factors to consider in adenocarcinoma.^{12–14} Therefore, a new prognostic evaluation algorithm should be created in terms of stage IA lung adenocarcinoma.

The visual format of nomograms, which represent a statistical prognostic model, is readily understood by physicians. The main goals of this study were to identify significant prognostic variables of disease-free survival (DFS), to develop a reliable prognostic nomogram for the estimation of outcomes and to validate its prognostic capacity in an independent cohort. In addition, this study also evaluated whether this model could provide a more accurate prediction of DFS compared to the conventional TNM staging system.

Methods

Patient Population and Data Collection

From September 2011 to December 2015, we retrospectively reviewed a total of 1502 patients diagnosed with stage IA LADC at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College as a training cohort. The study inclusion criteria were as follows: (1) patients pathologically diagnosed with stage IA1 to IA3 LADC using the AJCC 8th TNM system; and (2) all patients underwent R0 tumor resection and had systemic lymph node dissection with at least 10 lymph nodes. The exclusion criteria of this study were as follows: (1) patients receiving neoadjuvant chemotherapy or radiotherapy; (2) patients receiving adjuvant chemotherapy, radiotherapy or targeted therapy before disease recurrence; and (3) a diagnosis with multiple primary carcinomas. In addition, the validation cohort included 82 patients with stage IA LADC from the Tianjin Medical University, Cancer Institute and Hospital, National Clinical Research Center for Cancer in 2012.

This study was approved by the institutional review board of Cancer Hospital, Chinese Academy of Medical Sciences

and Peking Union Medical College and Tianjin Medical University, Cancer Institute and Hospital, National Clinical Research Center for Cancer. All patients provided written informed consent, in accordance with the Declaration of Helsinki.

A total of 11 baseline characteristics, including sex, age, smoking history, tumor differentiation, lymphatic vessel invasion (LVI), tumor stage, operation methods, surgical intervention, surgical side, *EGFR* mutation and *KRAS* mutations, were documented. All these variables related to recurrence were selected based on their clinical importance and previous references. Smoking history was divided into never smokers and smokers. Tumor stage was classified according to the 8th edition of the AJCC Cancer Staging Manual. Tumor differentiation were divided into five grades as follows: grade 1: lepidic predominant; grade 2: two main components with grade 1 and grade 3; grade 3: acinar or papillary predominant; grade 4: two main components with grade 3 and grade 5; and grade 5: solid or micropapillary predominant; these grades correspond to well-, moderate-well-, moderately, moderate-poorly and poorly differentiated tumors, respectively. The surgical intervention included thoracotomy and video-assisted thoracoscopic surgery (VATS). Anatomic pulmonary resection was classified as sublobar resection, segmentectomy and wedge resection. *EGFR* mutations were mainly using surgical specimen with the polymerase chain reaction (PCR) technology. Unknown genetic status existed because some patients without recurrence had not undergone genetic testing due to the absence of a clinical need, and some tissue samples could not be tested because of long-term storage and gene degradation.

DFS was defined as the time from radical surgery for lung cancer to any kind of recurrence. Recurrence referred to regional and distant recurrences. Regional recurrence was recorded as recurrence on resection margins such as bronchial stumps or stapler lines or within ipsilateral subcarinal lymph nodes. Distant recurrence was defined as any recurrence occurring in the contralateral lung, brain, liver, adrenal gland, bone, and other locations. Disease recurrence was assessed by CT scan, magnetic resonance imaging (MRI), and bone scanning. PET-CT was also permitted for the screening or confirmation of recurrences.

Follow-up information was obtained through hospital visits or by telephone contact with patients or relatives. Surveillance with history and physical and chest CT (with or without contrast) was recommended according to NCCN guidelines during the first 2–5 years. April 2,

2018 was the last follow-up time. The median follow-up was 45.4 months (95% CI: 44.1–46.8).

Statistical Analysis

The chi-square test or Fisher's exact probability method was used to determine differences between groups, and a univariate Cox proportional hazards model was used to analyze the association between factors and DFS. Multivariate analysis using a Cox proportional hazards regression model was based on the significant factors in univariate analysis. The nomogram was established mainly on the basis of the Cox model. The AJCC TNM stage for each patient was entered into the Cox regression model to determine whether traditional staging was an independent predictor of survival. Model performance was evaluated using discrimination and calibration with a bootstrap approach with 1000 resamples. The index of probability of concordance (C-index) between the predicted probability and DFS was calculated for the model to assess the discrimination of the nomogram. The discrimination of the AJCC TNM staging system was also analyzed. Statistical tests with two-sided $P < 0.05$ were considered statistically significant. All statistical analyses were performed using SAS 9.4 software and R 3.1.1 software.

Results

Baseline Characteristics

There were a total of 1502 enrolled patients as a training cohort in the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences from September 2011 to December 2015. The cases were stage IA lung adenocarcinoma patients who underwent radical surgery, and recurrence was recorded in the database of cancer hospitals. The controls were selected among cohort members who had no confirmed recurrence prior to selection. We included at least three controls for each case. Finally, 52 cases were confirmed relapses cases and the corresponding recurrence rate was 3.5%. Then, 180 surgery-time-matched controls were analyzed in this study, as shown in [Figure S1](#). The patients' baseline characteristics, including patients in the training and validation cohorts, are shown in [Table 1](#).

In addition, five patients were recorded relapse in the validation cohort from the Tianjin Medical University, Cancer Institute and Hospital, National Clinical Research Center for Cancer in 2012.

Predictors of DFS and the Nomogram Model

The Cox proportional hazards regression analysis identified that tumor differentiation and *EGFR* mutation were strongly associated with recurrence risk ([Tables 2 and 3](#)). We established a nomogram model based on the above variables, as shown in [Figure 1](#), and the corresponding scoring system is shown in [Table S1](#). This nomogram model had a higher C-index of 0.880 (95% CI 0.833–0.926) in the training cohort, while the 8th TNM staging system had a dramatically lower C-index of 0.598 (95% CI 0.486–0.711). The C-index for the validation cohort was 0.798 (95% CI 0.738–0.857). In addition, the integrated time-dependent area under the curve (AUC) of this nomogram was 0.915. The correspondence between the predicted and actual survival in the nomogram's calibration plot was well calibrated in the development cohort and validation cohort ([Figure 2](#)).

Different Risk Groups Classified by DFS Rate

A Kaplan-Meier curve of the nomogram model was constructed for the development cohort when patients were stratified into risk groups including high-, average- and low-risk groups. Groups with higher scores were associated with a higher risk of death, and each group was correlated with a markedly different DFS according to the log rank test ($p < 0.001$).

Stage IA LADC patients with nomogram scores greater than 131 points had the highest risk, those with 13 to 131 points had an average risk, and those with less than 13 points had the lowest risk of relapse or metastasis. This nomogram well distinguished the three risk groups with significant differences both in the training cohort ($p < 0.0001$) and in the validation cohort ($p = 0.0380$), as shown in [Figure 3A and B](#), respectively. However, the AJCC 8th TNM staging system was unable to clearly distinguish between the average-risk and high-risk groups in the training cohort ($p = 0.0610$) and in the validation cohort ($p = 0.0720$), as shown in [Figure 3C and D](#). The 3-year DFS rates were 98.1%, 84.3% and 21.8% in the low-, average- and high-risk groups, respectively. The 5-year DFS rates were 98.1%, 78.2% and 10.9% in the low-, average- and high-risk groups, respectively ([Table S2](#)).

Discussion

Nearly 30% of stage IA NSCLC patients die of tumor recurrence or metastasis, despite the performance of regular

Table I Demographics and Clinicopathologic Characteristics of the Training Set and Validation Set

Characteristics	Training		P value	Validation		P value
	No Recurrences (N%) N=180	Recurrences (N%) N=52		No Recurrences (N%) N=77	Recurrences (N%) N=5	
Total						
Age, years			0.394			0.493
<65	132 (73.3)	35 (67.3)		57 (74.0)	3 (60.0)	
≥65	48 (26.7)	17 (32.7)		20 (26.0)	2 (40.0)	
Sex			0.288			0.870
Female	65 (36.1)	23 (44.2)		28 (36.4)	2 (40.0)	
Male	115 (63.9)	29 (55.8)		49 (63.6)	3 (60.0)	
Smoking History			0.118			0.728
No	131 (72.8)	32 (61.5)		52 (67.5)	3 (60.0)	
Yes	49 (27.2)	20 (38.5)		25 (32.5)	2 (40.0)	
LVI			0.040			
No	149 (82.8)	49 (94.2)		77 (100)	5 (100)	
Yes	21 (11.7)	3 (5.8)		0	0	
Tumor differentiation			<0.0001			
High grade	76 (42.2)	7 (13.5)		13 (16.9)	1 (20.0)	
High-middle grade	27 (15.0)	6 (11.5)		0	0	
Middle grade	55 (30.5)	22 (42.3)		22 (28.6)	0	
Middle-low grade	10 (5.6)	11 (21.2)		0	0	
Low grade	3 (1.7)	4 (7.7)		31 (40.2)	4 (80.0)	
Uncertain	9 (5.0)	2 (3.8)		11 (14.3)	0	
EGFR mutation			<0.0001			0.272
No	12 (6.7)	18 (34.6)		33 (42.8)	3 (60.0)	
<i>L858R</i>	10 (5.6)	20 (38.5)		4 (5.2)	1 (20.0)	
<i>L858R</i>	19 (10.5)	10 (19.2)		13 (16.9)	1 (20.0)	
Unknown	139 (77.2)	4 (7.7)		27 (35.1)	0	
KRAS mutation			<0.0001			0.0002
No	38 (21.1)	39 (75.0)		49 (63.6)	5 (100.0)	
Yes	3 (1.7)	5 (9.6)		2 (2.6)	0	
Unknown	139 (77.2)	8 (15.4)		26 (33.8)	0	
Operation methods			0.821			0.252
Lobectomy	156 (86.7)	45 (86.5)		77 (100.0)	5 (100.0)	
Segmental resection	10 (5.6)	2 (3.9)		0	0	
Wedge resection	14 (7.7)	5 (9.6)		0	0	
Surgical intervention			0.995			0.093
Video-assisted thoracoscopic surgery	142 (78.9)	41 (78.9)		45 (58.4)	1 (20.0)	
Thoracotomy	38 (21.1)	12 (21.1)		32 (41.6)	4 (80.0)	
Surgical site			0.068			0.767
Right site	112 (62.2)	25 (48.1)		57 (74.0)	4 (80.0)	
Left site	68 (37.8)	27 (51.9)		20 (26.0)	1 (20.0)	
Tumor stage (8th AJCC)			0.074			0.070
IA1	49 (27.2)	7 (13.5)		15 (19.5)	0	
IA2	89 (49.4)	27 (51.9)		36 (46.7)	5 (100.0)	
IA3	42 (23.3)	18 (34.6)		26 (33.8)	0	

Abbreviation: LVI, lymphatic vessel invasion.

Table 2 Univariable Analysis

Characteristics	Univariable Analysis	
	HR (95% CI)	P-value
Age		
<65 years old	Reference	
≥65 years old	1.359 (0.768–2.407)	0.292
Sex		
Male	Reference	
Female	0.832 (0.480–1.443)	0.514
Smoking History		
No	Reference	
Yes	1.384 (0.787–2.435)	0.259
LVI		
No	Reference	
Yes	0.324 (0.101–1.041)	0.058
Tumor differentiation		
High grade	Reference	
High-middle grade	2.713 (0.909–8.098)	0.074
Middle grade	3.843 (1.641–8.998)	0.002
Middle-low grade	9.017 (3.478–23.379)	<0.001
Low grade	10.007 (2.919–34.312)	<0.001
Uncertain	2.357 (0.489–11.368)	0.286
EGFR mutation		
No	Reference	
L9del	1.251 (0.662–2.367)	0.491
L858R	0.472 (0.218–1.025)	0.058
Unknown	0.029 (0.010–0.086)	<0.001
KRAS mutation		
No	Reference	Ref
Yes	1.187 (0.468–3.011)	0.719
Unknown	0.063 (0.028–0.141)	<0.001
Operation methods		
Lobectomy	Reference	
Segmental resection	0.872 (0.211–3.602)	0.850
Wedge resection	1.215 (0.482–3.062)	0.679
Surgical intervention		
Video-assisted thoracoscopic surgery	Reference	
Thoracotomy	1.046 (0.548–1.995)	0.893
Surgical site		
Right site	Reference	
Left site	1.510 (0.877–2.601)	0.137
Tumor stage (8th AJCC)		
IA1	Reference	
IA2	2.028 (0.883–4.657)	0.096
IA3	2.278 (1.158–6.647)	0.022

Table 3 Multivariable Analysis

Characteristics	HR (95% CI)	P-value
Tumor differentiation		
High grade	Reference	
High-middle grade	3.675 (1.210–11.157)	0.022
Middle grade	3.173 (1.350–7.462)	0.008
Middle-low grade	6.807 (2.554–18.141)	<0.001
Low grade	8.748 (2.387–32.057)	0.001
Uncertain	2.420 (0.500–11.713)	0.272
EGFR mutation		
No	Reference	
L9del	1.282 (0.671–2.450)	0.452
L858R	0.556 (0.254–1.221)	0.144
Unknown	0.031 (0.010–0.095)	<0.001

follow-ups. Therefore, we developed a nomogram to determine which stage IA LADC patients with radical surgery and without adjuvant treatment were susceptible to relapse.

This study may have significant implications for our understanding of tumor heterogeneity and surveillance in stage IA LADC patients. This nomogram model consisted of two variables, tumor differentiation and *EGFR* mutation, which are well documented and easy to use in clinical practice. Different from TNM staging, the prognostic model reflected the tumor biology other than anatomic features.

Both factors presented in this study have been previously associated with the outcomes of stage IA NSCLC patients.

First, tumor differentiation is a well-known risk factor. Several studies have demonstrated that poor or moderate histology is related to recurrence in patients with stage I NSCLC.^{9,15,16} The finding in our study that tumor differentiation was a statistically significant prognostic variable was consistent with the finding of the previous study.

EGFR mutation was found to be another prognostic variable, and its efficacy was more important than tumor differentiation in this study. Recent studies have demonstrated that *EGFR* mutation is an early trunk mutation during the carcinogenesis of LADC.^{17–21} When tracking the evolution of NSCLC, *EGFR* mutation was demonstrated to be one of the most common clonal driver mutations in early-stage NSCLC tumors with radical resection and before systemic therapy.¹¹ Therefore, *EGFR* mutations have a vital implication in resected lung carcinoma.

Izar et al previously reported that the presence of *EGFR* mutations ($p=0.026$) was identified as an

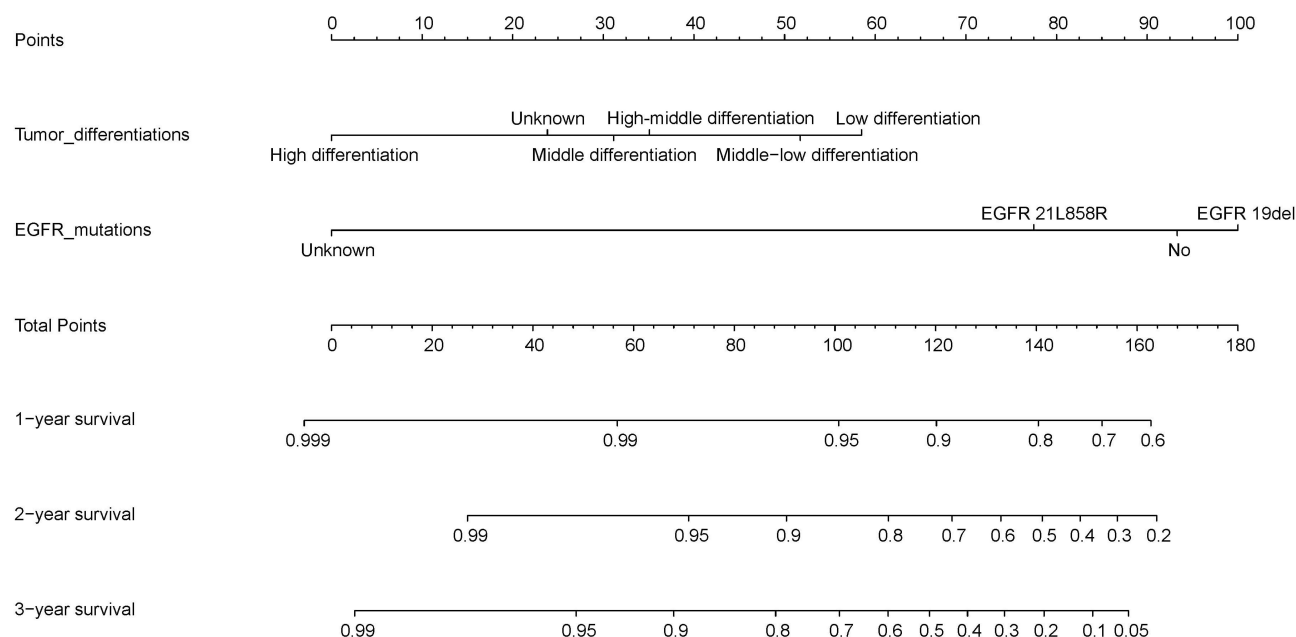


Figure 1 Nomogram predicting DFS in stage IA LADC with radical resection.

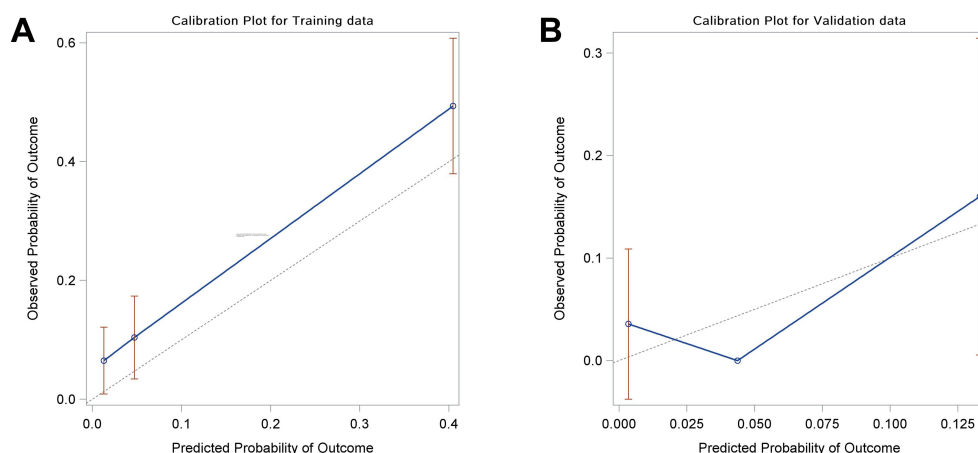


Figure 2 Calibration plots in training set (A) and validation set (B).

independent prognostic marker for DFS in stage I NSCLC.^{12,13} However, the prognostic value of different subtypes in *EGFR* mutations remains controversial.^{22,23} A recent study conducted in 835 patients with stage IA to stage III LADC who underwent radical surgery and did not have *EGFR* TKIs as neoadjuvant or adjuvant therapy showed that patients with the *L858R* mutation had a significantly longer recurrence-free survival than patients without *EGFR* mutation and with the *19del* mutation, which is consistent with the findings of our study. It has been demonstrated in this nomogram that the *EGFR 19del* group and *WT* group were associated with poor prognosis in stage IA LADC patients.²⁴

The nomogram aimed to integrate the efficacy of these two different variables into one methodology and provide clinicians and patients with an individualized risk assessment. Most importantly, this nomogram is not only practical but also reliable. Our proposed nomogram demonstrated a higher C-index of 0.880 in the training cohort and 0.798 in the validation cohort and had better calibration than previous nomograms. The C-index of previous nomograms ranged from 0.612 to 0.838.^{16,25–27} Then, further risk stratifications in this study were classified, with the aim of accurately identifying high-risk patients with this methodology. The 3-year DFS rates of the high-risk and low-risk groups were 98.1% and 21.8%, respectively. The 5-year DFS rates of the high-risk and low-

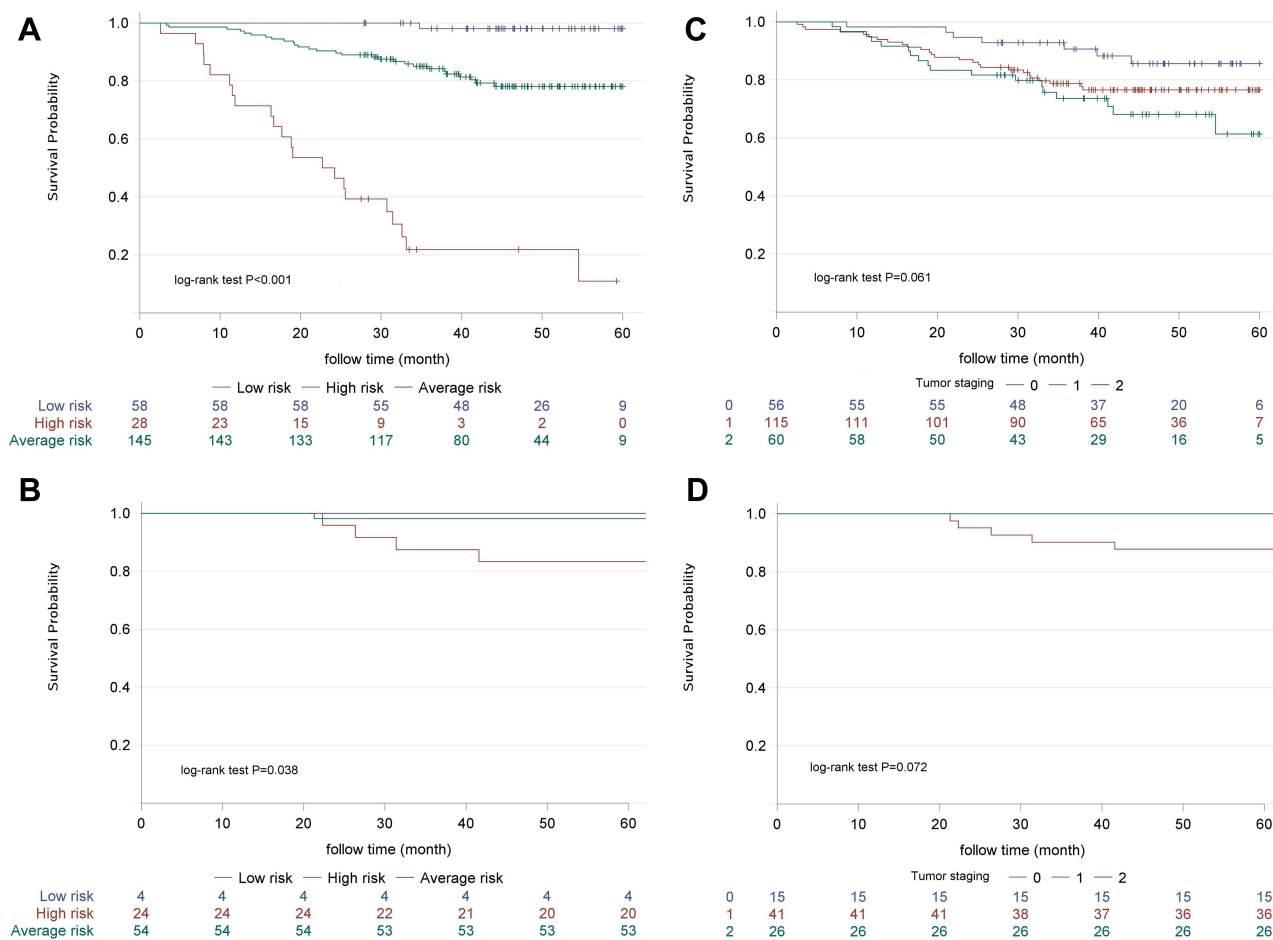


Figure 3 Kaplan–Meier curves demonstrating DFS in stage IA LADC with radical resection according to TNM staging and prognostic nomogram. The nomogram well distinguished the three risk groups with significant differences both in the training cohort ($p < 0.0001$) and in the validation cohort ($p = 0.0380$), as shown in (A and B) respectively. The AJCC 8th TNM staging system was unable to clearly distinguish between the average-risk and high-risk groups in the training cohort ($p = 0.0610$) and in the validation cohort ($p = 0.0720$), as shown in (C and D).

risk groups were 10.9% and 98.1%, respectively. Obviously, the prognosis of patients in the high-risk group was worse.

Currently, there are some stage II studies addressing neoadjuvant immunotherapy (NCT03634241) and targeted therapy (NCT00188617) in early-stage lung cancer, including stage IA, but there are few trials on adjuvant therapy in this high population to the best of our knowledge. The patients in the high-risk group with a relatively younger age might benefit from adjuvant therapy. However, this conclusion needs to be validated in a prospective study.

This study integrated the efficacy of two variables, *EGFR* mutation and tumor differentiation, into one methodology to provide clinicians and patients with an individualized risk assessment for stage IA LADC with radical surgery. When stratified into tertiles, the proposed nomogram was able to identify distinct groups with different risks of recurrence, which may contribute to guiding individual surveillance and help to guide adjuvant treatment in the future. Future

studies are warranted to evaluate the efficacy of this nomogram in stage IA LADC patients with curative resection.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest for this work.

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