



Predicting prognosis in patients with stage IA lung adenocarcinoma with a micropapillary component using a nomogram based on computed tomography radiomics and clinicopathologic factors: a retrospective analysis

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Background: Patients with stage IA lung adenocarcinoma (ADC) with an micropapillary (MIP) component are at a higher risk of recurrence after radical surgical resection; however, adding adjuvant chemotherapy (ACT) to their postoperative course remains controversial. This study determined the predictive factors that influence the prognosis of these patients and identified those at high risk of recurrence.

Methods: Between January 2012 and December 2018, 254 eligible patients with stage IA lung ADC with an MIP component were categorized into training (n=169) and validation (n=85) cohorts. Clinicopathological and radiomics features were included in univariate and multivariate analyses, and statistically significant predictors were used to develop the nomogram. Area under the curve (AUC) of receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) were used to validate the model. The calculated risk scores for each patient were risk-stratified using the X-tile procedure, and survival analyses were performed among the different risk subgroups.

Results: T1c stage, MIP $\geq 1\%$, spread through air space (STAS), carcinoembryonic antigen (CEA) $> 5 \mu\text{g/L}$, and radiomics features were independent predictors of overall survival (OS) and disease-free survival (DFS) in patients with lung ADC with an MIP component at stage IA. Incorporating this into the nomogram, the AUCs of the nomogram predicting 3-, 5-, and 7-year OS and DFS were 0.910, 0.914, and 0.904 and 0.868, 0.838, and 0.848, respectively, in the training cohort and 0.879, 0.895, and 0.899 and 0.817, 0.805, and 0.811, respectively, in the validation cohort, showing good differentiation. The OS and DFS survival analyses among different risk subgroups showed that the nomogram could well distinguish between low- and high-risk groups.

Conclusions: We developed and validated a nomogram based on clinicopathological factors and radiomics features, which can be used as a powerful tool for predicting postoperative recurrence and survival in patients with stage IA lung ADC containing an MIP component.

Keywords: Lung adenocarcinoma (lung ADC); micropapillary (MIP); adjuvant therapy; radiomics

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Introduction

Background

Globally, lung cancer is the primary cause of cancer-related deaths, and adenocarcinoma (ADC) is the most common histological type of lung cancer (1). Patients with early-stage lung ADC still have a high probability of recurrence and metastasis after surgical resection. The study by Ito *et al.* assessed the 10-year overall survival (OS) rate after lobectomy in patients with clinical T1 N0 lung cancer to be 80.4% and the 10-year recurrence-free survival rate to be 77.1% (2). Nomori *et al.* followed up patients with early-stage postoperative lung cancer and found that the 10-year probability of recurrence-free survival was 97% for T1a, 69% for T1b, and 69% for T1c (3). Patients with early-stage lung ADC have a higher risk of lymph node metastasis after surgical resection (approximately 20–40%) (4,5).

Therefore, to improve the postoperative survival of patients with early-stage lung ADC, the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) proposed a new classification system in 2011 to categorize invasive lung ADC into the following five subtypes: lepidic, acinar, papillary, micropapillary (MIP), and solid predominant (6).

Rationale and knowledge gap

The MIP subtype is characterized by a poor prognosis and high aggressiveness and is usually accompanied by extensive lymphovascular invasion and lymph node metastases (7-9). Even with early surgical resection, a high risk of lymph node metastasis remains (10-12). However, the decision on whether to perform postoperative adjuvant chemotherapy (ACT) in patients with stage IA lung ADC with an MIP component remains inconclusive. The 2023 National Comprehensive Cancer Guidelines only recommend postoperative ACT in patients with stage IB lung ADC with high-risk factors, and the guidelines on the need for ACT in those with an MIP component in stage IA are not mentioned (13). However, the results of a retrospective analysis by Wang *et al.* showed that postoperative ACT was a favorable prognostic factor in patients with stage IA lung ADC with an MIP component and that they could benefit from ACT (9). Therefore, there is a need for a predictive model that can better identify patients at higher risk of recurrence based on clinicopathological factors, such as an MIP component, and administer postoperative ACT to reduce the risk of recurrence and improve survival. Radiomics is a quantitative analysis tool that is promising for cancer diagnosis, lymph node metastasis prediction, and prognosis. It works by high-throughput extraction of quantitative features from medical images to create mineable data (14-16). Studies have been conducted to analyze the high-risk factors for poor prognosis in patients with MIP-positive lung ADC, including T-stage and preoperative carcinoembryonic antigen (CEA) levels (17-20).

Highlight box

Key findings

- We identified clinicopathological factors and radiomics features that can predict prognosis in patients with stage IA lung adenocarcinoma containing a micropapillary (MIP) component.

What is known and what is new?

- While the high-risk factors for poor prognosis in patients with MIP-positive lung adenocarcinoma have been analyzed, whether stage IA lung adenocarcinoma has a higher risk of recurrence after surgery and the need for postoperative adjuvant chemotherapy remains unresolved.
- T1c stage, an MIP percentage $\geq 1\%$, spread through air space, a preoperative carcinoembryonic antigen level $>5 \mu\text{g/L}$, and radiomics score were independent predictors of disease-free survival and overall survival in patients with stage IA lung adenocarcinoma containing an MIP component.

What is the implication, and what should change now?

- We established and validated a nomogram based on clinicopathologic factors and radiomics features, which can be used as a powerful tool for predicting postoperative recurrence and survival in patients with stage IA lung adenocarcinoma containing an MIP component.

Objective

The question of whether patients with MIP-containing stage IA lung ADC have a higher risk of recurrence after surgery and whether postoperative ACT should be given remains unresolved. Therefore, this study aimed to comprehensively analyze radiomics features and clinicopathological factors to identify predictive factors affecting the prognosis of patients with stage IA lung ADC containing an MIP component and those patients with a high risk of recurrence in order to guide clinical treatment and improve prognosis. We present this article in accordance with the TRIPOD reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-24-544/rc>).

Methods

Patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethics Committee of Cancer Hospital Affiliated to Shandong First Medical University (No. SDTHEC2023011030) and individual consent for this retrospective analysis was waived. Patients with stage IA lung ADC who underwent radical lung cancer resection and whose pathological results showed an MIP component from January 2012 to December 2018 at the Shandong Cancer Hospital and Institute were retrospectively analyzed in this study. The inclusion criteria were as follows: (I) patients with pathologically confirmed lung ADC containing an MIP component and negative margins; (II) pathological stage pT1a–1cN0M0; (III) patients without significant cardiopulmonary abnormalities and specific postoperative complications; and (IV) patients who did not receive any adjuvant therapy postoperatively. Exclusion criteria included: (I) no record of CT examination at our study institution prior to surgical treatment; (II) pathological confirmation of the presence of a solid subtype; (III) death from non-cancer causes; and (IV) incomplete documentation of imaging information or clinicopathologic information and loss of visits. Ultimately, 254 patients with stage IA lung ADC with an MIP component were eligible for this study and were randomly assigned to the training (n=169) and validation (n=85) cohorts in a 7:3 ratio using the “complete_ra” function of the “randomizr” package in R software version 4.3.2 (Figure 1). The Ethics Committee of the Shandong Cancer Hospital and Institute approved this study, within which the International Union Against Cancer/

American Joint Committee on Cancer 8th edition tumor-node-metastasis (TNM) staging system was used (21).

Surgical treatment

All patients underwent a multidisciplinary consultation to assess the disease and select an appropriate treatment plan before starting treatment, and they were clinically evaluated as having resectable non-small-cell lung cancer (NSCLC). The surgical modalities included video-assisted thoracoscopic surgery or thoracotomy. Lung resection methods included lobectomy, sleeve resection, and segmentectomy. All patients were returned to the thoracic surgery department postoperatively, encouraged to cough and expectorate sputum to promote drainage and lung re-expansion, and instructed to perform activities soon after surgery.

Study endpoints and follow-up

The study endpoints in this study were OS and disease-free survival (DFS), with OS defined as the span between radical lung cancer resection and death due to cancer or the last follow-up. DFS was defined as the time interval between radical resection of lung cancer and the first recorded recurrence, death due to a cancer-related cause, or the last follow-up visit. All enrolled patients received regular outpatient reviews and telephone follow-up after admission, with regular physical examination and chest-enhancing computed tomography (CT) during follow-up, as well as positron emission tomography (PET)-CT, ultrasound, endoscopy, magnetic resonance imaging, or whole-body skeletal imaging when necessary. For patients whose last case record in the case system was recorded more than 1 month before the cut-off time of this study, telephone follow-up was used to complete the collection of patients' clinical data and establish a database for statistical analysis, and they were asked for details of their disease progression and survival. Follow-up ended on July 31, 2023, and the median duration of follow-up for all patients was 73 months (range, 17–133 months).

CT image acquisition

All patients underwent enhanced CT scanning of the chest. Enhanced scanning was performed by injecting the iodine contrast agent iohexol (350 mg I/mL) through the anterior vein of the elbow using a high-pressure syringe at

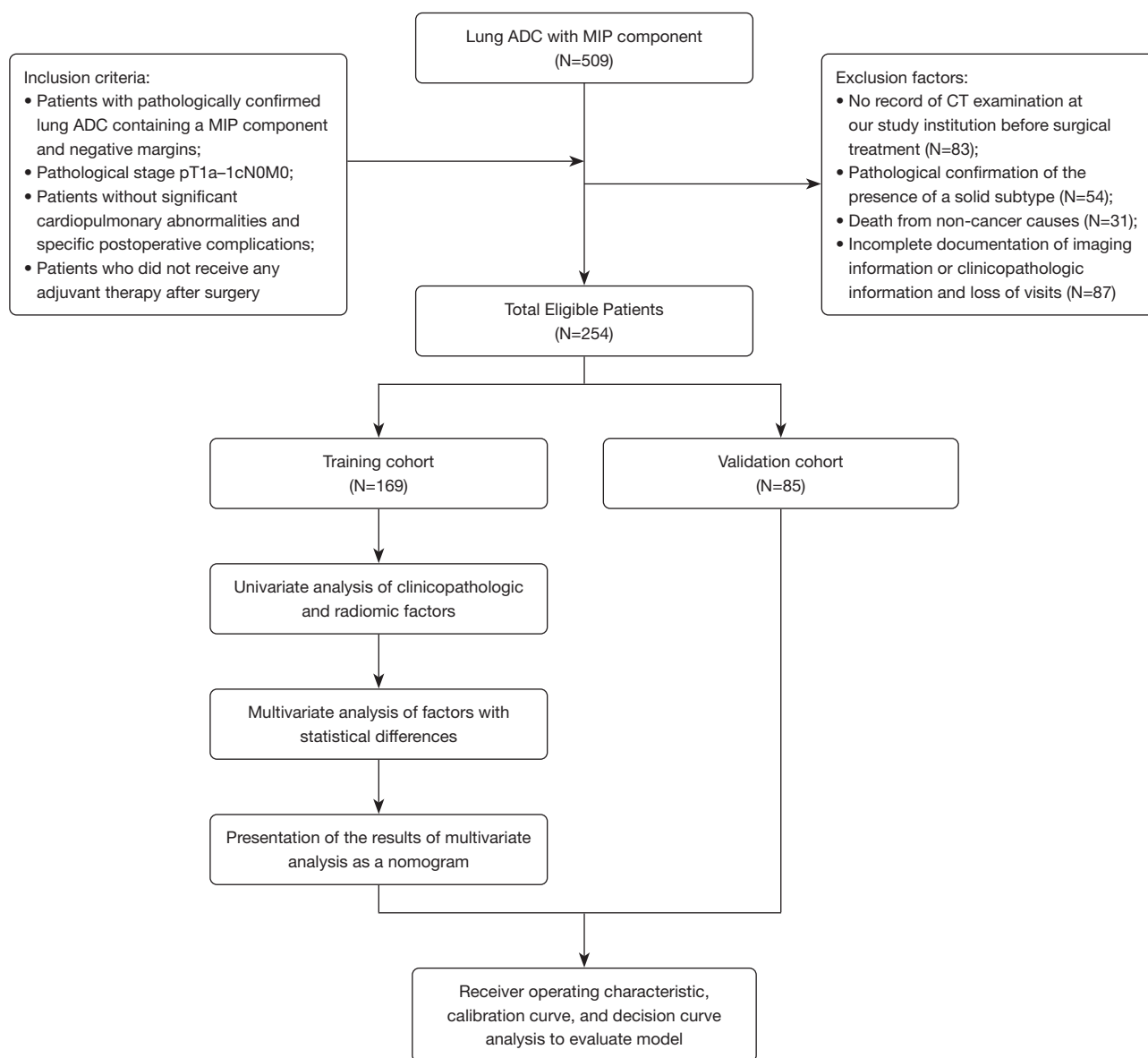


Figure 1 Flow chart of the study design. ADC, adenocarcinoma; MIP, micropapillary; CT, computed tomography.

an injection rate of 3.0 mL/s with a dose of 60–100 mL of iodine contrast. CT-enhanced images of the arterial and venous phases were acquired 20 and 40 s after the iodine contrast injection, respectively. The scanning parameters used were as follows: voltage 120 kV, tube current 200 mA, reconstruction layer thickness 5 mm, reconstruction interval 5 mm, and matrix 512×512. CT images obtained from the scan were uploaded to the Picture Archiving and Communication System, and the enhanced CT images were exported in DICOM format. Scanning area: scanning

layer by layer from top to bottom, starting from the thyroid cartilage and ending at the lower edge of the liver.

Radiomics

CT scans obtained before radical lung cancer resection in patients with stage IA lung ADC containing an MIP component were analyzed in this study. If multiple CT scans were available, the most recent CT scan preoperatively was used. All tumor target areas were manually depicted

layer by layer by an oncologist using the medical image processing and navigation software 3D Slicer (version 5.2.1). The regions of interest were subsequently confirmed by a radiologist with advanced experience in chest CT analysis. All data were Z-score normalized to reduce the variation between images from different patients. To reduce any bias or overfitting caused by many features, feature selection was conducted through a two-step process as follows: first, features with high repeatability and stability were screened by calculating the intra-class correlation coefficient (ICC) index, and features were screened with the criterion of an ICC index >0.9 . Features with high repeatability were screened; subsequently, these features were further downscaled and screened for key features using the least absolute shrinkage and selection operator (LASSO) regression (22,23). Finally, a radiomics score (Rad score) was calculated for each patient by weighting the selected features according to their respective coefficients (24).

Model construction and evaluation

Based on previous studies on the prognosis of patients with MIP-containing lung ADC, we retrospectively analyzed clinicopathological information, such as spread through air space (STAS), the proportion of MIP components, and radiomics information (7-10). First, a univariate Cox proportional hazard model was used in the training cohort to evaluate the predictive ability of clinicopathological and radiomics features for OS and DFS. Next, factors with $P<0.05$ in univariate analyses were assessed in multivariate analyses. Finally, a nomogram was constructed using factors with significant predictive value in multivariate Cox regression analyses, and 3-, 5-, and 7-year risk values for death or progression were calculated for each patient in the training and validation cohorts. Subsequently, receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) were used in the training and validation cohorts to evaluate the predictive performance of the nomogram for OS and DFS at 3, 5, and 7 years. We used X-tile software (version 3.6.1) to determine the optimal cut-off value for the risk value in the nomogram and classified the population into low- and high-risk groups for death or disease progression based on this cut-off value. OS and DFS survival analyses of patients in these two risk groups were performed in the training cohort and validation cohort to assess the prognosis of patients with different risks.

Statistical analysis

The independent samples *t*-test or rank-sum test was used to compare continuous variables; the Chi-squared or Fisher's exact test was used to compare categorical variables. Univariate and multivariate analyses were performed to identify independent prognostic factors for OS and DFS using Cox proportional risk models. Patients' DFS and OS were assessed and compared using the Kaplan-Meier method and log-rank test, respectively. All tests were two-sided, and statistical significance was set at $P<0.05$. All data analyses and graphing were performed using R software version 4.3.2.

Results

Patient characteristics

Overall, 254 patients with stage IA lung ADC with an MIP component were enrolled in this study; 112 (44.1%) and 142 (55.9%) patients were males and females, respectively. As of the end of follow-up, a total of 109 patients (42.9%) had progressed, of which 45 patients (41.3%) had local recurrence (the recurrence within the lung on the side where the primary tumor was located or local lymph node recurrence) and 64 patients (58.7%) had distant metastasis (nonregional lymph node metastasis, systemic metastasis, or malignant pleural effusion); a total of 92 patients (36.2%) died. Additionally, 124 (48.8%) and 130 (51.2%) patients were aged <60 and ≥ 60 years, respectively; 225 (88.6%) patients received lobectomy, and the remaining 29 (11.4%) underwent non-lobectomy. Of them, 169 and 85 patients were included in the training and validation cohorts, respectively, with death occurring in 64 (37.9%) and 28 (32.9%) and progression occurring in 71 (42.0%) and 38 (44.7%), respectively. *Table 1* summarizes the baseline characteristics of the training and validation cohorts, with each clinical factor satisfying $P>0.05$.

Univariate and multivariate analyses of prognosis in the training cohort

In the univariate analysis of patients' clinicopathological factors, we found that the percentage of the MIP component (OS $P<0.001$, DFS $P<0.001$), STAS (OS $P<0.001$, DFS $P<0.001$), T-stage (OS $P=0.009$, DFS $P=0.007$), and CEA levels (OS $P<0.001$, DFS $P<0.001$) were significantly correlated with patients' OS and DFS (*Tables 2,3*).

Table 1 Clinicopathologic characteristics of patients in the training and validation cohorts

Characteristics	Training (n=169)	Validation (n=85)	P
Sex, n (%)			
Female	89 (52.7)	53 (62.4)	0.18
Male	80 (47.3)	32 (37.6)	
Age (years), n (%)			
<60	75 (44.4)	49 (57.6)	0.13
≥60	94 (55.6)	36 (42.4)	
Smoking, n (%)			
Yes	46 (27.2)	22 (25.9)	0.94
No	123 (72.8)	63 (74.1)	
Drinking, n (%)			
Yes	34 (20.1)	21 (24.7)	0.50
No	135 (79.9)	64 (75.3)	
Family history, n (%)			
Yes	37 (21.9)	20 (23.5)	0.89
No	132 (78.1)	65 (76.5)	
MIP proportion, n (%)			
<1%	78 (46.2)	47 (55.3)	0.39
1–5%	49 (29.0)	20 (23.5)	
>5%	42 (24.9)	18 (21.2)	
ECOG, n (%)			
0	10 (5.9)	7 (8.2)	0.67
1	159 (94.1)	78 (91.8)	
FEV ₁ , n (%)			
≤70%	23 (13.6)	7 (8.2)	0.30
>70%	146 (86.4)	78 (91.8)	
T-stage, n (%)			
T1a–1b	138 (81.7)	69 (81.2)	>0.99
T1c	31 (18.3)	16 (18.8)	
Surgical excision method, n (%)			
Lobectomy	149 (88.2)	76 (89.4)	0.93
Non-lobectomy	20 (11.8)	9 (10.6)	
Location, n (%)			
Lower lobe	60 (35.5)	31 (36.5)	0.81
Middle lobe	16 (9.5)	10 (11.8)	
Upper lobe	93 (55.0)	44 (51.8)	

Table 1 (continued)**Table 1** (continued)

Characteristics	Training (n=169)	Validation (n=85)	P
CEA level, n (%)			
≤5 µg/L	128 (75.7)	69 (81.2)	0.41
>5 µg/L	41 (24.3)	16 (18.8)	
STAS, n (%)			
Yes	21 (12.4)	9 (10.6)	0.82
No	148 (87.6)	76 (89.4)	
Length of surgery (minutes) [†]	115.57±33.73	118.21±36.82	0.57
Amount of intraoperative bleeding (mL) [†]	95.21±63.71	93.76±40.68	0.85
Rad score [†]	−1.99±2.22	−1.79±1.87	0.47

[†], data are presented as mean ± standard deviation. MIP, micropapillary; ECOG, Eastern Cooperative Oncology Group; FEV₁, forced expiratory volume in one second; CEA, carcinoembryonic antigen; STAS, spread through air space; Rad score, radiomics score.

After screening using the ICC index and LASSO regression, a total of 11 radiomics features most valuable for predicting OS were selected, and the calculated Rad score was -2.37 ± 1.19 vs. -0.47 ± 0.82 ($P < 0.001$) in patients with and without death, respectively. The 12 radiomics features most valuable for predicting DFS were selected, and the Rad score was -1.58 ± 2.56 vs. -2.07 ± 2.10 ($P = 0.047$) in patients with and without progression, respectively (Figure S1).

Multivariate Cox regression analysis was subjected to clinicopathological and imaging characteristics with $P < 0.05$ in univariate analysis. In multivariate Cox regression analysis of OS, MIP percentages of 1–5% and >5% [hazard ratio (HR): 3.467, 95% confidence interval (CI): 1.635–7.347, $P = 0.001$ and HR: 2.294, 95% CI: 1.096–4.805, $P = 0.03$, respectively], STAS (HR: 4.954, 95% CI: 2.252–10.902, $P < 0.001$), the T1c stage (HR: 3.779, 95% CI: 1.791–7.972, $P < 0.001$), CEA level >5 µg/L (HR: 2.410, 95% CI: 1.237–3.711, $P = 0.001$), and Rad score (HR: 2.219, 95% CI: 1.685–2.923, $P < 0.001$) were five independent prognostic factors for OS. In multivariate Cox regression analysis of DFS, MIP percentages of 1–5% and >5% (HR: 3.800, 95% CI: 2.012–7.178, $P < 0.001$ and HR: 3.221, 95% CI: 1.634–6.349, $P < 0.001$, respectively), STAS (HR: 2.872, 95% CI: 1.517–5.436, $P = 0.001$), T1c stage (HR: 2.089, 95% CI: 1.157–3.772, $P = 0.02$), CEA >5 µg/L (HR: 1.245, 95%

Table 2 Univariate and multivariate analysis of clinicopathologic and radiomics characteristics for OS prediction

Characteristics	Univariate analysis			Multivariate analysis		
	Death (n=64)	No (n=105)	P value	Regression coefficient	HR (95% CI)	P value
Sex, n (%)						
Female	35 (54.7)	54 (51.4)	0.62			
Male	29 (45.3)	51 (48.6)				
Age (years), n (%)						
<60	25 (39.1)	49 (46.7)	0.11			
≥60	39 (60.9)	56 (53.3)				
Smoking, n (%)						
Yes	19 (29.7)	27 (25.7)	0.85			
No	45 (70.3)	78 (74.3)				
Drinking, n (%)						
Yes	15 (23.4)	19 (18.1)	0.55			
No	49 (76.6)	86 (81.9)				
Family history, n (%)						
Yes	10 (15.6)	27 (25.7)	0.28			
No	54 (84.4)	78 (74.3)				
MIP proportion, n (%)						
<1%	11 (17.2)	67 (63.8)	<0.001	Ref	Ref	
1–5% (ref = “<1%”)	27 (42.2)	22 (21.0)		1.243	3.467 (1.635, 7.347)	0.001
>5% (ref = “<1%”)	26 (40.6)	16 (15.2)		0.830	2.294 (1.096, 4.805)	0.03
>5% (ref = “1–5%”)				0.413	1.511 (0.860, 2.655)	0.15
FEV ₁ , n (%)						
≤70%	10 (15.6)	13 (12.4)	0.33			
>70%	54 (84.4)	92 (87.6)				
T-stage, n (%)						
T1a–1b	49 (76.6)	89 (84.8)	0.009	Ref	Ref	
T1c	15 (23.4)	16 (15.2)		1.329	3.779 (1.791, 7.972)	<0.001
Location, n (%)						
Lower lobe	25 (39.1)	35 (33.3)	0.84			
Middle lobe	6 (9.4)	10 (9.5)				
Upper lobe	33 (51.6)	60 (57.1)				
CEA level, n (%)						
≤5 µg/L	33 (51.6)	95 (90.5)	<0.001	Ref	Ref	
>5 µg/L	31 (48.4)	10 (9.5)		0.892	2.410 (1.237, 3.711)	0.001

Table 2 (continued)

Table 2 (continued)

Characteristics	Univariate analysis			Multivariate analysis		
	Death (n=64)	No (n=105)	P value	Regression coefficient	HR (95% CI)	P value
STAS, n (%)						
Yes	13 (20.3)	8 (7.6)	<0.001	1.600	4.954 (2.252, 10.902)	<0.001
No	51 (79.7)	97 (92.4)		Ref	Ref	
Surgical excision method, n (%)						
Lung lobectomy	56 (87.5)	93 (88.6)	0.65			
Non-lobectomy	8 (12.5)	12 (11.4)				
Length of surgery (minutes) [†]	113.25±34.69	116.98±33.21	0.72			
Amount of intraoperative bleeding (mL) [†]	86.41±37.35	100.57±75.06	0.28			
Rad score [†]	-2.37±1.19	-0.47±0.82	<0.001	0.797	2.219 (1.685, 2.923)	<0.001

[†], data are presented as mean ± standard deviation. OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; MIP, micropapillary; FEV₁, forced expiratory volume in one second; CEA, carcinoembryonic antigen; STAS, spread through air space; Rad score, radiomics score.

Table 3 Univariate and multivariate analysis of clinicopathologic and radiomics characteristics for DFS prediction

Characteristics	Univariate analysis			Multivariate analysis		
	Progression (n=71)	No (n=98)	P value	Regression coefficient	HR (95% CI)	P value
Sex, n (%)						
Female	38 (53.5)	51 (52.0)	0.89			
Male	33 (46.5)	47 (48.0)				
Age (years), n (%)						
<60	26 (36.6)	48 (49.0)	0.10			
≥60	45 (63.4)	50 (51.0)				
Smoking, n (%)						
Yes	23 (32.4)	23 (23.5)	0.37			
No	48 (67.6)	75 (76.5)				
Drinking, n (%)						
Yes	18 (25.4)	16 (16.3)	0.35			
No	53 (74.6)	82 (83.7)				
Family history, n (%)						
Yes	10 (14.1)	27 (27.6)	0.08			
No	61 (85.9)	71 (72.4)				

Table 3 (continued)

Table 3 (continued)

Characteristics	Univariate analysis			Multivariate analysis		
	Progression (n=71)	No (n=98)	P value	Regression coefficient	HR (95% CI)	P value
MIP proportion, n (%)						
<1%	17 (23.9)	61 (62.2)	<0.001	Ref	Ref	
1–5% (ref = “<1%”)	29 (40.8)	20 (20.4)		1.335	3.800 (2.012, 7.178)	<0.001
>5% (ref = “<1%”)	25 (35.2)	17 (17.3)		1.170	3.221 (1.634, 6.349)	<0.001
>5% (ref = “1–5%”)			0.87	–0.165	0.848 (0.474, 1.517)	0.58
FEV ₁ , n (%)						
≤70%	10 (14.1)	13 (13.3)	0.69			
>70%	61 (85.9)	85 (86.7)				
T-stage, n (%)						
T1a–1b	54 (76.1)	84 (85.7)	0.007	Ref	Ref	
T1c	17 (23.9)	14 (14.3)		0.736	2.089 (1.157, 3.772)	0.02
Location, n (%)						
Lower lobe	27 (38.0)	33 (33.7)	0.82			
Middle lobe	8 (11.3)	8 (8.2)				
Upper lobe	36 (50.7)	57 (58.2)				
CEA level, n (%)						
≤5 µg/L	39 (54.9)	89 (90.8)	<0.001	Ref	Ref	
>5 µg/L	32 (45.1)	9 (9.2)		1.408	1.245 (1.144, 2.416)	<0.001
STAS, n (%)						
Yes	14 (19.7)	7 (7.1)	<0.001	1.055	2.872 (1.517, 5.436)	0.001
No	57 (80.3)	91 (92.9)		Ref	Ref	
Surgical excision method, n (%)						
Lung lobectomy	63 (88.7)	86 (87.8)	0.93			
Non-lobectomy	8 (11.3)	12 (12.2)				
Length of surgery (minutes) [†]	113.30±33.52	117.21±33.95	0.31			
Amount of intraoperative bleeding (mL) [†]	84.37±36.63	103.06±76.89	0.06			
Rad score [†]	–1.58±2.56	–2.07±2.10	0.047	0.132	1.141 (1.016, 1.282)	0.03

[†], data are presented as mean ± standard deviation. DFS, disease-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; MIP, micropapillary; FEV₁, forced expiratory volume in one second; CEA, carcinoembryonic antigen; STAS, spread through air space; Rad score, radiomics score.

CI: 1.144–2.416, $P < 0.001$), and Rad score (HR: 1.141, 95% CI: 1.016–1.282, $P = 0.03$) were five independent prognostic factors for DFS.

Establishment and evaluation of the nomogram

Based on the multivariate Cox regression analysis, the predictive model was visualized in the form of a nomogram (Figure 2). A ROC was created for the model to assess its predictive efficacy (Figure 3). In the training cohort, the area under the curve (AUC) values of the nomogram predicting 3-, 5-, and 7-year OS were 0.910 (95% CI: 0.787–0.933), 0.914 (95% CI: 0.835–0.973), and 0.904 (95% CI: 0.845–0.962), respectively; the AUC values of the nomogram predicting 3-, 5-, and 7-year DFS were 0.868 (95% CI: 0.761–0.976), 0.838 (95% CI: 0.761–0.912), and 0.848 (95% CI: 0.775–0.921), respectively (Tables S1,S2). In the validation cohort, the AUC values of the nomogram predicting 3-, 5-, and 7-year OS were 0.879 (95% CI: 0.776–0.982), 0.895 (95% CI: 0.815–0.975), and 0.899 (95% CI: 0.822–0.977), respectively; the AUC values of the nomogram predicting 3-, 5-, and 7-year DFS were 0.817 (95% CI: 0.697–0.936), 0.805 (95% CI: 0.694–0.917), and 0.811 (95% CI: 0.699–0.922), respectively. Additionally, the calibration curves of the training and validation cohorts of the two predictive models showed good agreement between the predicted OS and DFS and the actual observations (Figures S2,S3), and the DCA demonstrated a satisfactory net benefit for the two predictive models in most of the threshold probabilities, suggesting that the models have a favorable potential clinical outcome (Figures S4,S5).

Development of a prediction stratification model

Based on the individual total scores calculated from the nomograms predicting OS and DFS, cut-off values were calculated in the total population using the X-tile procedure, which classified the total population into two risk groups: low risk ($n = 217$, total point ≤ 111.9 ; $n = 173$, total point ≤ 97.2) and high risk ($n = 37$, total point > 111.9 ; $n = 81$, total point > 97.2). Subsequent Kaplan-Meier survival analyses of the two risk groups in the total population based on the above cut-off values showed good differentiation, with significant differences in OS at 3, 5, and 7 years (3-year OS: 97.7% *vs.* 56.9%; 5-year OS: 90.6% *vs.* 15.1%; and 7-year OS: 75.3% *vs.* 3.4%; $P < 0.001$) and the same significant differences in DFS at 3, 5, and 7 years (3-year DFS: 96.0% *vs.* 70.3%; 5-year DFS: 86.5% *vs.* 34.0%; and

7-year DFS: 75.8% *vs.* 0.0%; $P < 0.001$) (Figure 4).

Discussion

Surgery is the most effective treatment for patients with early-stage lung cancer; however, the prognosis of patients varies considerably, and there is still a risk of tumor recurrence and metastasis postoperatively. The results of a meta-analysis in 1995 showed that patients with early-stage lung cancer who received postoperative platinum-based ACT had an approximately 5% increase in 5-year survival (25). This meta-analysis was followed by three randomized trials evaluating postoperative chemotherapy, including The Adjuvant Lung Project Italy study (26), The Big Lung Trial (27), and The Cancer and Leukemia Group B 9633 Trials (28), which demonstrated that patients with early-stage lung cancer after surgery did not benefit from ACT. In 2011, IASLC/ATS/ERS proposed a new classification system for lung ADC, which classified MIP involvement for the first time as a new histological subtype. It has been demonstrated that the MIP subtype is more prone to lymph nodes and distant metastases and has a higher risk of recurrence postoperatively (8,29–32). Although the current guidelines do not list the MIP component levels as a high-risk pathological factor for postoperative ACT (13) and do not recommend postoperative ACT for patients with the MIP subtype in early stages, an increasing number of studies have indicated that those with early-stage lung ADC with an MIP component benefit from postoperative ACT (9,33–35). In this study, we constructed and validated a clinical prediction model for predicting patients' OS and DFS based on preoperative CT imaging and clinicopathological factors in individuals with stage IA lung ADC, achieving an effective prediction of those with early-stage lung ADC with MIP components who have a poor prognosis for clinical development of treatment strategies.

Key findings

In this study, using multifactorial analysis, we found that MIP component percentage, T-stage, STAS, CEA levels, and Rad score were independent high-risk pathological factors for poor prognosis in patients with early lung ADC containing an MIP component. In the training cohort, the AUC values of the nomogram for predicting 3-, 5-, and 7-year OS and DFS were 0.910, 0.914, and 0.904 and 0.868, 0.838, and 0.848, respectively; in the validation cohort, it

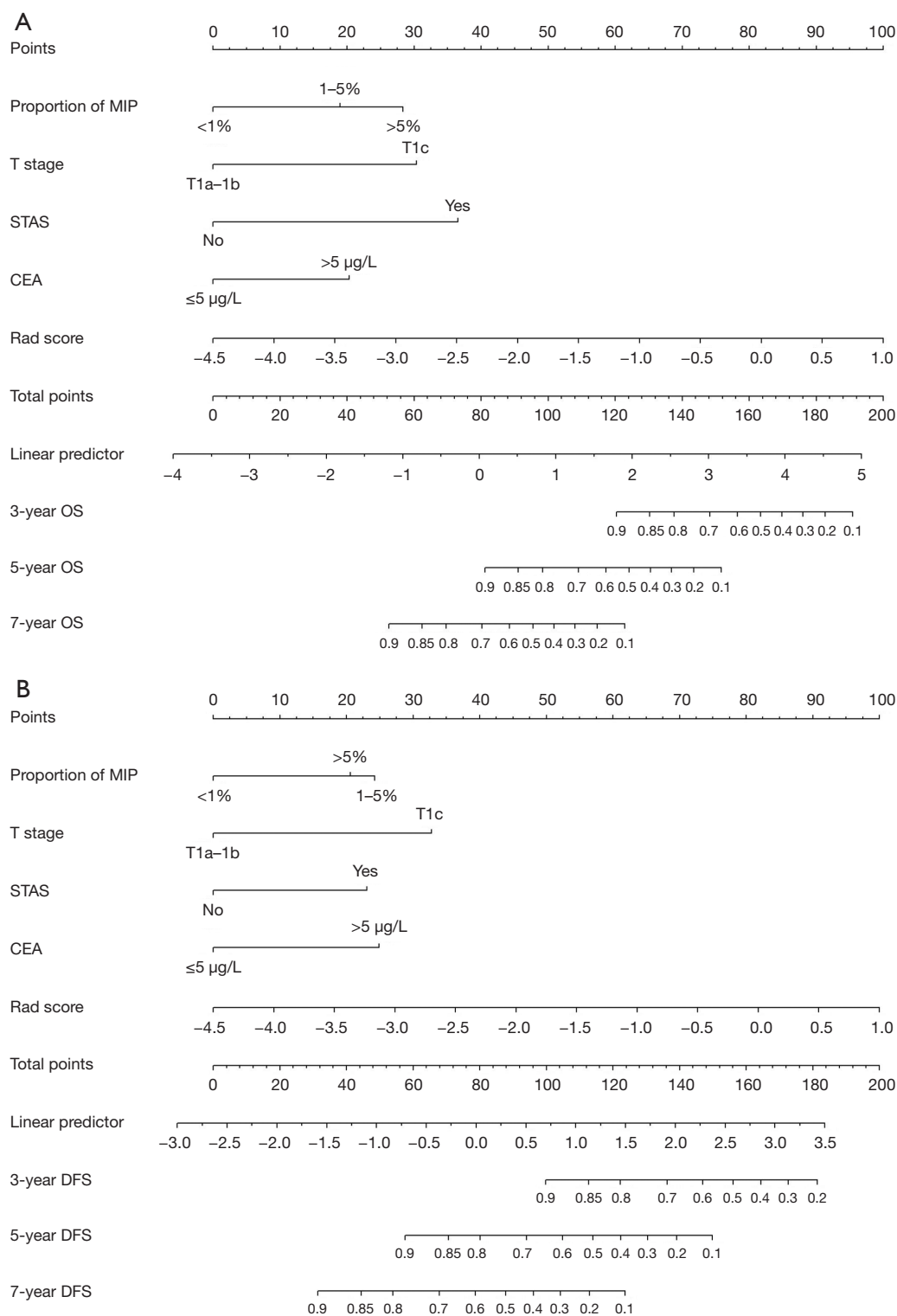


Figure 2 Nomograms for predicting OS and DFS. (A) Nomograms for predicting OS. (B) Nomograms for predicting DFS. MIP, micropapillary; STAS, spread through air space; CEA, carcinoembryonic antigen; Rad score, radiomics score; OS, overall survival; DFS, disease-free survival.

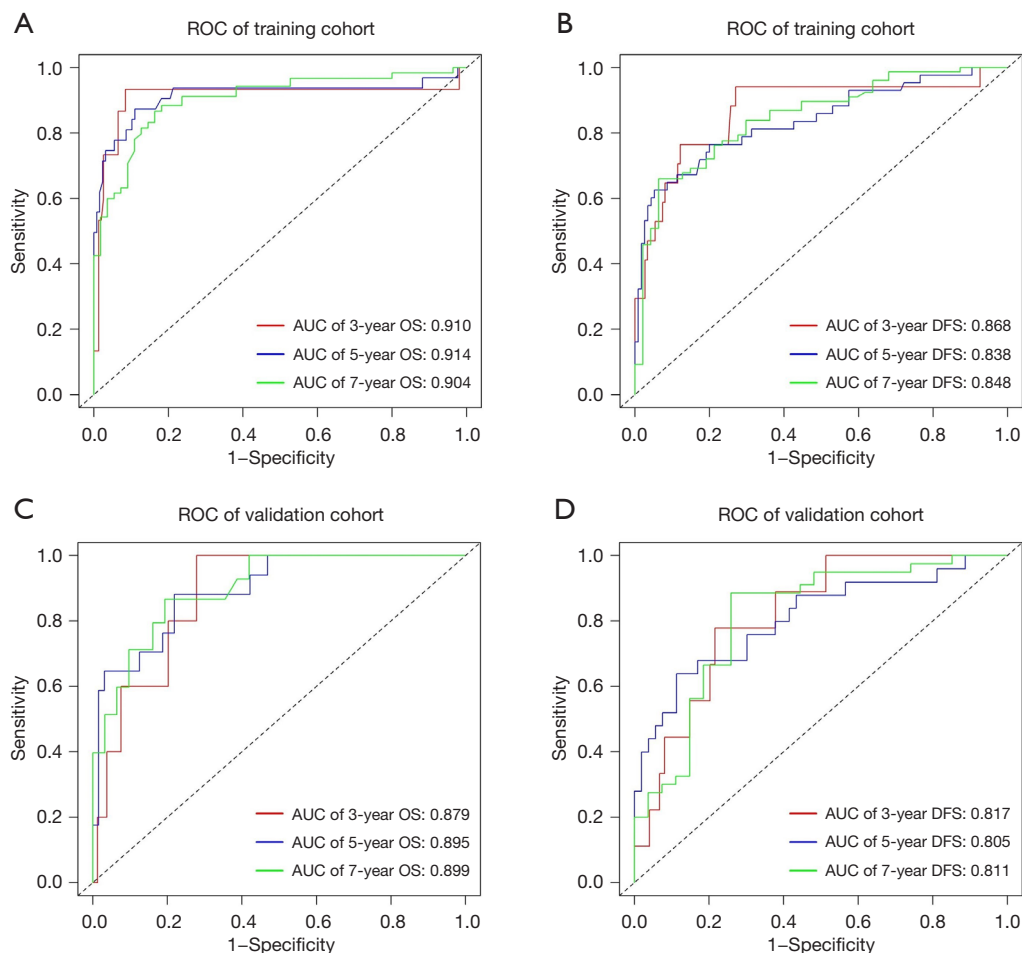


Figure 3 ROC curves for predicted OS and DFS in the training and validation cohorts. ROC curves for predicted OS (A) and DFS (B) in the training cohort and predicted OS (C) and DFS (D) in the validation cohort. ROC, receiver operating characteristic; AUC, area under the curve; OS, overall survival; DFS, disease-free survival.

was 0.879, 0.895, and 0.899 and 0.817, 0.805, and 0.811, respectively. The AUC values of the nomogram were significantly higher than those of each factor in both the training and validation cohorts, which demonstrated the high predictive value of the nomogram. Subsequently, we used the X-tile program to calculate the cut-off value of the nomogram individual total score in the total population and divided the people in the total population into two risk groups. When comparing the survival risk of the two risk groups, we found significant differences in both DFS and OS between patients in the low- and high-risk groups.

Comparison with similar researches

Several previous studies have explored CT radiomics as a

predictor of treatment response and prognosis (16,36,37). For example, Perez-Johnston *et al.* retrospectively analyzed 219 preoperative CT images of patients with completely surgically resected stage I lung ADC, and CT-based imaging consensus clustering identified individual patients at high risk of recurrence or metastasis in those with lung ADC (36). Chang *et al.*'s study based on PET/CT parameter prediction found that patients with an MIP component had a higher risk of lymph node metastasis regardless of whether it was the major component or not (38). Therefore, it is feasible to predict recurrent metastasis in lung ADC patients with MIP components at stage IA by CT imaging histology, as in our study. We retrospectively examined 254 patients with stage IA pulmonary ADC containing an MIP component, analyzing their preoperative CT images

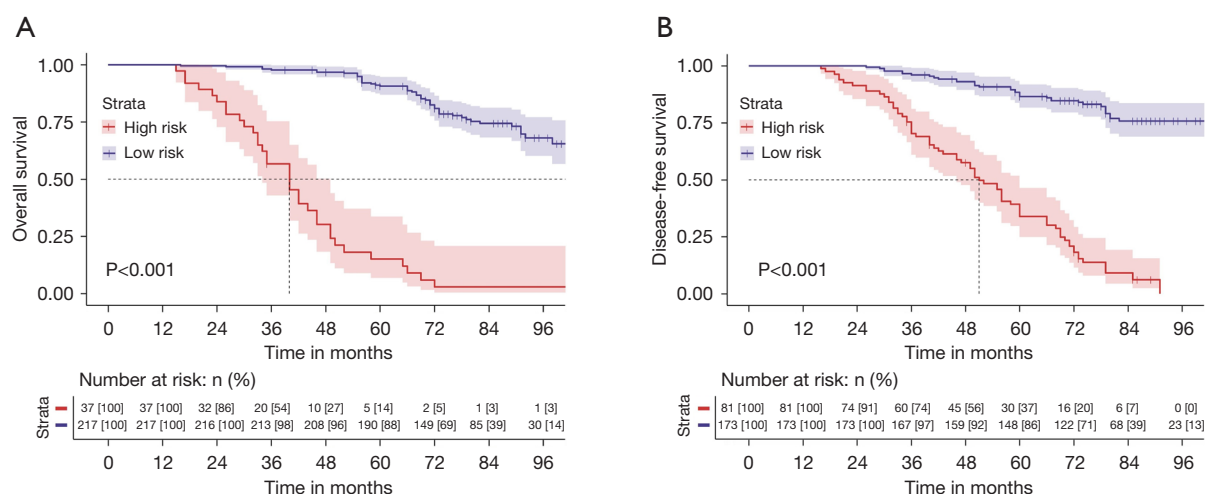


Figure 4 Kaplan-Meier survival analysis of OS and DFS for different risk subgroups in the total population. (A) Kaplan-Meier survival analysis of OS for different risk subgroups in the total population. (B) Kaplan-Meier survival analysis of DFS for different risk subgroups in the total population. Dashed lines are the median OS or DFS. OS, overall survival; DFS, disease-free survival.

and incorporating clinicopathological factors. In contrast, our study focused more on the effect of one pathological subtype, the MIP subtype, on recurrent metastasis in patients with stage IA lung ADC; therefore, we excluded patients with solid subtype, a high-risk pathology, to avoid bias in our results and included other clinicopathological factors, such as STAS. Our model will be beneficial in providing a predictive tool for clinicians for the purpose of individualized treatment, allowing them to identify which patients would most benefit from ACT.

In our analysis of postoperative pathological characteristics, we found that patient prognosis was significantly correlated with MIP percentage, T-stage, STAS, and CEA levels, which is consistent with previous findings. Lee *et al.* found that even the presence of only a small percentage of MIP components (<5%) significantly affected OS (20). Their survival analyses showed significantly better OS in patients without an MIP component (<1%) than in those with MIP percentages of 1–5% or >5%; however, no significant difference was found between patients with MIP percentages of 1–5% and >5%, which is consistent with our results. Regarding DFS, patients with MIP percentages of <1% and 1–5% had significantly better survival than those with MIP percentages >5%; however, no significant difference was observed between patients with MIP percentages of 1–5% and <1%, which contradicts our results. In our study, patients with percentages of MIP 1–5% and >5% had significantly worse OS and DFS

than those with MIP percentages of <1%; however, no significant difference was found between patients with MIP percentages of 1–5% and >5%. The risk was higher for patients with MIP percentages of >5% and 1–5% in the prediction models predicting OS and DFS, respectively; however, the difference was not statistically significant. We believe that the lack of a significant difference between individuals with MIP percentages of 1–5% and >5% in our study may be because we included patients at the earliest stage of lung cancer, i.e., stage IA. Additionally, because of the high malignancy and rapid growth of the MIP component, even if the MIP accounts for only 1–5%, there is a high likelihood that the MIP will become a major component of the tumor during tumor progression in patients with lung ADC at stage IA, thereby affecting the prognosis. Furthermore, we excluded patients with lymph node metastasis, which is increased by the MIP component; the higher the percentage of MIP components, the greater the risk of lymph node metastasis in patients (39).

Previous research has shown that tumor size has an important prognostic value in early-stage lung cancer; studies by Hattori *et al.* and Hung *et al.* indicated that tumor size significantly affected the 5-year OS of patients (40,41). Additionally, Takenaka *et al.* concluded that data on tumor diameter are more readily available and can directly reflect the extent of lesion progression. This study analyzed the impact of maximum diameter, total volume, and consolidation tumor ratio (CTR) on patient prognosis

in stage IA NSCLC (42). Data from this study showed that 5-year DFS was better in patients who had tumors with diameters ≤ 20 mm than in those with tumor diameters > 20 mm. The study by Huang *et al.* predicted the risk of recurrence of stage IA lung ADC based on the percentage of MIP and solid components, and T-stage was a high-risk factor in their study (43). Consistent with our findings, patients with stage T1c cancer had a significantly worse prognosis than those with stage T1a–1b. The study by Wang *et al.* yielded the same results, where univariate and multivariate analyses of the T-stage revealed that it was a significant predictor of OS and PFS (9). With regard to the effectiveness of ACT in patients with stage T1c cancer, the results of Tsutani *et al.* demonstrated that the RPF and OS of T1c-stage patients who received ACT were significantly longer than those who did not receive ACT (44).

Through in-depth research in pathology, a new mode of metastasis, STAS, in addition to the common metastatic modes of lymphatic, hematogenous, and local implantation metastasis, has been identified. The World Health Organization defines STAS as airspace dissemination in the form of MIP clusters, solid nests, or single cancer cells in the peripheral lung parenchyma beyond the margins of the main tumor nests (45). In lung ADC, STAS is present in approximately 14.8–60.5% of cases and frequently in aggressive histologic types, such as the MIP or solid subtypes. The presence of high-level histologic subtypes is an independent predictor of STAS (6,18,46,47). Many studies have confirmed that the presence of STAS is one of the causes of shortened recurrence-free survival time and OS in patients postoperatively (41,47–49). Our study similarly demonstrated that STAS is a pathological factor affecting patient prognosis. Ding *et al.* determined, through a detailed examination of pathological serial sections, that clusters in the complex structure of the MIP appear to extend into the air (50). The lungs contain sufficient air, and the MIP component cells may have acquired anoikis resistance, enabling them to remain viable even after detachment. Thus, the cells constituting the MIP component, accompanied by air, can easily and extensively extend beyond the main tumor; through this mechanism, STAS occurs (51). In addition to biological factors, physical factors, including detachment of tumor cells caused by extrusion pressure during surgery and contamination of the scalpel blade with tumor cells, are also major factors affecting the presence of STAS (47,52). Therefore, further studies on the mechanism of STAS are needed to inform clinicians' medical decisions. STAS is a common

biological phenomenon that can seriously interfere with the effectiveness of surgical treatment for early-stage lung cancer and even affect the treatment strategy.

Serum CEA is crucial in the diagnosis and prognostic assessment of lung cancer. Patients who have lung cancers with positive CEA indexes are mostly clinically progressive or advanced; moreover, elevated CEA levels can be used as an indicator of lung cancer metastasis (53–56). In our study, the prognosis of patients with preoperative CEA > 5 $\mu\text{g/L}$ was significantly worse than that of those with CEA ≤ 5 $\mu\text{g/L}$, which is consistent with the findings of Huang *et al.* (43). Therefore, it is recommended that clinicians monitor the CEA levels of patients with early-stage lung ADC preoperatively to guide their diagnosis and treatment postoperatively.

In addition, the current study calculated risk scores for each patient by nomogram, and cut-off values for different risks in the nomogram were obtained using X-tile software. In the survival analysis between different risk subgroups, we found that the higher the risk, i.e., the higher the score, the higher the probability of postoperative progression of the patient and the worse the patient's prognosis. Thus, for the patients who were judged to be at high risk by the prediction model used in this study, we recommend postoperative adjuvant therapy to improve the patient's prognosis. For low-risk patients, although we do not recommend postoperative adjuvant therapy, we should conduct regular reviews and pay close attention to the changes in each risk factor.

Strengths and limitations

This study has some limitations. First, due to the nature of the retrospective analysis in this study, it is difficult to avoid selection bias; therefore, we recommend more prospective clinical studies on adjuvant therapy for stage IA lung ADC containing an MIP component. Second, this was a single-center study, and although internal validation indicates that the current prediction model has a superior AUC regarding OS and DFS, the results would be more convincing with external validation. Third, the sample size of this study was relatively small.

Implications and actions needed

Thus, future studies should include data from various research centers and larger sample sizes to enhance the reliability and generalizability of the findings. Nevertheless,

our study provided important insight into the clinical management of high- and low-risk patients with stage IA lung ADC containing an MIP component.

Conclusions

This study found that the T1c stage, an MIP percentage $\geq 1\%$, STAS, a CEA level $>5 \mu\text{g/L}$, and Rad score were independent predictors of DFS and OS in patients with stage IA lung ADC containing an MIP component. We established and validated a nomogram based on clinicopathologic factors and radiomics features, which can be used as a powerful tool for predicting postoperative recurrence and survival in patients with stage IA lung ADC containing an MIP component.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tclr.amegroups.com/article/view/10.21037/tclr-24-544/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). The study was approved

by Institutional Ethics Committee of Cancer Hospital Affiliated to Shandong First Medical University (No. SDTHEC2023011030) and individual consent for this retrospective analysis was waived.

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