Original Article

Nomogram for predicting prognosis and identifying chemotherapy beneficiaries for completely resected stage I invasive mucinous lung adenocarcinoma

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Background: At present, there is a lack of studies in invasive mucinous adenocarcinoma (IMA) that combine clinicopathological and imaging features to stratify risk and select optimal treatment regimen. We aimed to develop and validate a nomogram for predicting recurrence-free survival (RFS) and identifying adjuvant chemotherapy (ACT) beneficiaries for completely resected stage I primary IMA.

Methods: This retrospective study included 750 patients from three hospitals. Patients from two hospitals were divided into training (n=424) and validating cohort (n=185), and patients from the remaining other one hospital constituted external test cohort (n=141) and preoperative computed tomography (CT) image features of each patient were consecutively evaluated. The nomogram was developed by integrating significant prognostic factors of RFS identified in the multivariate analysis. The risk score (RS) based on nomogram was calculated in the entire cohort and the optimal cut-off point for risk stratification was obtained by X-tile software. The Kaplan-Meier method, log-rank test and interaction were used to evaluate the difference in RFS and overall survival (OS) between different risk and treatment groups.

Results: Visceral pleural invasion (VPI, P<0.001), lymph-vascular invasion (LVI, P<0.001), tumor size (P<0.001), smoking history (P<0.001), lobulation (P<0.001) were identified as independent prognostic factors for RFS. The concordance index (C-index) of the nomogram was higher than that of tumor-node-metastasis (TNM) staging system (validation cohort: 0.73±0.09 *vs.* 0.62±0.08, P<0.001; external test cohort: 0.74±0.10 *vs.* 0.70±0.09, P=0.035). The patients with higher RS were associated with worse RFS [hazard ratios (HRs) ≥4.76] and OS (HRs ≥2.55) in all included cohorts. Chemotherapy benefits in terms of RFS and OS were observed for patients in higher RS group in both stage IB (interaction P=0.012 for RFS and P=0.037 for OS) and stage I IMA (interaction P<0.001 for both RFS and OS).

Conclusions: The nomogram based on CT image and clinicopathologic features showed superior performance in predicting RFS for stage I IMA and might identify ACT candidates for personalized patient treatment.

Keywords: Invasive mucinous adenocarcinoma (IMA); nomogram; recurrence-free survival (RFS); overall survival (OS); adjuvant chemotherapy (ACT)

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Introduction

The histopathological features of invasive mucinous adenocarcinoma (IMA) are tumors with goblet or columnar cells containing abundant intracytoplasmic mucin (1). IMA accounts for only 1.5–10% of all lung adenocarcinomas (2,3). The clinical, pathological, imaging, prognosis, and gene expression features are different from non-mucinous invasive adenocarcinoma and highly contradictory conclusions about prognosis have been drawn in different studies (4-6). Therefore, it is unclear whether the risk factors for recurrence and treatment guidelines of non-small cell lung cancer (NSCLC) also apply to IMA.

Complete surgical resection is regarded as the standard treatment of early-stage NSCLC (7). However, there is still a 30% of 5-year recurrence rate in completed resection stage I NSCLC (8), which implies that patients with a poorer prognosis might benefit from adjuvant chemotherapy (ACT). The National Comprehensive Cancer Network (NCCN) guideline of NSCLC version 2.2023 does not recommend ACT for stage IA (9). Different guidelines give inconsistent recommendations for stage IB patients (10,11) and different randomized controlled studies also showed discordant results (12-14). Optimizing ACT application depends on more precise prognostic stratification within the same stage and identifying those with high risk of recurrence.

Computed tomography (CT) is an important tool in lung cancer diagnosis and could assist prognosis estimation and treatment decision-making. Recently, Nie *et al.* (15) and Xie *et al.* (16) observed that nomogram based on radiomics signature showed good performance in prognostic prediction and identified ACT benefits of patients with resected stage I lung adenocarcinoma. Although radiomics has been shown to have a promising performance in the prognosis assessment of different types of cancer, it has not been applied in clinical practice due to the complex extraction process of imaging features. IMA presents unique CT findings like air bronchogram, and mixed air-space consolidation (17). Few studies focused on prognostic prediction by making use of CT imaging features in IMA and there is limited comprehensive imaging or clinicopathologic research on IMA due to its low incidence.

Nomograms, integrating and clarifying important prognostic factors for tumors, has been accepted as reliable tools to quantify risk (18) and showed better predictive performance than traditional tumor-node-metastasis (TNM) staging systems in several types of cancers (19,20). Therefore, this study aimed to develop and validate a nomogram combining CT imaging and clinicopathologic features to predict recurrence-free survival (RFS) in resected stage I IMA and to further explore its potential in identifying patients who can benefit from ACT. We present this article in accordance with the TRIPOD reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-675/rc).

Highlight box

Key findings

- The nomogram combined computed tomography imaging with clinicopathologic features showed superior performance in predicting recurrence-free survival and might identify adjuvant chemotherapy (ACT) candidates for stage I invasive mucinous lung adenocarcinoma.

What is known and what is new?

- The integrated nomogram displayed robust performance in prognostic prediction and risk stratification.
- The nomogram developed in our study could identify ACT beneficiaries.

What is the implication, and what should change now?

- The integrated nomogram was of great necessity for stage I invasive mucinous lung adenocarcinoma for guiding personalized treatment.

Methods

Patient selection

The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committees of The First Hospital of Lanzhou University (No. LDYYLL2023-70), The First Affiliated Hospital of Chengdu Medical College (No. 2023CYFYIRB-SQ-30), and the Henan Provincial People's Hospital (No. 2023-202). All participating hospitals were informed and agreed with the study. Written informed consents were waived for the retrospective cohort study. Three cohorts from three hospitals were included in this retrospective study (n=750) (Figure S1). A total of 609 patients who received complete resection with pathological stage I IMA from January 2011 to June 2020 were randomly divided into training cohort (n=424) and validating cohort (n=185) at a 7:3 ratio. A total of 141 patients diagnosed at another hospital during the same period were included as external test cohort. All patients who received complete resection and diagnosed with pathological stage I primary IMA according to the 8th TNM staging system (21) were identified. The exclusion criteria were as follows: (I) patients with a history of malignancy or accompanied by invasive non-mucinous adenocarcinoma or other types of lung cancer; (II) patients without thin-slice CT images within one month before surgery; (III) patients who were lost to follow-up or had incomplete clinicopathologic information.

The clinicopathological and demographic characteristics were retrieved from electronic medical databases of the three hospitals. Chemotherapy decisions were made by the attending physician based on the patient's general physical condition and pathologic reports as well as the patient's wishes. The basic regimen was platinum-based doublet chemotherapy (cisplatin or carboplatin) for four cycles, unless severe adverse effects occurred and other drugs included gemcitabine, vinorelbine, pemetrexed or paclitaxel.

Surgical procedures and pathological evaluation

All patients underwent lobectomy or segmentectomy with systematic lymph node dissection (SND) or lobe-specific lymph node dissection (L-SND). SND is defined as resection of at least three N1 nodes from three N1 stations in addition to at least three N2 nodes from three N2 stations including subcarinal lymph nodes (22). L-SND is performed by dissection of hilar lymph nodes and specific mediastinal lymph node stations depending on the lobar location of the primary tumor (stations 7, 8, and 9 for lower lobe tumors of both sides; stations 2R and 4R for right upper lobe tumors; and stations 4L, 5L and 6L for left upper lobe tumors). To ensure the quality of the retrospective study, two pathologists (10 and 15 years of experience in pathological diagnosis of lung cancer, respectively) re-evaluated all histological slides which were formalin-fixed and stained with hematoxylin and eosin.

Follow-up

The primary endpoint was RFS, which was defined as the time from surgery to the date of recurrence, death from any cause or last follow-up. Overall survival (OS) was defined as the time from surgery to death from any cause. Patients were followed up every three months within 2 years after surgery, then every 6 months for 3 to 5 years, and every 12 months thereafter. The chest CT scans, abdominal CT scans and ultrasonography of the supraclavicular regions were routinely performed to detect any evidence of recurrence at each scheduled visit. Brain magnetic resonance imaging (MRI) or brain CT and bone scanning were performed annually. Positron emission tomography/CT (PET/CT) scan or biopsy was recommended to confirm suspected recurrences. Telephone follow-up was also performed to complement the follow-up schedule.

CT image acquisition and interpretation

The CT imaging features of all patients were interpreted by two researchers using both the lung [width, 1,500 Hounsfield unit (HU); level, –400 HU] and mediastinal (width, 400 HU; level, 40 HU) window settings, which was verified and corrected by a senior thoracic surgeon. All the readers were blinded to the survival outcomes. The detailed CT scanning parameters are shown in Appendix 1. The CT imaging features were used to characterize the lesions and their surroundings including border (clear or obscured), lesion in non-tumor lobe (any lesions suspected to be malignant or indeterminate in other lobes), overall shape (round or irregular), tumor density (pure solid or sub-solid), location (peripheral tumor involved subsegmental bronchus or smaller airway; central tumor involved in the lobar or segmental proximal bronchi), emphysema, air bronchogram (tubelike or branching air structure within the tumor), patterns of usual interstitial pneumonia (UIP, with the signs of subpleural reticulations, traction bronchiectasis, or honeycombing area), obstructive pneumonia, pleural retraction, pleural attachment (tumor attaches to the pleura, which obscured the border), lobulation (deep or shallow), spiculation (fine or coarse), lymphadenopathy (hilar or mediastinal lymph node with size greater than 1 cm),

bubblelike lucency (mall air bubbles in the tumor less than 2–3 mm). Wang *et al.* described these CT image features in detail in previous research (23).

Statistical analysis

Continuous variables were compared using the *t*-test or Mann-Whitney rank-sum test and Pearson's Chi-square test or Fisher's exact test for Categorical variables. The Kaplan-Meier method and log-rank test were used to estimate survival curves. The independent factors of RFS were analyzed through multivariable Cox proportional hazards model with backward stepwise manner in training cohort. Multivariate analyses were conducted along with the hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. The nomogram was constructed based on independent risk factors to calculate the risk score (RS). Patients were stratified into the high- and low-risk groups based on the cut-off point of RS determined by X-tile software (version 3.6.1; Yale University School of Medicine, New Haven, Conn). Interaction between ACT and RS groups was assessed by the method of the Cox model. Performance of nomogram for predicting RFS was assessed by C-index, calibration curve and decision curve analysis.

All analyses were performed with SPSS software (version 25.0, IBM) and R software (version 3.6.2, www.R-project.org) with the following R packages: "survival", "rms". A two-sided P<0.05 indicated a significant difference.

Results

Patient characteristics

The demographic, clinicopathological characteristics, and CT imaging features of training (n=424), validating (n=185) and external test cohort (n=141) are summarized in *Tables 1*,*2*. The median age of the entire cohort was 61 years, 276 (36.8%) were male. There were 527 (70.3%), 223 (29.7%) IMA patients with stage IA and IB respectively. A total of 133 (17.7%) patients received ACT and 617 (82.3%) did not. The median follow-up time was 65.3 months in the training cohort, 68.0 months in the validating cohort, 79.7 months in the external test cohort.

Nomogram variable screening as well as construction and validation

After univariate analysis, the variables of Visceral pleural invasion (VPI, P<0.001), lymph-vascular invasion (LVI, P<0.001), tumor density (P=0.019), smoking history (P<0.001), tumor size (P<0.001), air bronchogram (P=0.002), pleural attachment (P=0.008), border (P=0.041) and lobulation (P<0.001) were entered into the multivariate COX regression analysis. In the multivariate Cox regression analysis, VPI (HR: 3.87; 95% CI: 2.39–6.26; P<0.001), LVI (HR: 4.24; 95% CI: 1.97–9.11; P<0.001), smoking history (HR: 2.43; 95% CI: 1.54–3.83; P<0.001), tumor size (0–<1: reference; 1–<2: HR: 2.19; 95% CI: 1.71–6.72; P=0.035; 2–<3: HR: 4.22; 95% CI: 1.33–13.38; P=0.015; 3–<4: HR: 10.21; 95% CI: 3.28–31.78; P<0.001), lobulation (absence: reference; shallow: HR: 1.99; 95% CI: 1.12–3.56; P=0.020; deep: HR: 3.36; 95% CI: 1.98–5.67; P<0.001) were significantly associated with RFS of patients with stage I IMA (*Table 3*). We constructed this nomogram according to the variables screened (*Figure 1A*). In the training cohort, the concordance index (C-index) of the nomogram was significantly greater than that of the TNM staging system (0.83±0.04 *vs.* 0.71±0.05, P<0.001). In the validation cohort, the C-index was higher for the nomogram than for the TNM category (0.73±0.09 *vs.* 0.62±0.08, P<0.001). In the external test cohort, the C-index was also higher for the nomogram than for the TNM category (0.74±0.10 *vs.* 0.70±0.09, P=0.035). Satisfactory agreements at 3 years and 5 years between actual observations and prediction outcomes were observed in three cohorts (*Figure 1B-1D*). The decision curves show with a threshold probability (possibility of recurrence in this study) of more than 8% or 9%, intervening (i.e., chemotherapy) on IMA based on the nomogram has a higher net benefit compared to the clinical default strategies of "treat all" or "treat none" in training, validating and external test cohorts (*Figure 1E-1G*).

Prognostic stratification depending on nomogram-based RS

Each variable in the nomogram was assigned a score on the point scale (Table S1). It was easy to draw a straight line down to determine the corresponding predicted probability of recurrence at each score point by accumulating the total RS. For example, a patient with a pathological 2.6-cm IMA, with smoking history, absent VPI or LVI, and showing deep lobulation on CT imaging, total RS =66.7+42.6+0+0+60.8=170.1 points. Then, the corresponding 3-year RFS for this patient was about 85% (Table S2). The optimal cutoff value determined by X-tile

Table 1 Demographic and clinicopathological characteristics of patients in three cohorts

Characteristics	Training cohort (N=424)	Validating cohort (N=185)	External test cohort (N=141)
Age			
<65 years	274 (64.6)	131 (70.8)	97 (68.8)
≥65 years	150 (35.4)	54 (29.2)	44 (31.2)
Gender			
Male	163 (38.4)	71 (38.4)	42 (29.8)
Female	261 (61.6)	114 (61.6)	99 (70.2)
Smoking history			
No	345 (81.4)	139 (75.1)	116 (82.3)
Yes	79 (18.6)	46 (24.9)	25 (17.7)
Tumor location			
Upper lobe	120 (28.3)	56 (30.3)	38 (27.0)
Non-upper lobe	304 (71.7)	129 (69.7)	103 (73.0)
Tumor size			
0–<1 cm	86 (20.3)	38 (20.5)	52 (36.9)
1–<2 cm	154 (36.3)	74 (40.0)	44 (31.2)
2–<3 cm	97 (22.9)	41 (22.2)	17 (12.1)
3–<4 cm	87 (20.5)	32 (17.3)	28 (19.9)
LVI			
Present	14 (3.3)	4 (2.2)	4 (2.8)
Absent	410 (96.7)	181 (97.8)	137 (97.2)
VPI			
Present	56 (13.2)	28 (15.1)	17 (12.1)
Absent	368 (86.8)	157 (84.9)	124 (87.9)
Surgery types			
Lobectomy	347 (81.8)	151 (81.6)	109 (77.3)
Segmentectomy	77 (18.2)	34 (18.4)	32 (22.7)
Adjuvant chemotherapy			
ACT	71 (16.7)	30 (16.2)	32 (22.7)
Non-ACT	353 (83.3)	155 (83.8)	109 (77.3)
Pathological subtype			
MMNA	24 (5.7)	11 (5.9)	6 (4.3)
IMA	400 (94.3)	174 (94.1)	135 (95.7)
Pathological TNM stage			
IA	296 (69.8)	128 (69.2)	103 (73.0)
IB	128 (30.2)	57 (30.8)	38 (27.0)

Values are numbers of patients with percentages in parentheses for categorical variables. LVI, lymphovascular invasion; VPI, visceral pleural invasion; IMA, invasive mucinous adenocarcinoma; MMNA, mixed mucinous and nonmucinous adenocarcinoma; ACT, adjuvant chemotherapy; non-ACT, without adjuvant chemotherapy.

Table 2 CT imaging features of patients in three cohorts

Characteristics	Training cohort (N=424)	Validating cohort (N=185)	External test cohort (N=141)
UIP pattern			
Absence	400 (94.3)	176 (95.1)	135 (95.7)
Presence	24 (5.7)	9 (4.9)	6 (4.3)
Obstructive pneumonia			
Absence	413 (97.4)	179 (96.8)	134 (95.0)
Presence	11 (2.6)	6 (3.2)	7 (5.0)
Lesion in non-tumor lobe			
Absence	394 (92.9)	174 (94.1)	128 (90.8)
Presence	30 (7.1)	11 (5.9)	13 (9.2)
Lymphadenopathy			
Absence	371 (87.5)	170 (91.9)	124 (87.9)
Presence	53 (12.5)	15 (8.1)	17 (12.1)
Air bronchogram			
Absence	398 (93.9)	170 (91.9)	128 (90.8)
Presence	26 (6.1)	15 (8.1)	13 (9.2)
Bubblelike lucency			
Absence	368 (86.8)	169 (91.4)	124 (87.9)
Presence	56 (13.2)	16 (8.6)	17 (12.1)
Tumor density			
Sub-solid	114 (26.9)	62 (33.5)	44 (31.2)
Pure-solid	310 (73.1)	123 (66.5)	97 (68.8)
Cavitation			
Absence	353 (83.3)	162 (87.6)	122 (86.5)
Presence	71 (16.7)	23 (12.4)	19 (13.5)
Pleural attachment			
Absence	326 (76.9)	147 (79.5)	112 (79.4)
Presence	98 (23.1)	38 (20.5)	29 (20.6)
Pleural retraction			
Absence	340 (80.2)	153 (82.7)	113 (80.1)
Presence	84 (19.8)	32 (17.3)	28 (19.9)
Spiculation			
Absence	302 (71.2)	135 (73.0)	99 (70.2)
Fine	81 (19.1)	34 (18.4)	28 (19.9)
Coarse	41 (9.7)	16 (8.6)	14 (9.9)

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Training cohort (N=424)	Validating cohort (N=185)	External test cohort (N=141)
Border			
Clear	354 (83.5)	158 (85.4)	118 (83.7)
Obscure	70 (16.5)	27 (14.6)	23 (16.3)
Lobulation			
Absence	227 (53.5)	103 (55.7)	78 (55.3)
Shallow	112 (26.4)	53 (28.6)	33 (23.4)
Deep	85 (20.0)	29 (15.7)	30 (21.3)
Location			
Peripheral	397 (93.6)	174 (94.1)	132 (93.6)
Central	27 (6.4)	11 (5.9)	9 (6.4)
Emphysema			
Absence	381 (89.9)	168 (90.8)	127 (90.1)
Presence	43 (10.1)	17 (9.2)	14 (9.9)
Overall shape			
Round	140 (33.0)	53 (28.6)	49 (34.8)
Irregular	284 (67.0)	132 (71.4)	92 (65.2)

Values are numbers of patients with percentages in parentheses for categorical variables. UIP, usual interstitial pneumonia.

was 161.60 in the training cohort and the same cutoff value was used in the analysis of both validating and external test cohorts. There was significant difference in both RFS (adjusted HRs ≥4.76, P<0.001 for all cohorts) and OS (adjusted HRs ≥2.55, P<0.001 for training and validating cohort and P=0.010 for external test cohort) between the low- and high-risk groups after adjusting age, gender, surgery type, pathological subtype through multivariate analyses (*Figure 2A-2F*). Furthermore, the RS showed good prognostic stratification ability of RFS (Figure S2) and OS (Figure S3) in the clinic subgroups of all patients, including tumor size, gender, age, and pathological TNM stage. Comparing the characteristics of the high-and low-risk groups indicated that high-risk group accounted for more patients with male, smoker, larger tumor size, LVI presence, VPI presence, and CT imaging features with pure-solid, air bronchogram, pleural attachment, deep lobulation, and peripheral lesions (P<0.05) and patients in high-risk group were more likely to undergo lobectomy and receive chemotherapy (Table S3). Compared with patients in the non-ACT group, the ACT group had more patients with stage IB, larger tumor, presence of VPI, and male smokers who underwent lobectomy (Table S4).

ACT benefits analysis based on the nomogram

All patients with stage I IMA did not obtain RFS or OS improvement when they received indiscriminate ACT, even stage IB patients (Figure S4). The association between the two risk groups and survival was explored among stage I IMA from the entire cohorts (n=750) who received or did not receive ACT to assess the predictive value of nomogram. For RFS, patients in the high-risk group defined by the nomogram showed a favorable response to chemotherapy, while patients in low-risk group even showed detriment from chemotherapy in the stage I IMA (interaction P<0.001; *Figure 3A*). The interaction between risk groups and ACT efficacy was further tested in the stage IA and IB subgroups. Patients in the high-risk group of stage IB could obtain survival benefit from the ACT, while those in the low-risk group did not (interaction P=0.012; *Figure 3B*). In the stage IA subgroup, there was

Table 3 Univariate and multivariate COX regression analysis for predicting the RFS

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
VPI		<0.001		<0.001
Presence *vs.* absence	4.81 (3.10–7.47)		3.87 (2.39–6.26)	
LVI		<0.001		<0.001
Presence *vs.* absence	5.64 (2.72–11.72)		4.24 (1.97–9.11)	
Gender		0.268		
Male *vs.* female	1.28 (0.83–1.97)			
Tumor density		0.019		0.088
Pure-solid *vs.* sub-solid	2.03 (1.12–3.67)		0.55 (0.28–1.09)	
Smoking history		<0.001		<0.001
Yes *vs.* no	3.46 (2.23–5.36)		2.43 (1.54–3.83)	
Tumor size (cm)		<0.001		<0.001
1–<2 *vs.* 0–<1	2.98 (2.02–8.68)	0.005	2.19 (1.71–6.72)	0.035
2–<3 *vs.* 0–<1	6.25 (2.18–17.96)	<0.001	4.22 (1.33–13.38)	0.015
3–<4 *vs.* 0–<1	11.56 (4.10–32.59)	<0.001	10.21 (3.28–31.78)	<0.001
Age (years)		0.604		
≥65 *vs.* <65	0.89 (0.56–1.40)			
Tumor location		0.738		
Upper *vs.* non-upper lobe	0.92 (0.57–1.49)			
Surgery types		0.193		
Lobectomy *vs.* segmentectomy	0.66 (0.35–1.24)			
Pathology		0.594		
MMNA *vs.* IMA	0.76 (0.28–2.08)			
Adjuvant chemotherapy		0.090		
ACT *vs.* non-ACT	1.54 (0.94–2.52)			
Location		0.253		
Central *vs.* peripheral	1.53 (0.74–3.17)			
UIP pattern		0.759		
Presence *vs.* absence	0.85 (0.31–2.33)			
Obstructive pneumonia		0.587		
Presence *vs.* absence	1.38 (0.43–4.36)			
Lesion in non-tumor lobe		0.628		
Presence *vs.* absence	1.21 (0.56–2.62)			
Lymphadenopathy		0.660		
Presence *vs.* absence	0.86 (0.43–1.71)			

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Air bronchogram		0.002		0.856
Presence *vs.* absence	2.67 (1.42–5.04)		0.94 (0.46–1.90)	
Bubblelike lucency		0.406		
Presence *vs.* absence	1.28 (0.72–2.27)			
Cavitation		0.134		
Presence *vs.* absence	1.48 (0.89–2.47)			
Pleural attachment		0.008		0.645
Presence *vs.* absence	1.86 (1.18–2.94)		1.13 (0.68–1.87)	
Pleural retraction		0.753		
Presence *vs.* absence	0.92 (0.53–1.58)			
Spiculation		0.070		
Fine *vs.* absence	1.82 (1.11–2.98)	0.017		
Coarse *vs.* absence	1.40 (0.71–2.76)	0.329		
Border		0.041		0.296
Obscure *vs.* clear	0.45 (0.21–0.97)		0.65 (0.28–1.47)	
Lobulation		<0.001		<0.001
Shallow *vs.* absence	2.41 (1.37–4.24)	0.002	1.99 (1.12–3.56)	0.020
Deep *vs.* absence	4.88 (2.91–8.20)	<0.001	3.36 (1.98–5.67)	<0.001
Emphysema		0.733		
Presence *vs.* absence	0.88 (0.43–1.83)			
Overall shape		0.473		
Irregular *vs.* round	0.84 (0.53–1.35)			

Values are numbers of patients with percentages in parentheses for categorical variables. LVI, lymphovascular invasion; VPI, visceral pleural invasion; IMA, invasive mucinous adenocarcinoma; MMNA, mixed mucinous and nonmucinous adenocarcinoma; ACT, adjuvant chemotherapy; non-ACT, without adjuvant chemotherapy; UIP, usual interstitial pneumonia; CI, confidence interval; RFS, recurrence-free survival; HR, hazard ratio.

no significant interaction of RFS (interaction P=0.170; *Figure 3C*).

For OS, patients in the high-risk group showed a favorable response to chemotherapy, while patients in low-risk group even showed detriment from ACT in the stage I IMA (interaction P<0.001; *Figure 4A*). Patients in the high-risk group of stage IB could obtain survival benefit from the ACT, while those in the low-risk group did not (interaction P=0.037; *Figure 4B*). In the stage IA subgroup, patients in the high-risk group showed no survival benefit from ACT, but the low-risk group showed a shorter OS in the ACT group compared to the non-ACT group (interaction P=0.012; *Figure 4C*).

Discussion

IMA is a unique subtype of lung adenocarcinoma and it is unclear whether guidelines for lung adenocarcinoma apply to IMA. In addition, whether patients with stage I lung adenocarcinoma could benefit from chemotherapy

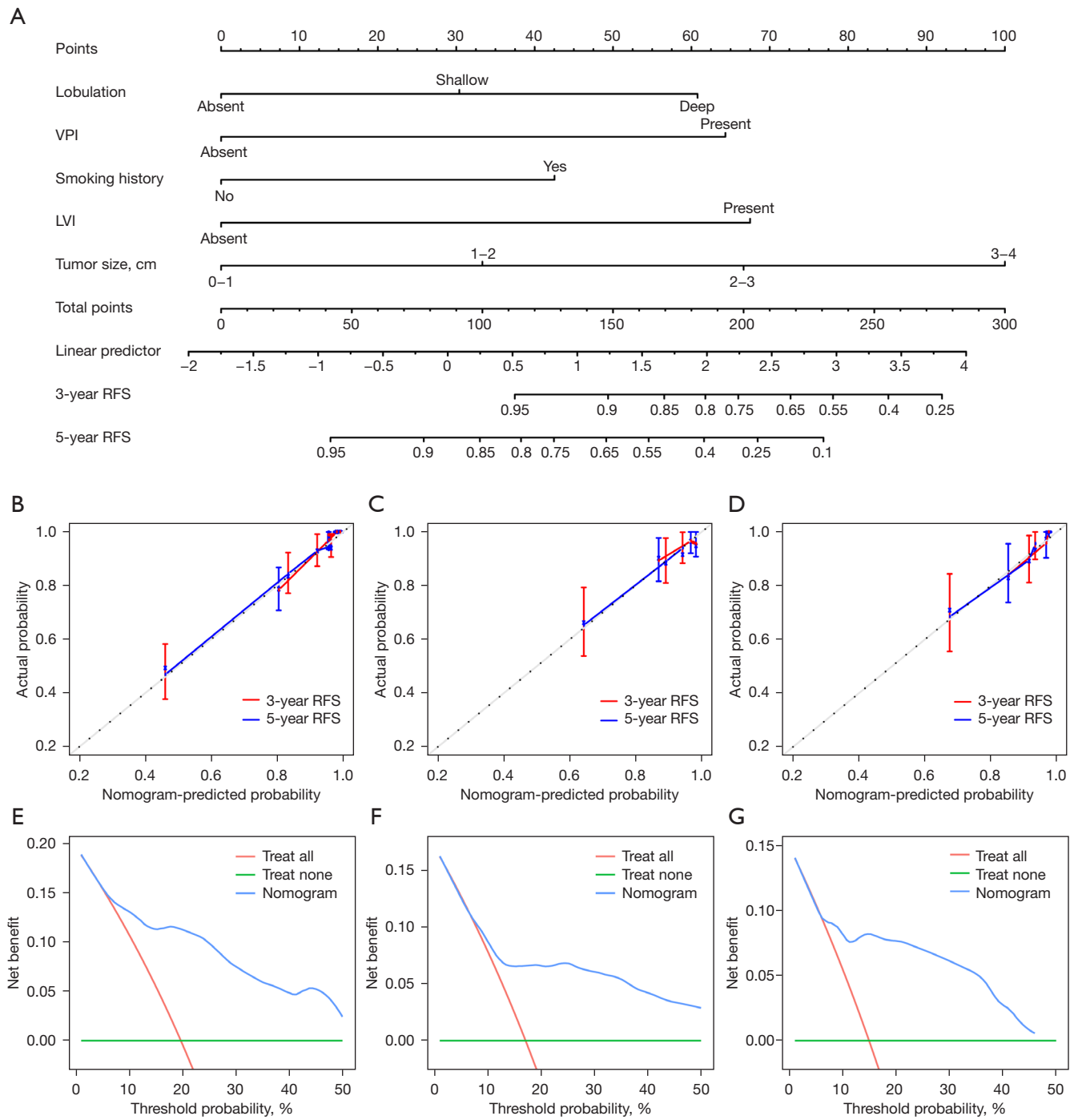

Figure 1 Nomogram, calibration curves and decision curves for estimating RFS. The nomogram for predicting 3- and 5-year RFS (A). The calibration curves for nomogram in terms of agreement between the predicted and observed 3- and 5-year RFS in training cohort (B), validating cohort (C) and external test cohort (D). The decision curves of the nomogram in the training cohort (E), validating cohort (F) and external test cohort (G). VPI, visceral pleural invasion; LVI, lymphovascular invasion; RFS, recurrence-free survival.

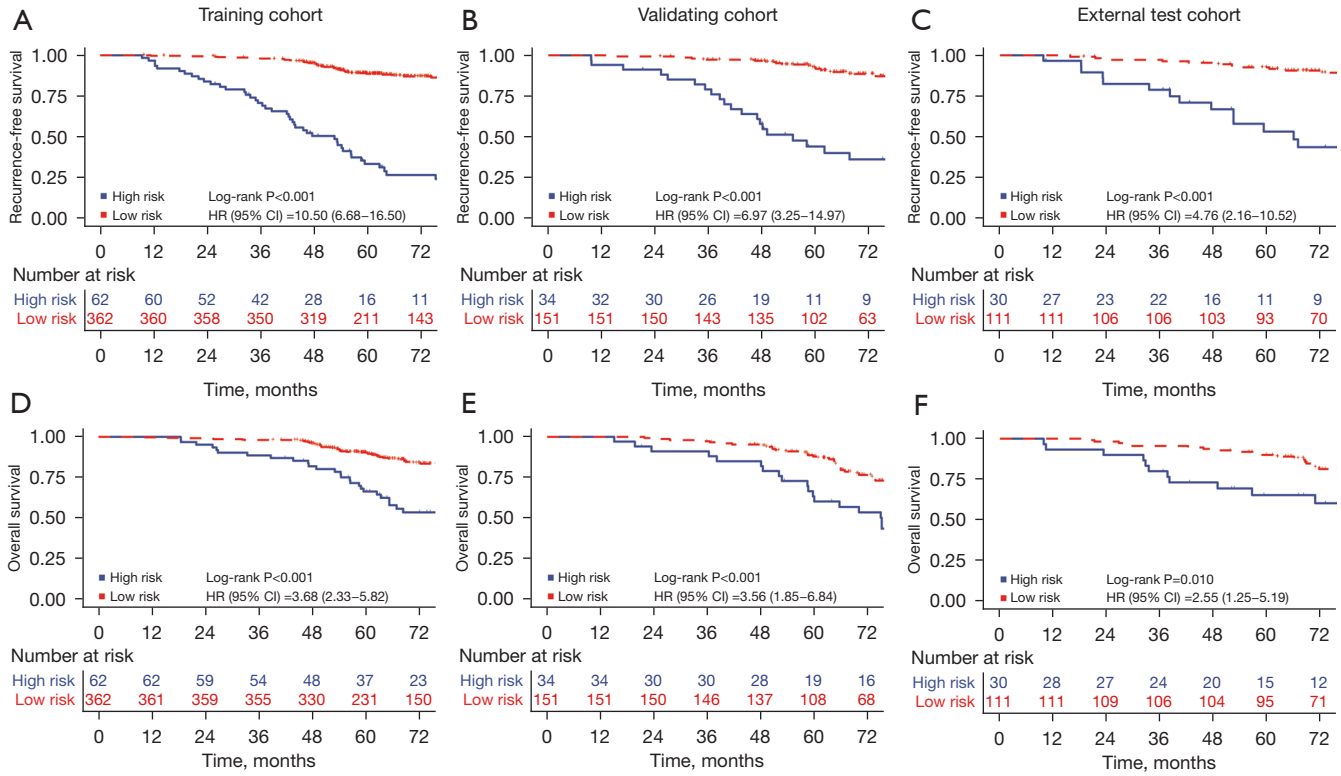

Figure 2 Kaplan-Meier curves according to two risk groups defined by the nomogram. Kaplan-Meier curves of RFS and OS in low- and high-risk groups in training cohort (A,D), validating cohort (B,E) and external test cohort (C,F). P values were calculated using two-sided log-rank test. RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio.

is controversial, especially in stage IB. In this study, we constructed a nomogram based on clinicopathologic and CT imaging features and validated its performance for predicting RFS of patients with completely resected stage I IMA in three cohorts from three hospitals. Furthermore, the nomogram not only displayed a satisfactory performance in prognostic prediction and risk stratification, but also could identify beneficiaries of chemotherapy in resected stage I IMA, especially in stage IB.

It is ambiguous about administration of ACT on stage IB adenocarcinoma in current guidelines. Recurrence is the main cause of nearly 18–32% stage I NSCLC death within 5 years after surgery (24,25). It is essential to have postoperative RFS evaluation to guide individualized patient's follow-up and treatment strategies because patients with high risk of recurrence are more likely to benefit from ACT theoretically. However, most current studies use a single RFS as the study endpoint about postoperative adjuvant therapy benefit (26,27). It is insufficient to use only RFS as the primary endpoints, given that the main goal of cancer treatment is to improve OS. Therefore, it is reasonable and necessary to use RFS as the study endpoint to screen patients who benefit from chemotherapy and evaluate whether OS benefit is obtained at the same time. Thus, we constructed a nomogram to predict RFS in resected stage I IMA patients and to explore whether selective chemotherapy could bring OS benefit ultimately.

The outcomes of our study indicated that patients who received ACT without selection could not obtain survival benefits even with patients in stage IB (P=0.076 for RFS, P=0.120 for OS). The study of Nie *et al.* (15) showed good prognostic predictive performance and predictive role for chemotherapy benefit in stage I adenocarcinoma (interaction P<0.001) by using radiomics signature. Xie *et al.* (16) also found that radiomics signature showed good disease-free survival (DFS) predictive performance with C-index of 0.71 and identified patients at high risk for recurrence who could benefit from chemotherapy (P=0.040). Two previous

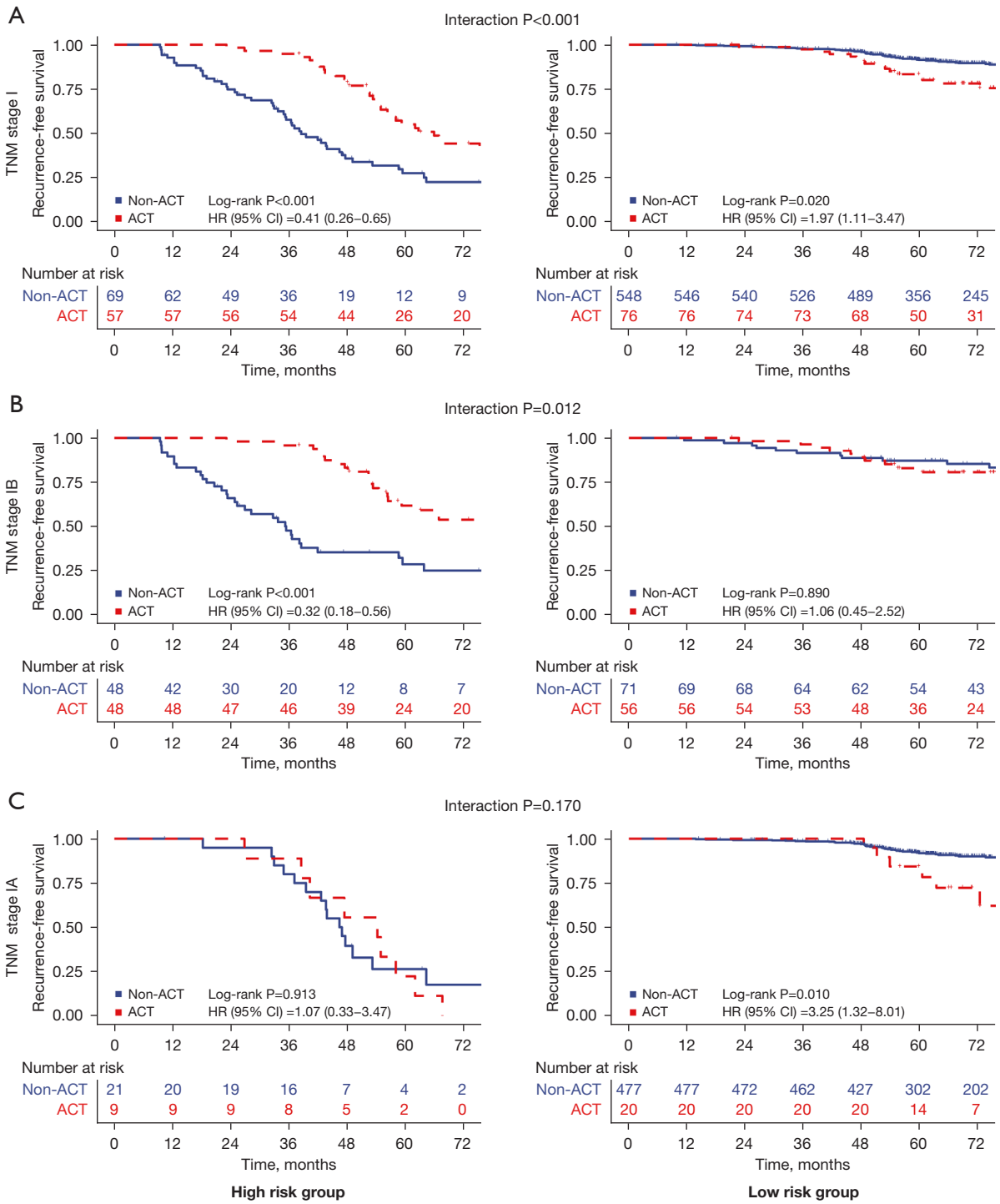

Figure 3 Kaplan-Meier curves of RFS according to the two treatment groups. The benefit analysis of ACT for RFS is stratified by treatment with ACT *vs.* non-ACT in patients with high or low risk group in stage I (A), stage IB (B), and stage IA (C) IMA. TNM, tumor-node-metastasis; ACT, adjuvant chemotherapy; non-ACT, without ACT; HR, hazard ratio; RFS, recurrence-free survival; IMA, invasive mucinous adenocarcinoma.

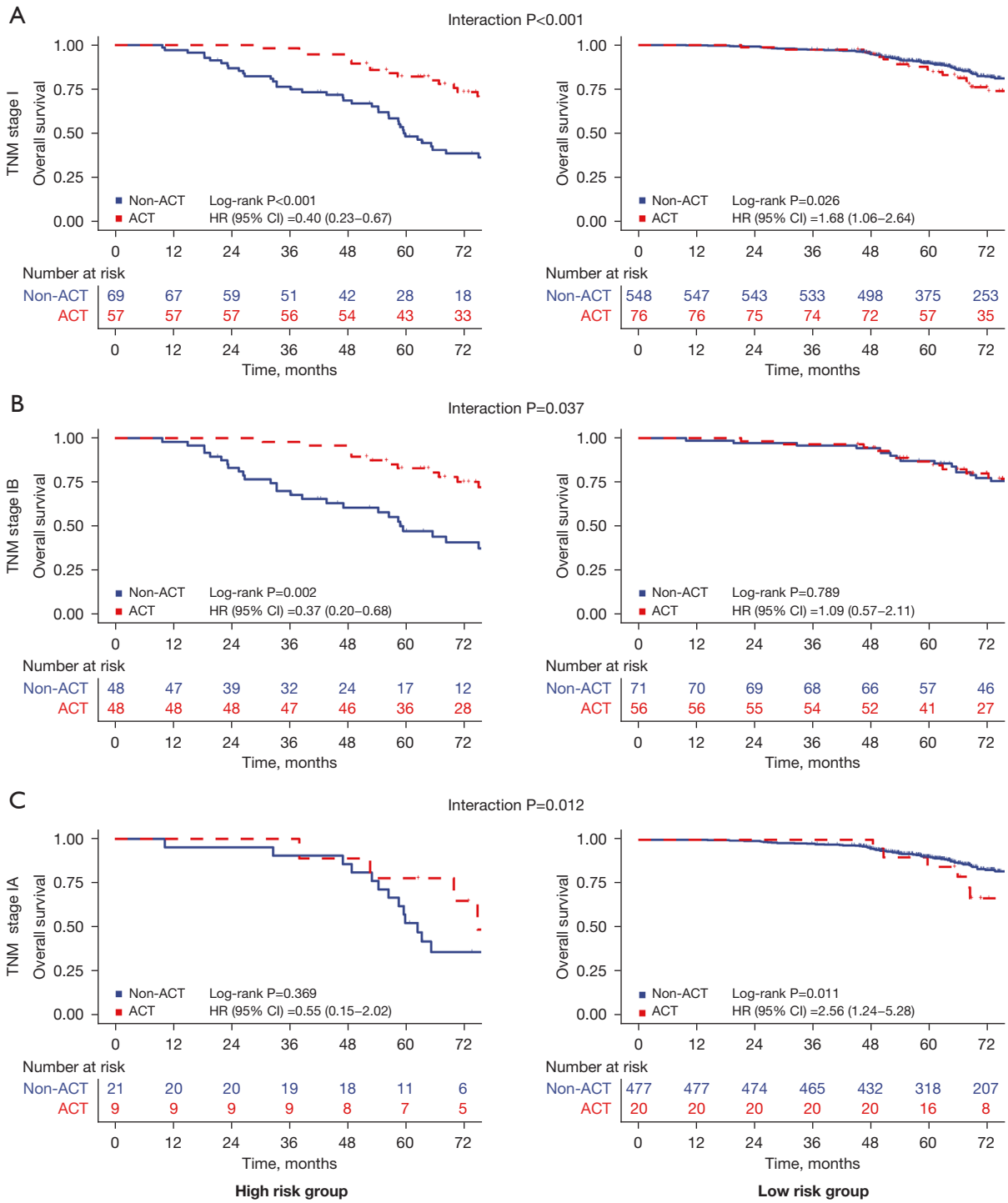

Figure 4 Kaplan-Meier curves of OS according to the two treatment groups. The benefit analysis of ACT for OS is stratified by treatment with ACT *vs.* non-ACT in patients with high- or low-risk group in stage I (A), stage IB (B), and stage IA (C) IMA. TNM, tumor-node-metastasis; ACT, adjuvant chemotherapy; non-ACT, without ACT; HR, hazard ratio; OS, overall survival; IMA, invasive mucinous adenocarcinoma.

studies indicated that patients with high-risk factors in stage IB could benefit from ACT (26,28). Consistent with these studies, we constructed a nomogram based on RFS predictions which demonstrated stage I IMA patients especially stage IB with high risk of recurrence could obtain survival benefits from chemotherapy. However, the study found that ACT was harmful for patients with stage IA even in high-risk group, which was accordance with previous studies (29).

Different risk factors have been reported in different studies and even have drawn conflicting conclusions about whether stage I adenocarcinoma could benefit from chemotherapy. One of the reasons for the contradictory conclusions may be that the absence of further risk stratification in stage I patients with survival heterogeneity masks the potential benefit of chemotherapy. VPI and LVI were identified as high-risk factors in this nomogram which were in accordance with current NCCN guidelines (10). Pathological T1 patients with VPI have been upgraded to T2 in the 8th edition TNM staging for lung cancer (30). The abundant lymphatic connections between the visceral pleura and lung parenchyma converge to the hilar lymph nodes, and lung cancers involving the visceral pleura have a poor prognosis and a higher risk of local and distant recurrence (31). Hamanaka *et al.* (32) demonstrated that both VPI and LVI are significant factors of poor prognosis in early-stage NSCLC. Therefore, some researchers (33,34) have proposed including LVI into the T stage as LVI has been demonstrated as a poor prognostic factor. Other factors such as advanced age, tumor size, sex, histological subtypes have also been reported as significant factors affecting survival (35,36). Interestingly, the proportion of female in our study are greater than male (63.2% *vs.* 36.8%). This is consistent with previous two studies with the proportion of female being 59.5% (37), and 61.0% (38) respectively. The phenomenon may be due to hormonal differences between men and women. But this is still a hypothesis, and reasons still need to be explored in depth. In addition to these clinicopathological factors, CT images are also considered a valuable tool for providing prognostic information (39). The lobulation in CT imaging corresponds to the different growth rates of pulmonary tumors in different directions, with tumor cells invading peripheral tissues which may attribute to tumor recurrence. Different from the conclusion of Wang *et al.*, our study did not find that spiculation and air bronchogram were related to increased HR of tumor recurrence (23). This may be related to the fact that only stage I patients were included in this study (tumor with size less than 2 cm account for 49.1%) resulting in failing to exhibit certain distinct tumor features of pulmonary lesions.

Nevertheless, the limitations of the present study should be acknowledged. First, this is a retrospective study, and selection bias are inevitable. Second, potential risk factors for recurrence such as spread through air space (STAS) and maximum standardized uptake value (SUVmax) of PET/CT were not included in this study. Third, molecular characteristics of IMA and the relationship between molecular profiling with histologic features and clinical outcomes were not analyzed. When potential molecular targeted therapies are available, the driver of mutations may be clinically significant. Further studies, including genetic information and treatment outcome of IMAs, are warranted in the future. Fourth, we did not analyze chemotherapy-related toxicities because of the large time span of the study and the lack of detailed documentation of chemotherapy-related adverse events in most patients.

Conclusions

In conclusion, we developed and validated a nomogram based on clinicopathologic and CT imaging features to precisely predict the likelihood of recurrence in stage I IMA after radical resection. This nomogram could assist physicians to provide personalized recommendations about whether to administer chemotherapy for stage I IMA patients by confirming that patients at high-risk would benefit from ACT.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-675/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-675/dss

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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-23-675/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 was approved by the Ethics Committees of The First Hospital of Lanzhou University (No. LDYYLL2023-70), The First Affiliated Hospital of Chengdu Medical College (No. 2023CYFYIRB-SQ-30), and the Henan Provincial People's Hospital (No. 2023-202). All participating hospitals were informed and agreed with the study. Written informed consents were waived for the retrospective cohort study.

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