Reviewer A' Comments:

Comment 1: Please give more detail on how the nomogram is generated, and how it is to be used. This is not clear from the text. How are the points calculated? How is the linear predictor scale used?

Reply:

We appreciate the reviewer for this critical recommendation and we have add corresponding description about how the nomogram is generated, how it is to be used, how are the points calculated and how is the linear predictor scale used.

Changes in the text:

Line 213: Nomogram variable screening as well as construction and validation

Line 214-222: After univariate analysis, the variables of VPI (p<0.001), 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)*.

Line 229-232: 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, VPI or LVI absence, 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 S1 -revised:

point assignment of each prognostic factor in nomogram and RFS rate corresponding to RS

Prognostic factor	Score
Lobulation	
Absent	0
Shallow	30.4
Deep	60.8
Smoking history	
No	0
Yes	42.6
VPI	
Absent	0
Present	64.3
LVI	
Absent	0
Present	66.7
Tumor size (cm)	
0-1	0
1-2	33.3
2-3	66.7
3-4	100

Notes: LVI, lymphovascular invasion; VPI, visceral pleural invasion

RS	3-year RFS (%)
112	0.95
148	0.90
170	0.85
185	0.80
198	0.75
218	0.65
234	0.55
255	0.40
276	0.25

RS	5-year RFS (%)
42	0.95
78	0.90
99	0.85
115	0.80
127	0.75
147	0.65
164	0.55
185	0.40

| 205 | 0.25 |
| 231 | 0.10 |

Comment 2: Fig 1- please explain the meaning of the decision curves. They are very hard to interpret for the non-expert

Reply:

We thank the reviewer for this significant suggestion. The y-axis of decision curves is benefit and x-axis is preference. When considering chemotherapy for stage I IMA, physicians are concerned both about the side effects of unnecessary chemotherapy and about missing treatment in patients who are at high risk of recurrence and may benefit from chemotherapy. Doctors may also vary in their propensity to intervene, some being more aggressive, others more conservative. If a doctor has a preference towards the left end of the x-axis weighs the relative harm of missing treatment as much greater than the harm of unnecessary treatment. A doctor with a preference for a given patients towards the right of the x-ais wants to avoid unnecessary treatment if possible.

Changes in the text:

Line 226-227: 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).*

Comment 3: Figure 3- please label the high- and low-risk groups (ie left column and right column)- this will help with interpretability.

Reply:

Thank you for this significant suggestion and we have labeled the high- and low-risk groups at the bottom of the picture.

Figure 3-revised:
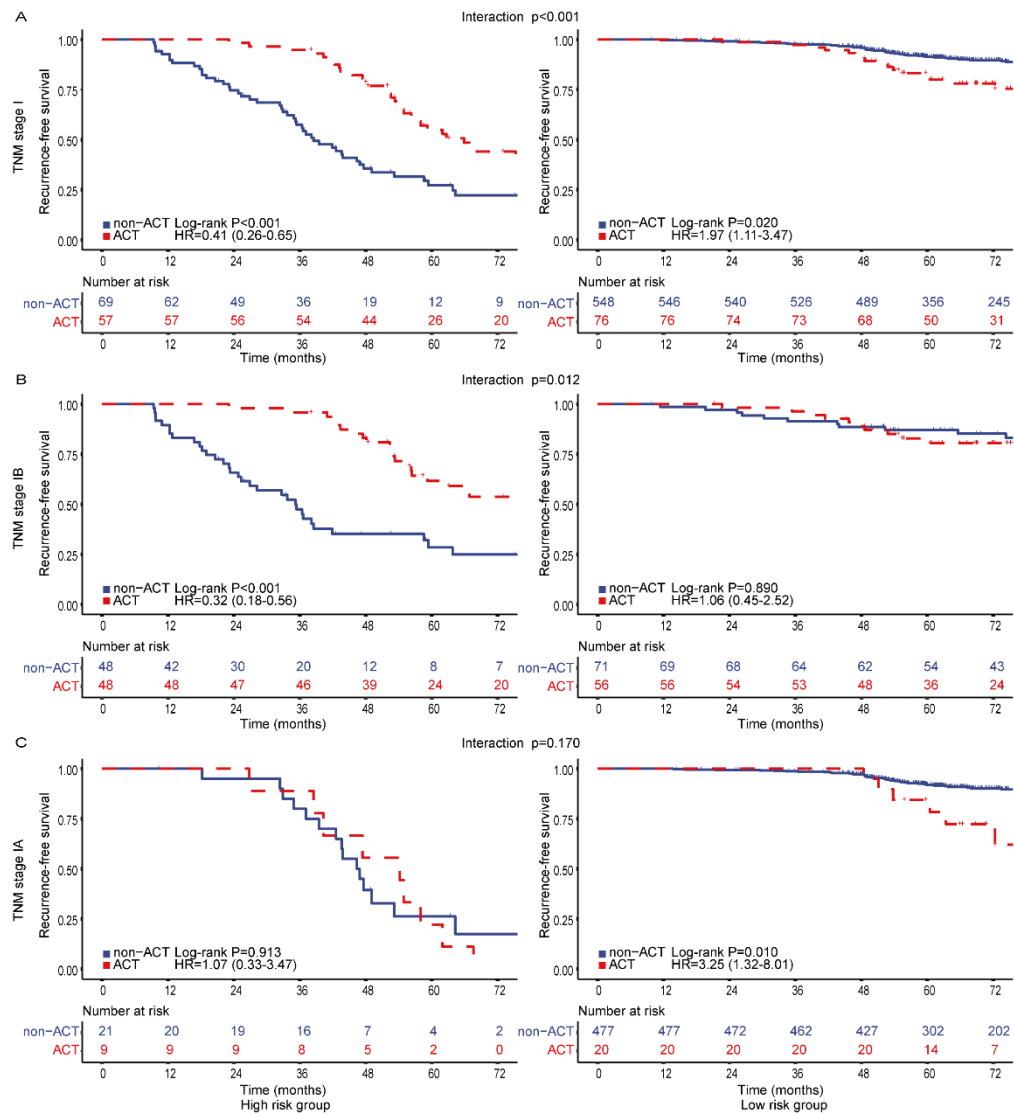
Comment 4: There is a dramatic bias towards female patients in the cohorts studied. Please comment on this, and compare to previous cohorts

Reply:

We thank the reviewer for this significant suggestion about gender bias in IMA patients of this study. We have added corresponding comment on this and compared to previous cohorts.

Changes in the text:

Line 315-316: Other factors such as advanced age, tumor size, sex, histological subtypes have also been reported as significant factors affecting survival [34, 35]. 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% [36], 61.0% [37] 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.

[36] Wang Y, Liu J, Huang C, Zeng Y, Liu Y, Du J. Development and validation of a nomogram for predicting survival of pulmonary invasive mucinous adenocarcinoma based on surveillance, epidemiology, and end results (SEER) database. *BMC cancer.* 2021;21(1):148.
[37] Chang JC, Offin M, Falcon C, et al. Comprehensive Molecular and Clinicopathologic Analysis of 200 Pulmonary Invasive Mucinous Adenocarcinomas Identifies Distinct Characteristics of Molecular Subtypes. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2021;27(14):4066-4076.

Reviewer B

Comment 1: As the authors touched upon in the discussion, the diagnosis and pathologic features were based on the pathologic report. Thus, I am concerned about the eligibility of study cases.

IMA is known to spread the adjacent lung parenchyma along with mucin often in a skip manner. Thus, an evaluation of the resection margin status can be challenging. Similar to those with STAS, no tumor cells at representative sections from the resection margin may not guarantee that no tumor tissue is left in the residual lung, in particular when the tumor is large and exhibits extensive "lepidic" pattern (lining alveolar walls) and/or acellular mucin is at or close to the resection margin. Therefore, careful re-review by a pathology co-author or two is warranted

Reply:

We appreciate the reviewer for pointing this out. According to the comment. Histological slides of all patients were re-reviewed by two pathologists.

Changes in the text: add a new section between line 157 and line 158

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.

[22] M.B. Amin, F.L. Greene, S.B. Edge, C.C. Compton, J.E. Gershenwald, R.K. Brookland, L. Meyer, D.M. Gress, D.R. Byrd, D.P. Winchester, The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging, CA: a cancer journal for clinicians 67(2) (2017) 93-99.

Line 4-16:

Hua He MD[1#], Xiaofei Zeng MD [2#], Quan Zhang MD [3#], Wenteng Hu MD [4], Rongfei Huang MD[5], Hongxin Zhao MD[6], Shuo Sun MD [4], Ruijiang Lin MD [4], Peng Yue MD [4], Biao Han MD [4], Minjie Ma MD [4]*, Chang Chen PHD [1, 4]*

[1] The First School of Clinical Medicine, Lanzhou University, Lanzhou, Gansu, 730030, China.

2 School of Clinical Medicine, Chengdu Medical College. Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chengdu Medical College, Chengdu 610500, Sichuan Province, China.

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5 Department of Pathology, The First Affiliated Hospital of Chengdu Medical College, Chengdu 610500, Sichuan Province, China.

6 Department of Pathology, The First Hospital of Lanzhou University, Lanzhou, Gansu, 730030, China.

Line 37: (IV) Collection and assembly of data: H He, X Zeng, Q Zhang, W Hu, R Huang, H Zhao, S Sun, R Lin, P Yue

Line 327-329: Second, potential risk factors for recurrence such as spread through air space (STAS) and maximum standardized uptake value (SUVmax) of PET/CT was not included in this study.

Comment 2: Given the difference in pathologic features and aggressiveness associated with certain genetic alterations and potential targeted therapy (upon recurrence) in IMA (33947695), molecular profiling in study cases (even in a subset) would be ideal.

Reply:

We appreciate the reviewer for pointing out this critical and significant recommendation. In recent years, the rapid development of molecular detection and immunohistochemistry technology has further opened the era of individualized treatment of lung cancer. Definitive correlations between genetic variants and histological features still require further research, such as comparative studies of genomic landscapes or mechanistic validation. In order to achieve more individualized treatment, few study have begun to focus on whether IMA has genetic variations or cancer-causing characteristics that differ from common subtypes. The research in this area is still in the preliminary exploration stage due to various reasons. Similarly, due

to the limitations of objective and subjective conditions in all aspects of our research institution, molecular spectrum analysis cannot be carried out immediately. In view of this critical suggestion from the reviewers, we plan to further explore the relationship between molecular profiling with histologic features and clinical outcomes in the future.

Changes in the text:

Line 329-331: 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.

Comment 3: IMA is known to recur after a very long interval (33839364). I am not certain whether the average 6-year follow-up is long enough.

Reply: Thank you for pointing this critical issue out. The study included patients over a relatively large time span (nearly 10 years from January 2011 to June 2020) which resulted in average 6-year follow-up. However, nearly half of patients (45.2%, 339/750) being followed more than 6 years. In addition, Of the 148 patients who relapsed in this study, only two patients relapsed more than eight years after surgery (at 9.2 and 9.3 years, respectively). Previous studies have reported a remarkable subset of IMA patients in whom intrapulmonary spread manifested after an exceptionally long latency, which may be due to the following reasons: 1. The follow-up strategy was not described in detail in this study, we cannot rule out the possibility of resuming follow-up after the loss of follow-up. 2.The study only reported the interval of recurrence in the lung, and it is unclear whether there was recurrence at other sites before lung recurrence. Therefore, an average follow-up of 6 years may be sufficient for this study.

Comment 4: Nomogram: HR of shallow lobulation with absent as the reference was 0.98. I am not certain why 30 points were given to the shallow lobulation in the nomogram.

Reply:

Thank you for your valuable comments to help us improve the quality of our manuscripts. This is a clerical error and we have made corresponding modification.

Changes in the text:

Line 214-222: After univariate analysis, the variables of VPI (p<0.001), 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)*.

Table 3-revised:

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		

	HR (95% CI)	p	HR (95% CI)	p
≥65 years vs <65 years	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		0.09		
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)			
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)	

Minor issues:

1. Lines 112-113: The version of the NCCN guideline should be updated.

Reply: Thank you for pointing this out and we have made corresponding modification.

Changes in the text:

Line 112-113: The NCCN guideline of NSCLC version 2.2023 does not recommend adjuvant chemotherapy for stage IA [9]

[9] Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines® Insights: Non-Small Cell Lung Cancer, Version 2.2023. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2023;21(4):340-350.

2. Emphysema was classified as obscure vs. clear. What do they mean?

Reply: Thank you for pointing this out. It's a clerical error, Emphysema was classified as presence vs absence. we have made corresponding modification.

Changes in the text:

Line179: bronchi), emphysema, air bronchogram (tubelike or branching air structure within the

Table 3-revised:

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)	

Variable	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
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 years vs <65 years	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		0.09		
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)			
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)			

In addition, there are numerous problems in the text; thus, it is worth editing / proofreading by a native English speaker in the field. One of the examples is as follows:

1. Lines 184-186: ….bubblelike lucency (mall air bubbles in the tumor less than 2–3 mm). Wang et al. described detailly these CT image features in previous research [22].

Reply: Thank you for pointing this out and this manuscript has been edited and proofread by a native English speaker in the field and we have made corresponding modification.

Changes in the text:

Line184-186: bubblelike lucency (mall air bubbles smaller than 2–3 mm within the tumor). Wang et al. described these CT image features in detail in previous research [22].

Comment 1: 1.I understand that prognostic factors were extracted in this study and that

a nomogram based on these factors would be useful.

However, it is questionable whether it is conclusive that postoperative adjuvant chemotherapy for high-risk groups is effective.

Provide the patient background of patients who received adjuvant treatment. Provide the background of patients who received and did not receive adjuvant treatment in the overall population, high-risk group and low-risk group respectively, and make statistical group comparisons.

Reply:

We appreciate the reviewer for pointing this out. According to the comment. We have provided the background of patients who received and did not receive adjuvant chemotherapy in the overall population, high-risk and low-risk group respectively and then Chi-square tests were used to statistically compare the results between the groups. The results are as follows, which we have described in the corresponding places in the manuscript.

supplements in the text:

Table S2

Demographic and clinicopathological characteristics of high risk and low risk group

Characteristics	High-risk group (N=126)	Low-risk group (N=624)	P value
Age (n, %)			0.128
<65 years	77 (61.1)	425 (68.1)	
≥65 years	49 (38.9)	199 (31.9)	
Gender (n, %)			**<0.001**
Male	69 (54.8)	207 (33.2)	
Female	57 (45.2)	417 (66.8)	
Smoking history (n, %)			**<0.001**
No	37 (29.4)	563 (90.2)	
Yes	89 (70.6)	61 (9.8)	
Tumor location (n, %)			0.992

Upper lobe	36 (28.6)	178 (28.5)	
Non-upper lobe	90 (71.4)	446 (71.5)	
Tumor size (cm)			**<0.001**
0-1	0	176 (18.2)	
1-2	6 (4.8)	266 (42.6)	
2-3	53 (42.0)	102 (16.3)	
3-4	67 (53.2)	80 (12.8)	
LVI (n, %)			**<0.001**
Presence	19 (15.1)	3 (0.5)	
Absence	107 (84.9)	621 (99.5)	
VPI (n, %)			**<0.001**
Presence	57 (45.2)	44 (7.1)	
Absence	69 (54.8)	580 (92.9)	
Surgery types (n, %)			**<0.001**
Lobectomy	118 (93.7)	489 (78.4)	
Segmentectomy	8 (6.3)	135 (21.6)	
Adjuvant chemotherapy (n, %)			**<0.001**
ACT	57 (45.2)	76 (12.2)	
Non-ACT	69 (54.8)	548 (87.8)	
Pathological subtype (n, %)			0.077
MMNA	11 (8.7)	30 (4.8)	
IMA	115 (91.3)	594 (95.2)	
Tumor density (n, %)			**<0.001**
Sub-solid	7 (5.6)	213 (34.1)	
Pure-solid	119 (94.4)	411 (65.9)	
UIP pattern (n, %)			0.844
Absence	7 (5.6)	32 (5.1)	
Presence	119 (94.4)	592 (94.9)	
Obstructive pneumonia (n, %)			0.404
Absence	120 (95.2)	606 (97.1)	
Presence	6 (4.8)	18 (2.9)	
Lesion in non-tumor lobe (n, %)			0.714
Absence	118 (93.7)	578 (92.6)	
Presence	8 (6.3)	46 (7.4)	
Lymphadenopathy (n, %)			0.219
Absence	116 (92.1)	549 (88.0)	
Presence	10 (7.9)	75 (12.0)	
Air bronchogram (n, %)			**0.001**
Absence	107 (84.9)	589 (94.4)	
Presence	19 (15.1)	35 (5.6)	
Bubblelike lucency (n, %)			0.132
Absence	106 (84.1)	555 (88.9)	
Presence	20 (15.9)	69 (11.1)	
Cavitation (n, %)			0.586

Absence	21 (16.7)	92 (14.7)	
Presence	105 (83.3)	532 (85.3)	
Pleural attachment (n, %)			**0.005**
Absence	86 (68.3)	499 (80.0)	
Presence	40 (31.7)	125 (20.0)	
Pleural retraction (n, %)			0.901
Absence	101 (80.2)	505 (80.9)	
Presence	25 (19.8)	119 (19.1)	
Spiculation (n, %)			0.083
Absence	82 (65.1)	454 (72.8)	
Fine	33 (26.2)	110 (17.6)	
Coarse	11 (8.7)	60 (9.6)	
Border (n, %)			0.598
Obscure	18 (14.3)	102 (16.3)	
Clear	108 (85.7)	522 (83.7)	
Lobulation (n, %)			**<0.001**
Absence	22 (17.5)	386 (61.9)	
Shallow	42 (33.3)	156 (25.0)	
Deep	62 (49.2)	82 (13.1)	
Location (n, %)			**0.014**
Peripheral	14 (11.1)	33 (5.3)	
Central	112 (88.9)	591 (94.7)	
Emphysema (n, %)			0.744
Absence	115 (91.3)	561 (89.9)	
Presence	11 (8.7)	63 (10.1)	
Overall shape (n, %)			0.603
Round	38 (30.2)	204 (32.7)	
irregular	88 (69.8)	420 (67.3)	
Stage (n, %)			**<0.001**
IA	30 (23.8)	497 (79.6)	
IB	96 (76.2)	127 (20.4)	

Notes: LVI, lymphovascular invasion; VPI, visceral pleural invasion; MMNA, mixed mucinous and nonmucinous adenocarcinoma; ACT, Adjuvant chemotherapy; non-ACT, without adjuvant chemotherapy; UIP, usual interstitial pneumonia. Bold indicates that the variable was statistically significant.

Table S3

Demographic and clinicopathological characteristics of ACT and non-ACT group

Characteristics	ACT (N=133)	Non-ACT (N=617)	*P* value
Age (n, %)			0.103
<65 years	81 (60.3)	421 (68.2)	
≥65 years	52 (39.1)	196 (31.8)	

Gender (n, %)			**0.003**
Male	64 (48.1)	212 (34.4)	
Female	69 (51.9)	405 (65.6)	
Smoking history (n, %)			**<0.001**
No	81 (60.9)	519 (84.1)	
Yes	52 (39.1)	98 (15.9)	
Tumor location (n, %)			0.518
Upper lobe	41 (30.8)	173 (28)	
Non-upper lobe	92 (69.2)	444 (72)	
Tumor size (cm)			**<0.001**
0-1	3 (2.3)	173 (28.0)	
1-2	16 (12.0)	256 (41.5)	
2-3	43 (32.3)	112 (18.2)	
3-4	71 (53.4)	76 (12.3)	
LVI (n, %)			0.235
Presence	6 (4.5)	16 (2.6)	
Absence	127 (95.5)	601 (97.4)	
VPI (n, %)			**<0.001**
Presence	45 (33.8)	56 (9.1)	
Absence	88 (66.2)	561 (90.9)	
Surgery types (n, %)			
Lobectomy	129 (97.0)	478 (77.5)	**<0.001**
Segmentectomy	4 (3.0)	139 (22.5)	
Pathological subtype (n, %)			**0.047**
MMNA	12 (9.0)	29 (4.7)	
IMA	121 (91.0)	588 (95.3)	
Tumor density (n, %)			**<0.001**
Sub-solid	13 (9.8)	207 (33.5)	
Pure-solid	120 (90.2)	410 (66.5)	
UIP pattern (n, %)			0.370
Absence	124 (93.2)	587 (95.1)	
Presence	9 (6.8)	30 (4.9)	
Obstructive pneumonia (n, %)			**<0.001**
Absence	12 (9.0)	12 (1.9)	
Presence	121 (91.0)	605 (98.1)	
Lesion in non-tumor lobe (n, %)			0.875
Absence	123 (92.5)	573 (92.9)	
Presence	10 (7.5)	44 (7.1)	
Lymphadenopathy (n, %)			0.561
Absence	116 (87.2)	549 (89.0)	
Presence	17 (12.8)	68 (11.0)	
Air bronchogram (n, %)			**<0.001**
Absence	25 (18.8)	29 (4.7)	
Presence	108 (81.2)	588 (95.3)	

Bubblelike lucency (n, %)			0.213
Absence	113 (85.0)	548 (88.8)	
Presence	20 (15.0)	69 (11.2)	
Cavitation (n, %)			0.504
Absence	110 (82.7)	527 (85.4)	
Presence	23 (17.3)	90 (14.6)	
Pleural attachment (n, %)			0.527
Absence	101 (75.9)	484 (78.4)	
Presence	32 (24.1)	133 (21.6)	
Pleural retraction (n, %)			0.709
Absence	109 (82.0)	497 (80.6)	
Presence	24 (18.0)	120 (19.4)	
Spiculation (n, %)			0.251
Absence	88 (66.2)	448 (72.6)	
Fine	32 (24.1)	111 (18.0)	
Coarse	13 (9.7)	58 (9.4)	
Border (n, %)			0.552
Obscure	19 (14.3)	101 (16.4)	
Clear	114 (85.7)	516 (83.6)	
Lobulation (n, %)			**0.007**
Absence	58 (43.6)	350 (56.7)	
Shallow	38 (28.6)	160 (25.9)	
Deep	37 (27.8)	107 (17.4)	
Location (n, %)			**0.031**
Peripheral	119 (89.5)	584 (94.7)	
Central	14 (10.5)	33 (5.3)	
Emphysema (n, %)			0.719
Absence	121 (91.0)	555 (90.0)	
Presence	12 (9.0)	62 (10.0)	
Overall shape (n, %)			0.315
Round	38 (28.6)	204 (33.1)	
irregular	95 (71.4)	413 (66.9)	
Stage (n, %)			**<0.001**
IA	29 (21.8)	498 (80.7)	
IB	104 (78.2)	119 (19.3)	

Notes: LVI, lymphovascular invasion; VPI, visceral pleural invasion; MMNA, mixed mucinous and nonmucinous adenocarcinoma; ACT, Adjuvant chemotherapy; non-ACT, without adjuvant chemotherapy; UIP, usual interstitial pneumonia. Bold indicates that the variable was statistically significant.

Line 245: group were more likely to undergo lobectomy and receive chemotherapy *(Table S2)*. 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 S3)*.

Comment 2: The approach of only entering factors that were significant (p<0.05) in the univariate analysis into the multivariate analysis is not recommended; factors with p<0.2 in the univariate analysis should be entered into the multivariate analysis, even though there are overfitting problems.

Reply:

Thank you for pointing this out. We tried to include the following factors with p<0.2 in the univariate analysis into the multivariate analysis: VPI (P<0.001), LVI (P<0.001), tumor density (P=0.019), smoking history (P<0.001), smoking history (P<0.001), pathological tumor size (P<0.001), surgery type (P=0.193), adjuvant chemotherapy (P=0.09), air bronchogram (P=0.002), cavitation (P=0.134), pleural attachment (P=0.008), spiculation (P=0.070), border (P=0.041), lobulation (P<0.001)and the final analysis results still showed only VPI (P<0.001), LVI (P<0.001), smoking history (P<0.001), pathological tumor size (P<0.001) and lobulation (P<0.001) were the independent influencing factors for recurrence. Since variables with P<0.05 were fed into multivariate analysis in most studies, including articles published in JTO (29902534) and JCO (25624438), we also used p<0.05 to screen variables in our study.

Comment 3: Has a comparison been made as to whether the prognostic value of this nomogram is superior to the stages based on the TNM classification?

Reply:

Thank you for pointing this out. We have added the comparison between nomogram and TNM classification in the corresponding place.

 Changes in the text:

Line 60-62: 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).

Line 222-224: In the training cohort, the 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).

*Comment 4 Is the "tumor size" in the manuscript the size on the CT image or the pathology?*

Reply：

Thank you for pointing this out. The "tumor size" in the manuscript is the size on the pathology

Changes in the text:

Line 142: patients who received complete resection with pathological stage I IMA from January 2011 to

Line 146: complete resection and diagnosed with pathological stage I primary IMA according to the 8th TNM

Figure S1-revised:
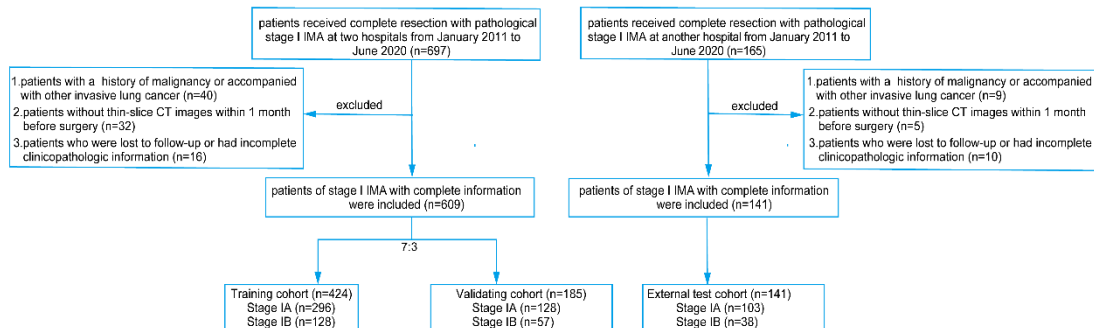
Comment 5: Was lymph node dissection performed in all patients?

Reply: Thank you for pointing this out. All patients in our studies underwent systematic lymph node dissection (SND) or lobe-specific lymph node dissection (L-SND) and we have added description in corresponding position.

Changes in the text: add a new section between line 157 and line 158

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.

[22] M.B. Amin, F.L. Greene, S.B. Edge, C.C. Compton, J.E. Gershenwald, R.K. Brookland, L. Meyer, D.M. Gress, D.R. Byrd, D.P. Winchester, The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging, CA: a cancer journal for clinicians 67(2) (2017) 93-99.

Comment 6: Does sub-lobar resection only include segmentectomy or also wedge resection?

What were the surgical indications for sub-lobar resection?

Reply:

Thank you for pointing this out. sub-lobar resection only includes segmentectomy, and We have described it more precisely in the manuscript.

Changes in the text: add a new section between line 157 and line 158

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 (11 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.

[22] M.B. Amin, F.L. Greene, S.B. Edge, C.C. Compton, J.E. Gershenwald, R.K. Brookland, L. Meyer, D.M. Gress, D.R. Byrd, D.P. Winchester, The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging, CA: a cancer journal for clinicians 67(2) (2017) 93-99.

Table 1-revised:

Characteristics	Training cohort (N=424)	Internal validating cohort (N=185)	External validating 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 (cm)			
0-1	86 (20.3)	38 (20.5)	52 (36.9)
1-2	154 (36.3)	74 (40.0)	44 (31.2)
2-3	97 (22.9)	41 (22.2)	17 (12.1)
3-4	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)

Table 3-revised:

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)	

	OR (95% CI)	P	OR (95% CI)	P
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 years vs <65 years	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		0.09		
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)			
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)			

Comment 7: Table 1; IQRs are listed in the notes, but there are no continuous variables in this table.

Reply:

Thank you for pointing this out and We've removed the superfluous description.

Table 1-revised:

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

Comment 8: Page 6, line222-223.

Please state the C-index of the training cohort.

Reply:

Thank you for pointing this out and we have stated the C-index of the training cohort.

Changes in the text:

Line 222-224: In the training cohort, the 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).