



The clinical prognostic factors of patients with stage IB lung adenocarcinoma

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Background: Lung adenocarcinoma (ADC) at stage IB has its own prognostic characteristics. This study aimed to investigate the clinical factors that may affect the prognosis of patients with stage IB ADC.

Methods: The data of ADC cases were selected from the Surveillance, Epidemiology, and End Results (SEER) database (2010–2016) and patients in Zhongshan Hospital, Fudan University (Department of Thoracic Surgery, 2015–2016). Kaplan–Meier method was used to obtain the overall survival (OS). Factors that significantly related to the prognosis were evaluated by univariate and multivariate analysis (UVA, MVA) using the Cox model. A nomogram was developed and validated to predict the 3-year OSs of those patients.

Results: 7,605 patients with stage IB ADC were included ultimately and were divided into two groups, a training cohort (n=5,324) and a test cohort (n=2,281). Besides, there was a validation cohort (n=272) for the verification of the nomogram model. Those with significantly older age, male, the white race, lower grades of tumor differentiation, larger tumor size (31–40 mm) without pleural layer (PL) invasion as well as receiving sublobectomy suffered from poorer survival ($P<0.001$), which were identified as independent factors for stage IB ADC ($P<0.001$), and according to which, a nomogram model was created.

Conclusions: Age, sex, race, histological grade, surgery to the primary site, and tumor size combined with PL invasion were independent risk factors for stage IB ADC, based on which a nomogram was constructed to predict the prognosis.

Keywords: Lung adenocarcinoma; prognosis; stage IB; AJCC

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Introduction

Lung cancer is the most common malignant tumor with the highest morbidity and mortality worldwide (1). Adenocarcinoma (ADC) has been the primary subtype of lung cancer, accounting for 55% in recent years, with a strong proliferative capacity and a high degree of malignancy. Some patients have localized tumor infiltration or distant metastasis at the time of diagnosis, and the

prognosis is poor (2,3).

The 8th edition of the TNM staging of the Lung Cancer, launched by the International Union Against Cancer (UICC) on January 1, 2018, had undergone numerous changes and additions compared to the 7th edition. It is now frequently used to predict the survival of patients with lung adenocarcinoma. In terms of tumor size, the 8th edition staged a more detailed classification of stage Ib

tumors ($3 \text{ cm} < T2a \leq 4 \text{ cm}$) (4-6). And tumor invasion of the pleural/elastic layer (PL) also belongs to stage IB, which has been reported as a poor prognostic factor in ADC (7,8). Differences and disputes still existed among patients with stage IB lung adenocarcinoma in survival status and related treatment recommendations (6,9-12). The influence of clinical factors on survival status was more or less various in studies (13-16).

SEER recently released the data of patients diagnosed with lung cancer in 2016. Therefore, the purpose of this study was to analyze the factors associated with the prognosis of patients with stage IB lung adenocarcinoma among 2010–2016, especially illustrated whether tumor size and PL play an important role or not, which may help improve the treatment strategy for early-stage lung cancer patients.

We present the following article in accordance with the TRIPOD reporting checklist (available at <https://dx.doi.org/10.21037/tcr-21-1174>).

Methods

Data sources and patient cohort

The data of patients were collected from the Surveillance, Epidemiology, and End Results (SEER) public use database SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (2010–2016).

A total of 8,846 patients with complete follow-up data were diagnosed as stage IB (AJCC 8th) ADC and performed surgery between 2010 and 2016 in the SEER database. Among them, 7,605 patients were finally enrolled in cohort I.

The characteristics of these patients are reported in *Table 1*, which includes age at the time of subsequent cancer diagnosis, race, gender, primary site, pathological classification (histology), grade, laterality, first malignant primary indicator, total no. of malignant and benign tumors, pleural/elastic layer invasion (PL) and tumor size. Finally, 5,324 patients with stage IB ADC from the SEER database were randomly assigned to the training cohort, and 2,281 were in the test cohort.

A total of 272 ADC at stage IB patients performed surgery for primary ADC lesion in the Department of Thoracic Surgery of Zhongshan Hospital Affiliated to Fudan University (ZHTS) were included. The selection process is shown in *Figure 1*.

Statistical analysis

The distribution of patients' characteristics (gender, race, age, primary site, pathological classification, differentiation grade, and chemotherapy, etc.) was summarized using counts and percentages. Statistical analysis was done using R Project (<https://www.r-project.org>) and SPSS 23.0 software (IBM). Kaplan-Meier method was used for the survival analysis. Multivariate survival analysis was calculated by the Cox proportional hazards regression. The test level was $\alpha=0.05$, and the difference was statistically significant at $P<0.05$.

The prognostic model was then used to predict the 3-year outcomes of OS. We validated the nomogram internally and externally both in the training group and in the validation group. Harrell Consistency Index (C-Index) were used to evaluate the nomogram, with a higher C-index indicating a more accurate prognostic predictions (17). The calibration plot was adopted to evaluate nomogram performance. The C-index, nomogram, calibration curves and Kaplan-Meier curves were generated in R with packages "rms", "survival", "foreign" and "regplot" respectively (18).

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committees of Zhongshan Hospital, Fudan University (Shanghai, China) (Approval No.: B2019-232R). Informed consent forms were exempt.

Results

Patient characteristics

Among stage IB patients, the predominant age group was 71–80 years in the SEER database, while ≤ 60 years was the majority in the validation cohort. For the differentiated grade, the vast majority was moderately differentiated in all databases. Most of the patients enrolled in our study were performed surgery with Lobectomy + LN dissection. Details were described in *Table 1*.

Survival time analysis

A Kaplan-Meier analysis was conducted to evaluate the cumulative risk for the development of stage IB lung and

Table 1 Demographic and disease characteristics of patients with IB lung cancer in SEER and validation cohort

Characteristics	Cohort 1		Validation cohort	
	SEER database, n=7,605		Our database, n=272	
	n	%	n	%
Age				
≤60 yr	1,181	15.53%	102	37.50%
61–70 yr	2,459	32.33%	92	33.82%
71–80 yr	2,910	38.26%	71	26.10%
>80 yr	1,055	13.87%	7	2.57%
Race				
Black	686	9.02%	0	0.00%
Others	53	0.70%	0	0.00%
Asian or Pacific islander	646	8.49%	272	100.00%
White	6,220	81.79%	0	0.00%
Sex				
Female	4,097	53.87%	147	54.04%
Male	3,508	46.13%	125	45.96%
Differentiated grade				
Well differentiated	1,241	16.32%	57	20.96%
Moderately differentiated	3,767	49.53%	155	56.99%
Poorly differentiated	2,465	32.41%	60	22.06%
Undifferentiated	132	1.74%	0	0.00%
Laterality				
Right	4,509	59.29%	172	63.24%
Left	3,096	40.71%	100	36.76%
Surgery to the primary site				
Sublobectomy	1,533	20.16%	0	0.00%
Multiple lobes	933	12.27%	5	1.84%
Lobectomy	5087	66.89%	262	96.32%
Pneumonectomy	52	0.68%	5	1.84%
Tumor size				
≤10 mm	210	2.76%	40	14.71%
11–20 mm	1,603	21.08%	112	41.18%
21–30 mm	1,684	22.14%	84	30.88%
31–35 mm	2,557	33.62%	21	7.72%
36–40 mm	1,551	20.39%	15	5.51%

Table 1 (continued)

Table 1 (continued)

Characteristics	Cohort 1		Validation cohort	
	SEER database, n=7,605		Our database, n=272	
	n	%	n	%
Pleural/Elastic Layer Invasion (PL)				
PL=0, No evidence of PL invasion	4,149	54.56%	78	28.68%
PL=1, Invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura	1,995	26.23%	160	58.82%
PL=2, Invasion to the surface of the pulmonary pleura	1,461	19.21%	34	12.50%
Tumor size & PL				
≤30 mm, PL=1 or 2	3,497	45.98%	236	86.76%
31–40 mm, PL=0	3,369	44.30%	12	4.41%
31–40 mm, PL=1 or 2	739	9.72%	24	8.82%

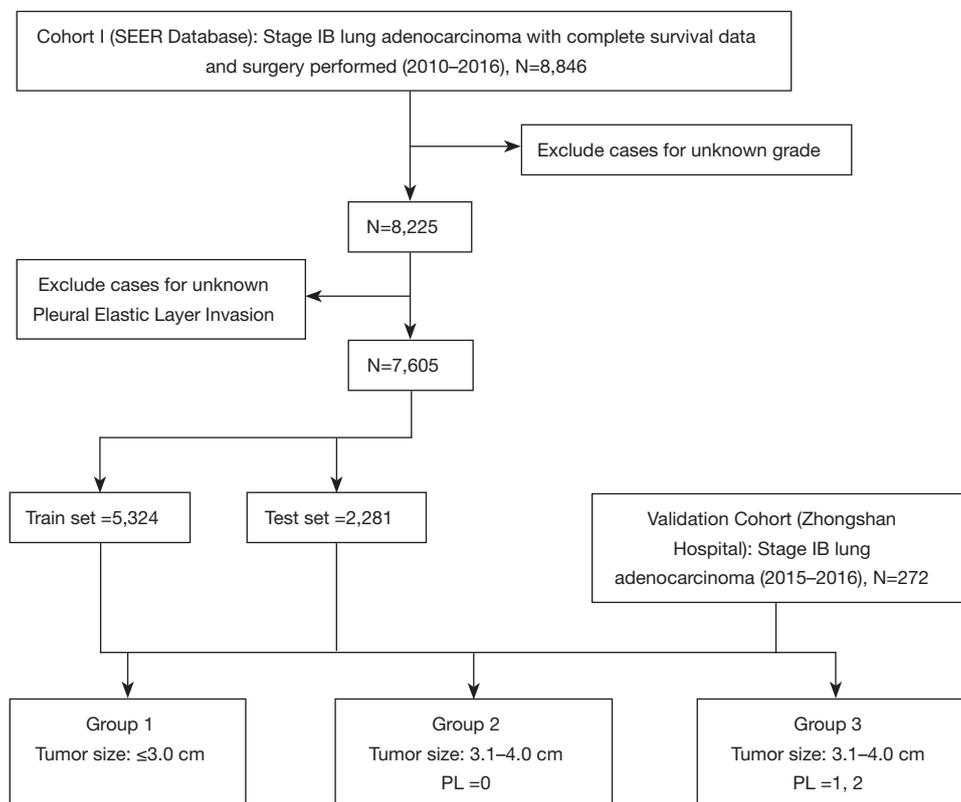


Figure 1 The selecting process of all cohorts utilized in this study.

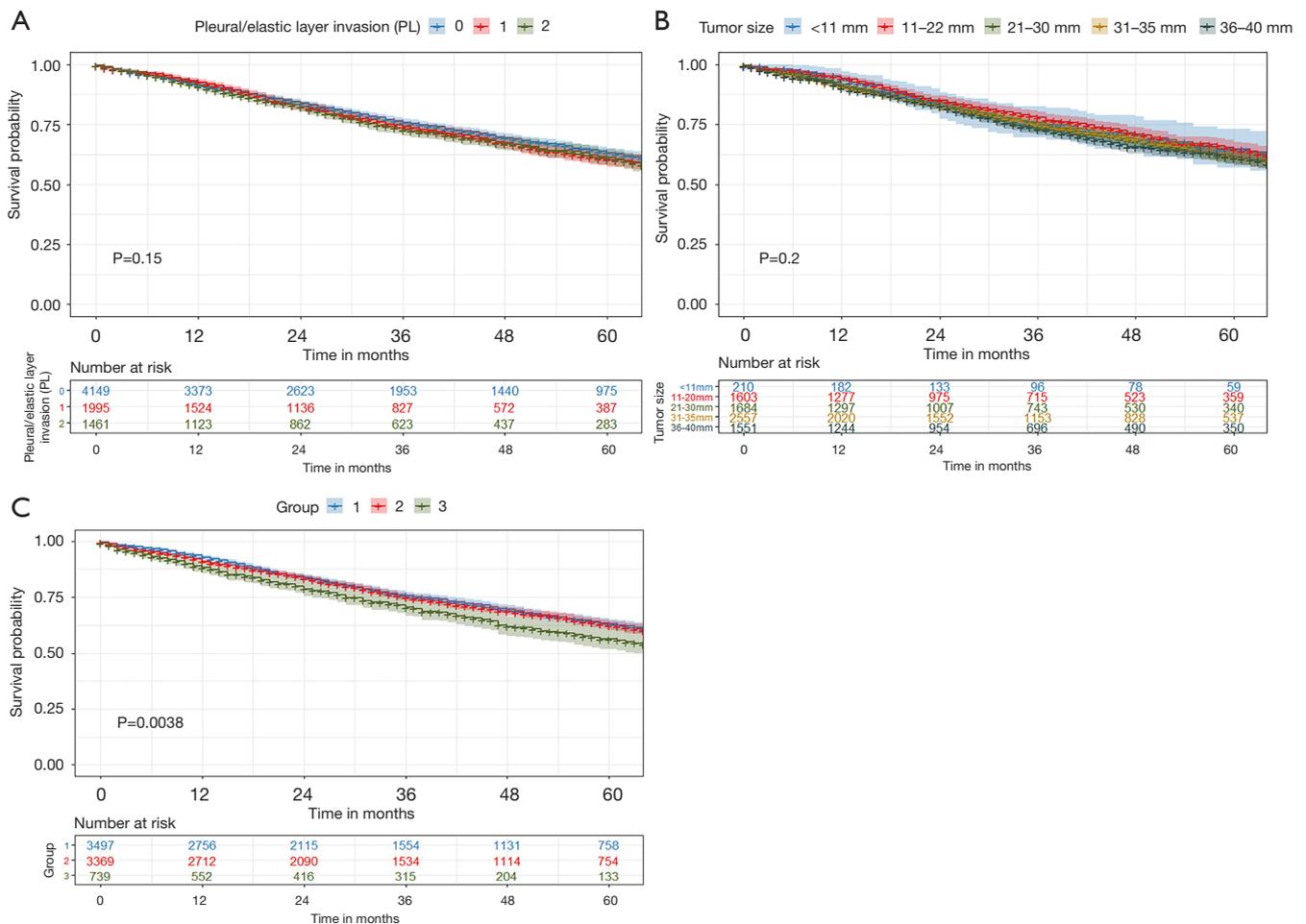


Figure 2 Survival time analysis of 7,605 patients with stage IB lung cancer; (A) for pleural/elastic layer invasion (PL); (B) for tumor size; (C) for the group considering both tumor size and pleural/elastic layer invasion (PL)

was illustrated in *Figure 2*. The risk for development of stage IB lung cancer was neither related to PL (PL=0, PL=1, PL=2, P=0.15, *Figure 2A*), nor the tumor size (≤ 1 cm, 1.1–2.0 cm, 2.1–3.0 cm, 3.1–4.0 cm, P=0.2, *Figure 2B*) alone. However, once tumor size was considered in combination with PL, patients with stage IB lung cancer showed a significantly different survival status (P=0.0038, *Figure 2C*).

Cox survival analysis

Univariate analysis (*Table 2*) revealed that age at diagnosed (P<0.001), race (P<0.001), sex (P<0.001), tumor differentiation grade (P<0.001), total no. of in situ/malignant tumors for the patient (P<0.001), surgery to the primary site (P<0.001), group (P=0.005) was significant

predictors of stage IB lung cancer patients. Multivariate Cox proportional hazard analysis of all IB staged patients (*Table 2*) demonstrated sex (P<0.001), age (P<0.001), race (P=0.003), tumor differentiation grade (P<0.001), surgery to the primary site (P<0.001), group (P<0.001), were independent prognostic factors for better survival in the IB staged patients (AJCC 8th). No significant difference was caused by tumor size or total no. of in malignant tumors for patient.

Contribution and validations of the nomogram

A nomogram relating to 6 independent risk factors (age, race, sex, tumor histological, grade, surgery, and group), which were concluded from MVA (*Figure 3*). 3-year overall survival (OS) could be calculated by the Points at the top

Table 2 Results of univariate and multivariate analysis model for stage IB patients

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age at diagnosed						
≤60 yr			reference			reference
61–70 yr	0.480	0.414–0.558	< 0.001	1.311	1.120–1.534	0.001
71–80 yr	1.372	1.225–1.537	< 0.001	1.889	1.625–2.196	<0.001
>80 yr	0.684	0.617–0.758	< 0.001	2.470	2.091–2.919	<0.001
Race			< 0.001*			0.003
White			reference			reference
Others	1.508	0.705–3.225	0.290	0.501	0.238–1.053	0.068
Asian or Pacific islander	1.889	0.888–4.016	0.098	0.742	0.621–0.886	0.001
Black	2.139	1.018–4.493	0.045	0.969	0.834–1.126	0.682
Sex			<0.001*			<0.001*
Female			reference			reference
Male	1.385	1.273–1.506	<0.001	1.326	1.218–1.443	<0.001
Differentiated Grade			<0.001*			<0.001*
Well differentiated			reference			reference
Moderately differentiated	0.560	0.409–0.767	<0.001	1.432	1.246–1.645	<0.001
Poorly differentiated	0.837	0.623–1.125	0.239	1.853	1.608–2.135	<0.001
Undifferentiated	1.100	0.818–1.480	0.528	1.869	1.364–2.560	<0.001
Laterality			0.169			Not included
Right			reference			
Left	1.062	0.975–1.156	0.169			
Surgery to the primary site			<0.001*			<0.001*
Sublobectomy			reference			reference
Multiple lobes	0.732	0.640–4.450	<0.001	0.839	0.727–0.969	0.017
Lobectomy + LN dissection	0.555	0.504–0.612	<0.001	0.684	0.605–0.773	<0.001
Pneumonectomy	0.528	0.197–1.413	<0.001	0.698	0.260–1.872	0.474
Tumor size			0.197			Not included
≤10 mm			reference			
11–20 mm	0.900	0.690–1.172	0.433			
21–30 mm	0.856	0.750–0.976	0.020			
31–35 mm	0.957	0.843–1.087	0.500			
35–40 mm	0.953	0.849–1.069	0.409			

Table 2 (continued)

Table 2 (continued)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Pleural/Elastic Layer Invasion (PL)			0.154			Not included
No evidence of PL invasion			reference			
Invasion beyond the visceral elastic pleura, but limited to the pulmonary pleura	1.074	0.971–1.188	0.164			
Invasion to the surface of the pulmonary pleura	1.101	0.985–1.230	0.090			
Tumor size & PL (group)			0.005	0.964	0.868–1.071	<0.001
≤30 mm			reference			reference
31–40 mm, PL=0	1.032	0.944–1.128	0.494	1.145	1.043–1.256	0.004
31–40 mm, PL=1 or 2	1.269	1.101–1.463	0.001	1.327	1.149–1.532	<0.001

*, indicate a statistical significance.

of the model (Figure 3A). The internal evaluation was performed (Figure 3B) as well as the external evaluation (Figure 3C) with the same database. The C-indexes for 3-year OS were 0.644 ± 0.015 (training cohort, SEER database) and 0.625 ± 0.024 (test cohort, SEER database).

Furthermore, we verified our nomogram model by individuals with entirely different characteristics of the data (Figure 4), the C-index of which was 0.690 ± 0.079 (database in our department).

In general, IB ADC patients who had a younger age, female sex, non-black-or-white race, lower differentiated level or performed pneumonectomy had longer predicting survival time. For the groups, those in group 1, which meant the tumor size was less than 30 mm had the best clinical outcomes, followed by 31–40 mm tumor size with no PL invasion, and those with 31–40 mm tumor size with PL invasion behaved worst in survival time.

Discussion

In our study, we found that in patients with stage IB ADC, the differences in tumor size or PL invasion didn't cause differences in living conditions, while the survival times appeared different once both of them were considered together. In all, six independent risk factors (age, race, sex, tumor histological, grade, surgery, and group) were concluded from MVA and contributed for nomogram model. Recently, study considering stage IB NSCLC concluding similar independent risk factors, including age,

sex, histology, tumor differentiation (19), and it was widely proved that among lung cancer patients, female patients have a better prognosis (20), which was also revealed in our research.

The pleural invasion was well-positioned as a T2 descriptor and led to a worse prognosis even after adjusting for the current tumor size cut points (21–25). Our result was similar to the research result that IB patients with both pleural invasion and tumor size between 3.1–4.0 cm had a closer survival status to the stage IIA patients (14). Rami-Porta's study also suggested that 3-cm cutoff point still separates T1 from T2 tumors, but tumor size arises as a more important prognostic factor, because, from ≤ 1 to 5 cm, each centimeter separates tumors with a significantly different prognosis (21), while Nitadori *et al.* found that PL distinguished OS in patients with lung adenocarcinoma with a tumor size of 2–3 cm, but failed to stratify patients with a tumor size of ≤ 2 cm (26). Other researchers showed that the presence of PL, not the depth of invasion, was associated with postoperative survival (23,27,28), but conflicted to the conclusion that survival differences existed among different PL stages (29,30). More studies can be focused on this phenomenon to illustrate the probable mechanism.

In addition to the tumor size and the degree of local invasion, for patients with stage IB lung adenocarcinoma, men, blacks, whites, etc., are related to poorer prognosis, so they are more likely to require further treatment. In addition, patients undergoing sublobectomy and multiple lobectomy also have a poorer prognosis, which may be

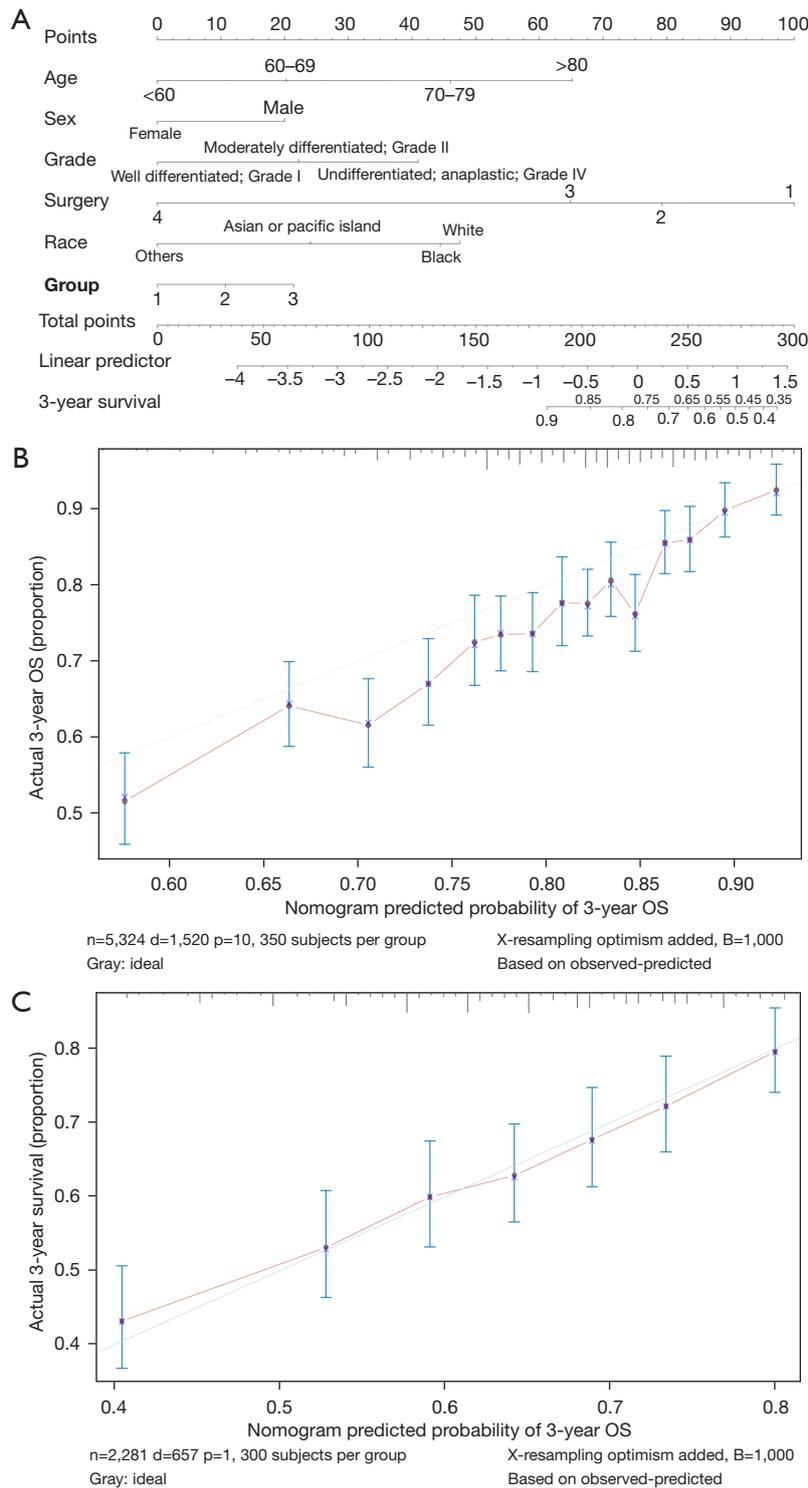


Figure 3 A nomogram model of stage IB ADC and its calibration curve for validations. (A) A nomogram for prediction of 3-year overall survival (OS) rates of patients with lung adenocarcinoma (ADC) in the training cohort; (B) Calibration curve of the nomogram predicting the 3-year OS rate of patients with lung ADC in the training cohort, the X-axis displays the nomogram-predicted OS and the Y-axis is the actual OS of the certain patients; (C) Calibration curve of the nomogram predicting the 3-year OS rate of patients with lung ADC in the test cohort, the X-axis displays the nomogram-predicted OS and the Y-axis is the actual OS of the certain patients.

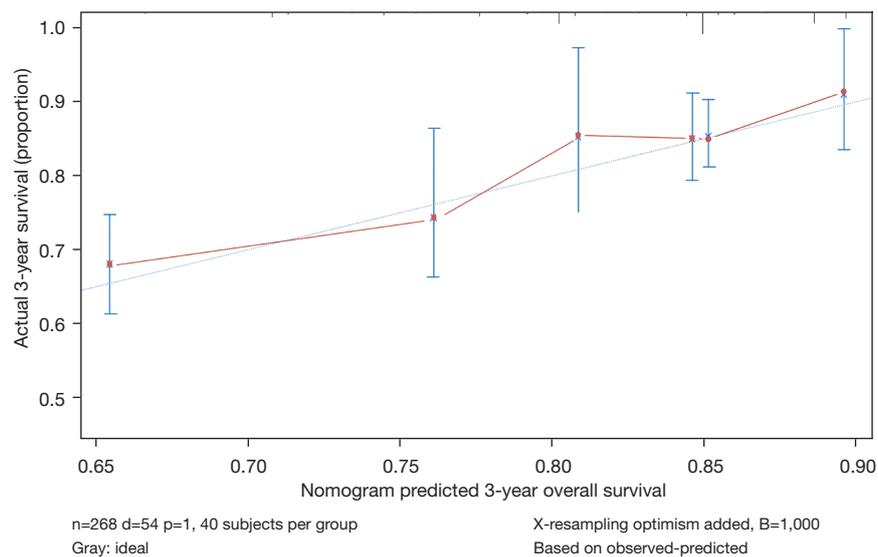


Figure 4 Calibration curve of the nomogram predicting the 3-year OS rate of patients in the Department of Thoracic Surgery of the Fudan University (Zhongshan Hospital).

related to the failure of complete removing of the lesion. Therefore, the follow-up after the operation should be more closely to better determine whether it is necessary to apply further treatment. In conclusion, those results indicate we should take different clinical decisions for different patients, even if they have the same clinical stage.

Furthermore, FDG-PET/CT SUV_{max}, the value of which reflects the biological activity of tumors, is also closely related to tumor proliferation, invasion, progression and metastasis (31). Kawakita/Toba reported that FDG-PET/CT SUV_{max}, total tumor size, and could predict the prognosis of pStage I lung adenocarcinoma based on the 7th edition of the TNM staging system (32). It was also found that solid predominant types have high SUV_{max} values and a shorter PFS than the other histologic subtypes (33).

Recently, the therapy strategy for IB lung cancer patients had been widely discussed. The recent National Comprehensive Cancer Network (NCCN) guidelines stated that adjuvant chemotherapy could be used for patients with stage IB NSCLC having high-risk factors including poorly differentiated tumors, vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx), which independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy (34). NSCLC Meta-analysis Collaborative Group's meta-analysis (35), mainly on stage IB–IIIA patients, achieved the conclusion that preoperative chemotherapy significantly improves overall

survival in resectable NSCLC and some other studies reached the similar conclusion that adjuvant chemotherapy may improve the OS of completely resected patients with a solid predominant tumor pattern in stage IB ADC (36,37). In contrast, there were also studies that showed that adjuvant chemotherapy was associated with worse OS than observation or no significant survival advantage for patients with stage IB NSCLC, but with significant OS benefit in stage IIA setting based on the 8th edition staging (6,9).

According to our research, visceral pleural involvement was not an independent prognostic factor in patients with stage IB lung cancer based on the 8th editions of AJCC TNM staging system. To decide whether patients should be treated with adjuvant chemotherapy, both tumor size and PL can be considered.

The limitation of this study is that, firstly, because the SEER database used in this study has no chemotherapy-related records for lung cancer patients diagnosed in 2016, it is unable to conduct further statistical analysis on lung cancer treatment. Since the SEER database is predominantly white, certain biases will be introduced when analyzing the impact of race on the prognosis, and further research is needed to explore whether race is really a factor influencing the prognosis of lung cancer. Furthermore, the patients' detailed clinical information is limited in the SEER database, as there is no record of PET/CT SUV_{max} value and other prognosis-related figures for the further analyze. In addition, this study is only a retrospective study,

and further experiments are needed to verify or clarify the relevant conclusions.

Conclusions

The combination of tumor size and PL invasion is a significant clinical character of different prognosis in patients with stage IB lung adenocarcinoma (AJCC 8th TNM classification), which may help the selection of patients who might benefit from chemotherapy and more advanced treatment.

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Footnote

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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 Zhongshan Hospital, Fudan University (Shanghai, China) (Approval No.: B2019-232R). Informed consent forms were exempt.

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