

# Lymphovascular invasion: A non-sized T descriptor for stage IA non-small cell lung cancer

Jing-Sheng Cai<sup>1,2</sup>  | Xun Wang<sup>1,2</sup> | Fei Yang<sup>3</sup> | Yun Li<sup>1,2</sup> | Man-Tang Qiu<sup>1,2</sup> 

<sup>1</sup>Department of Thoracic Surgery, Peking University People's Hospital, Beijing, People's Republic of China

<sup>2</sup>Peking University People's Hospital Thoracic Oncology Institute, Beijing, People's Republic of China

<sup>3</sup>Department of Pathology, Peking University People's Hospital, Beijing, People's Republic of China

## Correspondence

Man-Tang Qiu, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China.  
Email: qiumantang@163.com

## Abstract

**Background:** Lymphovascular invasion (LVI) has not been included in the tumor-node-metastasis (TNM) staging manual of non-small-cell lung cancer (NSCLC). We aimed to investigate the predictive value of LVI on stage IA NSCLC and proposed a method of incorporating LVI into the T category based on the latest TNM staging manual.

**Methods:** The least absolute shrinkage and selection operator (LASSO)-penalized Cox multivariable regression model was performed to identify prognostic factors. The Kaplan–Meier method was used to compare overall survival (OS) and disease-free survival (DFS) between groups. Propensity score matching (PSM) was used to minimize bias.

**Results:** A total of 1452 eligible stage I NSCLC cases (stage IA without LVI, 1022 cases; stage IA with LVI, 120 cases; stage IB, 310 cases) were included. LASSO-penalized multivariable Cox analysis revealed that LVI was an independent prognostic factor for both OS and DFS. Survival analysis demonstrated that the survivals of stage IA NSCLCs without LVI were better than those of stage IA with LVI and stage IB NSCLCs. In the matched cohort, the survivals of stage IA NSCLCs with LVI were comparable to those of stage IB NSCLCs.

**Conclusions:** Stage IA NSCLCs with LVI and stage IB NSCLCs had similar survivals, and we proposed that LVI might be a non-sized T descriptor that upstaged stage IA diseases to stage IB.

## KEYWORDS

lymphovascular invasion, non-small-cell lung cancer, TNM stage, upstage

## INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide.<sup>1–3</sup> Surgery is a preferred treatment for early-stage non-small-cell lung cancer (NSCLC). However, the recurrence rate of these completely resected node-negative diseases varies from 13% to 23%.<sup>4,5</sup> Larger tumor size, visceral pleural invasion (VPI), and lymphovascular invasion (LVI) etc. are recognized as contributors to the high relapse rate.<sup>6–9</sup> The first two have been incorporated into the tumor (T) category of the current tumor-node-metastasis (TNM) staging manual.<sup>10</sup>

LVI, defined as the identification of tumor emboli within a lymph or blood vessel lumen using hematoxylin and eosin (H&E) staining or elastic staining,<sup>11</sup> is reported to compromise the survival of NSCLC patients.<sup>12–19</sup> Although LVI has been considered in the supplementary TNM staging of NSCLC, it has not been incorporated into the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging manual.<sup>10</sup>

This study focused on stage IA NSCLC patients with or without LVI from a large Chinese cohort. Our aim was to investigate the predictive value of LVI on stage IA NSCLC and propose a method of incorporating LVI into the T category based on the latest TNM staging manual. We hypothesized that like VPI, LVI is also a non-sized T descriptor that upstages stage IA diseases to stage IB.

Jing-Sheng Cai and Xun Wang contributed equally to this paper and share first authorship.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd.

## MATERIALS AND METHODS

### Study design and patients

Between November 1999 and December 2018, a series of 7931 consecutive resected NSCLC cases were retrospectively reviewed from the Department of Thoracic Surgery at Peking University People's Hospital. All included cases met the following criteria: (1) diagnosis of primary NSCLC; (2) received surgery and lymph node dissection; and (3) pathological stage I diseases based on the 8th TNM staging manual. The exclusion criteria were: (1) positive margin (R1/R2 resection); (2) received neoadjuvant therapy; (3) previous or concurrent other malignant cancers; (4) perioperative death; (5) unavailable LVI information; and (6) age <18 years. The flow chart of patient selection is shown in Figure 1.

The eligible cases were assigned into three groups: stage IA without LVI (LVI-), stage IA with LVI (LVI+), and stage IB. The differences in demographic and tumor characteristics between the stage IA LVI- group and the stage IA LVI+ group were analyzed, and the survival outcomes among the stage IA LVI- group, stage IA LVI+ group, and stage IB group were investigated.

### Ethics

This study was approved by the Ethics Committee of Peking University People's Hospital (Approved number: 2020 PHB 421-02). Informed consent from individual patients was waived due to the retrospective design.

### Treatments

The routine preoperative evaluations, including medical history taking, physical examinations, blood routine, serum tumor

markers, pulmonary function test, spiral contrast-enhanced chest and abdomen computed tomography (CT) and magnetic resonance imaging (MRI) of the brain, were performed. Positron emission tomography (PET) imaging was not mandatory in our center because it has not yet been covered by medical insurance in mainland China. All included patients underwent complete surgical resection including lobectomy, sublobectomy and pneumonectomy, and systemic lymphadenectomy. In our center, adjuvant therapy is not regularly recommended for stage I patients.

### Pathologic evaluation

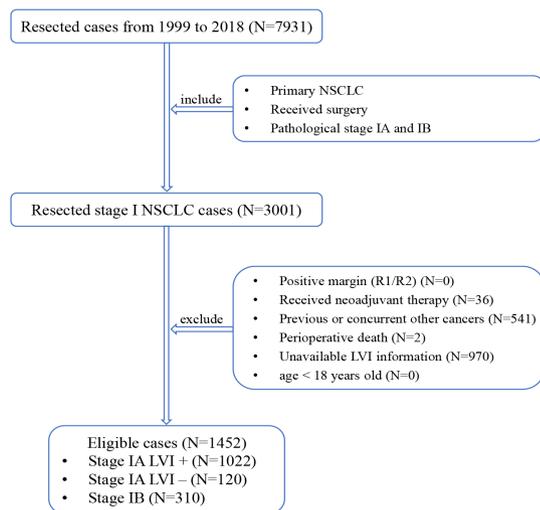
All the surgical resection specimens were processed according to the standard pathological procedures. In general, formalin-fixed paraffin-embedded tissue sections were stained with H&E staining. The LVI was defined as the presence of tumor emboli within a lymph or blood vessel lumen.<sup>11</sup> If it was difficult to define LVI, immunohistochemistry (IHC) staining analysis was performed. To be more specific, the undetermined specimens were stained with monoclonal antibodies against D2-40 (MXB Biotechnologies) and CD31 (ZSGB-BIO) to confirm lymphatic vessel and blood vessel invasion, respectively. All the specimens were assessed by two thoracic histopathologists. Figure 2 shows the typical histopathology of tumors with LVI.

### Follow-up and endpoints

Follow-up information was obtained through telephone calls, patients visits, and medical records. In general, postoperative follow-up was performed every 3 months for the first 2 years, every 6 months for the next 3–5 years, and annually thereafter. Detailed follow-up protocol included physical examinations, serum tumor markers, and contrast-enhanced chest CT scan. Brain MRI and bone scans were performed when clinically indicated. In this study, follow-up information was updated in October 2021. The primary endpoints of this study were overall survival (OS) and disease-free survival (DFS). OS was calculated from the date of surgery to the date of death or the last known contact. DFS was calculated from the date of surgery to the date of first recurrence or death.

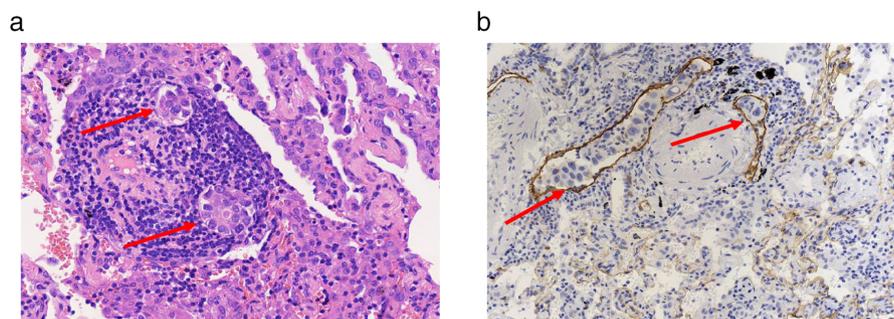
### Data collection

The demographic and clinicopathologic variables (age, sex, smoking status, family tumor history, preoperative comorbidity, body mass index (BMI), forced expiratory volume in 1 s (FEV1%), diffusion capacity for carbon monoxide (DLCO%), clinical TNM (cTNM) stage, the American Society of Anesthesiologists (ASA) physical status grade, surgical approach, surgical type, histology, VPI, LVI, pathological TNM (pTNM) stage, postoperative complication, and adjuvant therapy) were extracted from the institution's electronic



**FIGURE 1** The flow diagram for patient selection. NSCLC, non-small-cell lung cancer; LVI, lymphovascular invasion

**FIGURE 2** Histopathology of tumors with LVI. (a) H&E staining and (b) IHC staining. H&E, hematoxylin and eosin; IHC, immunohistochemistry



medical record system. Tumor staging was determined according to the 8th AJCC TNM staging manual.<sup>10</sup> Only patients with complete data were included in this study.

## Statistical analysis

Statistical analysis was performed using R version 4.1.1 (The R Foundation for Statistical Computing, <http://www.r-project.org>) and IBM SPSS Statistics (version 25.0, IBM Corp.). All times to event outcomes were estimated using the Kaplan–Meier method with a log-rank test. A one-to-one PSM between the stage IA LVI+ group and the stage IB group was carried out using the nearest-neighbor matching method with a caliper of 0.1. Potential confounding factors entered into the PSM algorithm were age, sex, smoking status, preoperative comorbidity, surgical approach, surgical type, histology, VPI, postoperative comorbidity, and adjuvant therapy. A least absolute shrinkage and selection operator (LASSO) regression model was performed to select and minimize potential prognostic variables using the R package “glmnet”.<sup>20</sup> The variables entered into the LASSO model were age, sex, smoking status, family tumor history, preoperative comorbidity, BMI, FEV1%, DLCO%, ASA grade, surgical approach, surgical type, histology, VPI, LVI, pTNM stage, postoperative complication, and adjuvant therapy. The selected factors were further included in a forward stepwise multivariable Cox proportional hazard regression model to determine the final independent prognostic factors. Continuous variables are presented as median (range) and categorical variables are presented as percentages. The Shapiro–Wilk test was used to analyze the normal distribution of the continuous variables and the Mann–Whitney *U* test was used to compare non-normally distributed variables. The Pearson Chi-square test or Fisher’s exact test was used to compare categorical variables. Two-sided  $p < 0.05$  was considered statistically significant.

## RESULTS

### Patient characteristics

Between November 1999 and December 2018, a total of 7931 resected NSCLC patients were retrospectively evaluated. After applying the inclusion and exclusion criteria, a sample size of 1452 eligible cases was retained. The entire cohort was

categorized into three groups (stage IA LVI–, 1022 cases; stage IA LVI+, 120 cases; stage IB, 310 cases). Table 1 shows the demographic and tumor characteristics of stage IA patients with or without LVI. In the comparative analyses, patients without LVI were younger than those with LVI (60 years vs. 65 years,  $p < 0.001$ ). There were higher percentages of females and non-smokers in the stage IA LVI– group compared with the stage IA LVI+ group (female 57.0% vs. 43.3%,  $p = 0.004$ ; nonsmoker 78.5% vs. 60.0%,  $p < 0.001$ ). The stage IA LVI– group had a higher proportion of patients who underwent sublobectomy than the stage IA LVI+ group (43.7% vs. 17.5%,  $p < 0.001$ ). Significantly more patients with LVI were diagnosed with larger-sized tumors ( $p < 0.001$ ) and administered with adjuvant therapy (6.7% vs. 1.0%,  $p < 0.001$ ). Supporting Information Table S1 shows the baseline characteristics of the stage IA LVI+ and stage IB patients before and after PSM. All covariates between these two groups were well balanced after PSM.

### LASSO-penalized multivariable Cox regression analysis

A total of 17 factors (age, sex, smoking status, family tumor history, preoperative comorbidity, BMI, FEV1%, DLCO%, ASA grade, surgical approach, surgical type, histology, VPI, LVI, pTNM stage, postoperative complication and adjuvant therapy), were entered into the LASSO regression model (OS: Figure 3a; DFS: Figure 3c). For OS, eight prognostic factors (age, sex, smoking status, surgical approach, histology, VPI, LVI, and pTNM stage) were selected using LASSO (Figure 3b). For DFS, seven prognostic factors (age, smoking status, surgical approach, histology, DLCO%, LVI and pTNM stage) were selected (Figure 3d).

The LASSO-selected factors were further included in the forward stepwise multivariable Cox analysis (Table 2). The results confirmed that age, VPI, LVI, and pTNM stage were independent prognostic factors of OS, and age, DLCO%, LVI, and pTNM stage were independent prognostic factors of DFS.

### Survival data

For OS, the survival rate of the stage IA LVI– patients was superior to that of stage IA LVI+ patients and stage IB patients (5-year OS rate 91.1% vs. 88.4% vs. 87.0%; stage IA

**TABLE 1** Characteristics of the stage IA NSCLC patients with and without LVI

Characteristics	NSCLC without LVI (N = 1022)	NSCLC with LVI (N = 120)	p
Age, year			<0.001 <sup>a</sup>
Median (range)	60 (26–86)	65 (36–84)	
Sex			0.004
Male	439 (43.0)	68 (56.7)	
Female	583 (57.0)	52 (43.3)	
Smoking status			<0.001
Nonsmoker	802 (78.5)	72 (60.0)	
Smoker	220 (21.5)	48 (40.0)	
Family tumor history			0.922
No	889 (87.0)	104 (86.7)	
Yes	133 (13.0)	16 (13.3)	
Preoperative comorbidities			0.661
Absent	413 (40.4)	46 (38.3)	
Present	609 (59.6)	74 (61.7)	
BMI			0.424 <sup>a</sup>
Median (range)	24.1 (15.6–38.9)	24.4 (17.4–33.7)	
FEV1 (%)			0.001 <sup>a</sup>
Median (range)	99.8 (36.9–157.0)	96.2 (51.0–133.4)	
DLCO (%)			0.001 <sup>a</sup>
Median (range)	90.3 (39.1–156.7)	86.6 (40.1–147.5)	
cTNM stage			<0.001 <sup>b</sup>
IA1	400 (39.1)	5 (4.2)	
IA2	395 (38.6)	48 (40.0)	
IA3	154 (15.1)	47 (39.2)	
IIB	2 (0.2)	3 (2.5)	
IIIA	71 (6.9)	17 (14.2)	
ASA grade			0.016 <sup>b</sup>
1	212 (20.7)	14 (11.7)	
2	770 (75.3)	96 (80.0)	
3	38 (3.7)	10 (8.3)	
4	2 (0.2)	0 (0.0)	
Surgical approach			0.203 <sup>b</sup>
VATS	1010 (98.8)	117 (97.5)	
Open	12 (1.2)	3 (2.5)	
Surgical type			<0.001 <sup>b</sup>
Lobectomy	573 (56.1)	98 (81.7)	
Sublobectomy	447 (43.7)	21 (17.5)	
Other	2 (0.2)	1 (0.8)	
Histology			<0.001
ADC	970 (94.9)	92 (76.7)	
Other	52 (5.1)	28 (23.3)	
VPI			0.324 <sup>b</sup>
Absent	1013 (99.1)	118 (98.3)	
Present	9 (0.9)	2 (1.7)	
pTNM stage			<0.001
IA1	418 (40.9)	7 (5.8)	
IA2	423 (41.4)	58 (48.3)	
IA3	181 (17.7)	55 (45.8)	

(Continues)

TABLE 1 (Continued)

Characteristics	NSCLC without LVI (N = 1022)	NSCLC with LVI (N = 120)	p
Postoperative complications			0.614 <sup>b</sup>
Absent	982 (96.1)	117 (97.5)	
Present	40 (3.9)	3 (2.5)	
Adjuvant therapy			<0.001
No	1012 (99.0)	112 (93.3)	
Yes	10 (1.0)	8 (6.7)	

Abbreviations: ADC, adenocarcinoma; ASA, the American Society of Anesthesiologists; BMI, body mass index; cTNM, clinical tumor-node-metastasis; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; LVI, lymphovascular invasion; NSCLC, non-small-cell lung cancer; pTNM, pathological tumor-node-metastasis; VATS, video-assisted thoracic surgery; VPI, visceral pleural invasion.

<sup>a</sup>Mann-Whitney *U* test.

<sup>b</sup>Fisher's exact test.

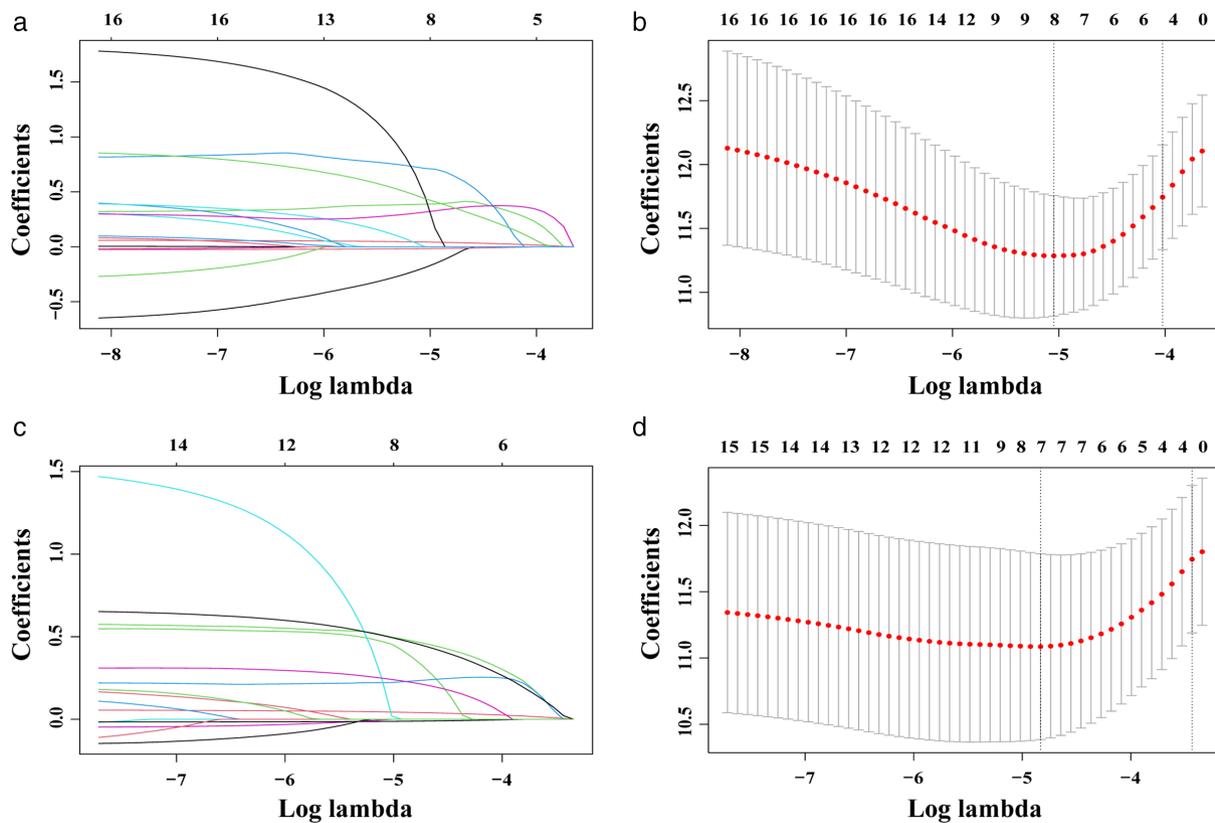


FIGURE 3 Prognostic factors selection for OS (A and B) and DFS (C and D) using the LASSO regression model. LASSO coefficient profiles of 17 included factors against the log ( $\lambda$ ) sequence for OS (A) and DFS (C). Tuning parameter ( $\lambda$ ) selection in the LASSO model used 10-fold cross-validation via minimum criteria (OS: B; DFS: D). OS, overall survival; DFS, disease-free survival; LASSO, least absolute shrinkage and selection operator

LVI- vs. stage IA LVI+,  $p = 0.018$ ; stage IA LVI- vs. stage IB,  $p = 0.006$ ; Figure 4a), and there was no significant survival difference between stage IA LVI+ patients and stage IB patients ( $p = 0.731$ ; Figure 4a). Similar results were obtained in the comparison of DFS (5-year DFS rate 89.1% vs. 76.4% vs. 87.4%; stage IA LVI- vs. stage IA LVI+,  $p < 0.001$ ; stage IA LVI- vs. stage IB,  $p = 0.001$ ; stage IA LVI+ vs. stage IB,  $p = 0.341$ ; Figure 4b).

In the matched cohort, the survivals of the stage IA LVI+ patients were comparable to those of stage IB patients

(5-year OS rate 77.6% vs. 66.9%,  $p = 0.204$ ; Figure 4C; 5-year DFS rate 70.8% vs. 82.3%,  $p = 0.880$ ; Figure 4D).

## DISCUSSION

Our comprehensive analysis of the predictive value of LVI on stage IA NSCLC patients demonstrated that LVI was an independent prognostic factor for stage IA NSCLC patients. The survival outcomes of stage IA LVI- patients were better

TABLE 2 LASSO-penalized multivariable Cox analysis of stage IA NSCLC patients

Characteristic	OS <sup>a</sup>			DFS <sup>b</sup>		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age			<0.001			0.001
Continue	1.078	1.035–1.123		1.068	1.026–1.111	
Sex			0.319			
Male	1					
Female	0.638	0.263–1.545				
Smoking status			0.119			0.100
Nonsmoker	1			1		
Smoker	1.982	0.839–4.686		1.922	0.882–4.187	
DLCO (%)						0.021
Continue				0.974	0.952–0.996	
Surgical approach			0.638			0.091
VATS	1			1		
Open	1.381	0.360–5.301		3.096	0.835–11.485	
Histology			0.407			0.537
ADC	1			1		
Other	1.428	0.615–3.317		1.316	0.550–3.148	
VPI			0.027			
Absent	1					
Present	9.286	1.215–86.632				
LVI			0.039			0.002
Absent	1			1		
Present	1.632	1.167–2.773		2.436	1.754–3.695	
pTNM stage			0.040			0.038
IA1	1			1		
IA2	2.381	0.941–8.648		2.082	0.583–7.439	
IA3	4.215	1.143–15.547		4.230	1.179–15.178	

**Abbreviations:** ADC, adenocarcinoma; DFS, disease-free survival; CI, confidence interval; DLCO, diffusion capacity for carbon monoxide; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; LVI, lymphovascular invasion; NSCLC, non-small-cell lung cancer; OS, overall survival; pTNM, pathological tumor-node-metastasis; VATS, video-assisted thoracic surgery; VPI, visceral pleural invasion.

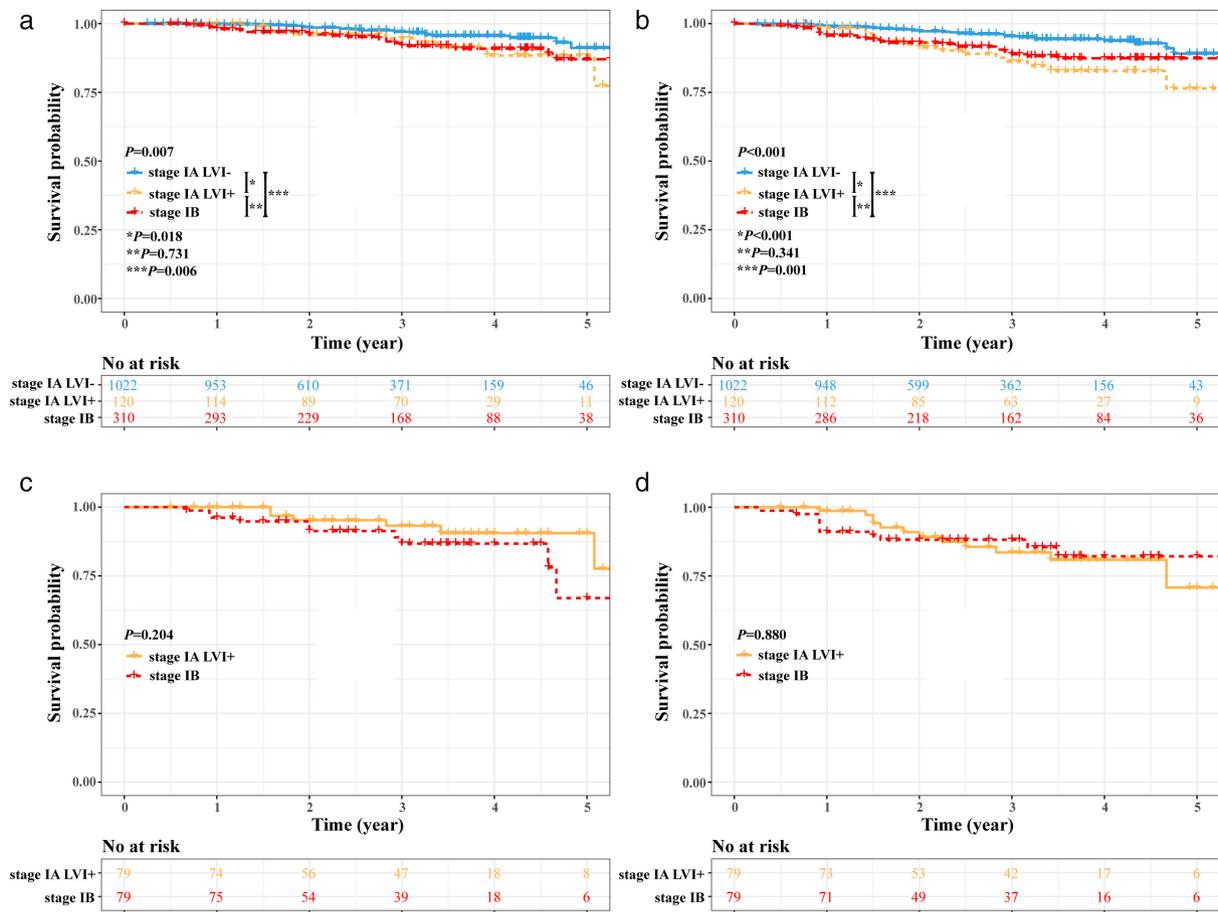
<sup>a</sup>Age, sex, smoking status, surgical approach, histology, VPI, LVI and pTNM stage were included in the multivariable Cox analysis of OS.

<sup>b</sup>Age, smoking status, DLCO (%), surgical approach, histology, LVI and pTNM stage were included in the multivariable Cox analysis of DFS.

than those of stage IA LVI+ patients and stage IB patients, and the latter two groups had comparable survival outcomes both before and after PSM analysis. Herein, we proposed that it might be better to upstage stage IA NSCLC patients with LVI to stage IB.

LVI, defined as the presence of neoplastic structures in the lumen of blood or lymphatic vessels,<sup>11</sup> is considered to be the first step of tumor metastasis.<sup>21,22</sup> To be more specific, tumor cells could reach the blood or lymph circulation by penetrating the vessels and travel to distant organs.<sup>21–23</sup> This was also confirmed in Brant et al.'s study<sup>5</sup> and Sung et al.'s study.<sup>24</sup> Therefore, LVI has been included in the TNM staging systems of several tumors such as hepatic carcinoma,<sup>25</sup> testicular cancer,<sup>26</sup> and penile cancer.<sup>27</sup> Although several studies evidenced that LVI has a strong adverse impact on NSCLC patient survivals,<sup>12–19</sup> it has not been incorporated into the current TNM staging manual of NSCLC.<sup>10</sup>

Intense interest has been focused on investigating the role of LVI in the TNM staging manual of NSCLC. In the study by Noma et al.,<sup>12</sup> the authors analyzed the data of 660 resected stage I NSCLC cases and demonstrated that stage IA patients with vascular invasion (VI) and stage IB patients had equivalent survival outcomes. Thus, they proposed that stage IA diseases with VI should be upstaged to stage IB.<sup>12</sup> The strength of their study was that the authors investigated the prognostic value of VI and lymphatic invasion (LI), respectively. However, their study only evaluated the disease-specific survival, which might have limited significance to clinical reference. Kudo et al.<sup>13</sup> presented a relatively large study of 694 resected stage I NSCLC patients and revealed that tumors with VI should be upstaged to the higher T category. The similar result was also observed in Tsuchiya et al.'s study.<sup>28</sup> However, the 7th and 5th TNM staging manuals were used in their studies, respectively, which might limit application in the current clinical practice.



**FIGURE 4** Kaplan–Meier estimate of OS and DFS: (A) OS comparisons: stage IA LVI– vs. stage IA LVI+ vs. stage IB; (B) DFS comparisons: stage IA LVI– vs. stage IA LVI+ vs. stage IB; (C) OS comparison after PSM: stage IA LVI+ vs. stage IB; and (D) DFS comparison after PSM: stage IA LVI+ vs. stage IB. OS, overall survival; DFS, disease-free survival; LVI, lymphovascular invasion

A study by Wang and colleagues evaluated the survivals between stage I NSCLC patients with LVI and those without LVI, and demonstrated that it is reasonable to upstage stage IA patients with LVI to stage IB.<sup>17</sup> The good points of their study were the large number of cases (2633 cases) with long-term follow-up. However, the baseline characteristics between stage IA patients with LVI and stage IB patients are not balanced well in their study, which might lead to bias and compromise their conclusions. The sample size of our study was large and the dataset that we used was well-managed and included well-annotated clinicopathologic data and complete follow-up information. Therefore, our results had good clinical reference value. Rigor and efficient statistical methodology (PSM analysis and LASSO regression model) was also used in our study, which could reduce bias and made our results more persuasive and reliable.

Our results showed that stage IA NSCLC patients with LVI and stage IB patients had similar survival rates. Therefore, we support the idea that it might be reasonable to upstage these LVI+ diseases from stage IA to stage IB. It is known that TNM stage is a strong determinant in guiding clinical decision making.<sup>29</sup> A more accurate assessment of the prognosis is conducive to formulate a more appropriate treatment strategy for patients. According to the National

Comprehensive Cancer Network (NCCN) guidelines, stage IA patients with LVI are recommended to adopt a regular follow-up strategy.<sup>29</sup> In our perspectives, closer follow-up or more intensive care should be administered to these patients owing to the high relapse rate.<sup>6–9</sup>

Prudence should be exercised when applying our results in daily clinical practice. First, we did not distinguish VI from LI. Previous study suggested that LI is not an independent prognostic factor for stage IA NSCLC.<sup>12</sup> Future studies are warranted to evaluate the prognostic values of VI and LI, respectively. Second, this was a retrospective study from a single center and inevitable bias exists, although PSM was used in this study. Finally, although the sample size of this study was relatively large, the number of cases was small in one subgroup (stage IA LVI+: 120 cases), therefore multicenter studies with larger volume are necessary to confirm our conclusions.

## CONCLUSIONS

In conclusion, our study demonstrated that the survivals of stage IA NSCLC with LVI were similar to those of stage IB patients. Hence, we proposed that LVI might be a non-sized T descriptor that could upstage stage IA diseases to stage IB.

## AUTHOR CONTRIBUTIONS

Conception and design: Man-Tang Qiu. Administrative support: Yun Li. Provision of study materials or patients: Jing-Sheng Cai, Xun Wang and Fei Yang. Collection and assembly of data: Jing-Sheng Cai and Xun Wang. Data analysis and interpretation: Jing-Sheng Cai. Manuscript writing: All authors. Final approval of manuscript: All authors.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

## ORCID

Jing-Sheng Cai  <https://orcid.org/0000-0003-3859-7159>

Man-Tang Qiu  <https://orcid.org/0000-0002-0419-9139>

## REFERENCES

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70:7–30.
- Zheng RS, Sun KX, Zhang SW, Zeng HM, Zou XN, Chen R, et al. Report of cancer epidemiology in China, 2015. *Zhonghua Zhong Liu Za Zhi.* 2019;41:19–28.
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68:394–424.
- Thornblade LW, Mulligan MS, Odem-Davis K, Hwang B, Waworuntu RL, Wolff EM, et al. Challenges in predicting recurrence after resection of node-negative non-small cell lung cancer. *Ann Thorac Surg.* 2018;106:1460–7.
- Brandt WS, Bouabdallah I, Tan KS, Park BJ, Adusumilli PS, Molena D, et al. Factors associated with distant recurrence following R0 lobectomy for pN0 lung adenocarcinoma. *J Thorac Cardiovasc Surg.* 2018;155(1212–24):e3.
- Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic impact of intratumoral vascular invasion in non-small cell lung cancer patients. *Thorax.* 2010;65:1092–8.
- Maeda R, Yoshida J, Ishii G, Hishida T, Aokage K, Nishimura M, et al. Long-term survival and risk factors for recurrence in stage I non-small cell lung cancer patients with tumors up to 3 cm in maximum dimension. *Chest.* 2010;138:357–62.
- De Giglio A, Di Federico A, Gelsomino F, Ardizzoni A. Prognostic relevance of pleural invasion for resected NSCLC patients undergoing adjuvant treatments: a propensity score-matched analysis of SEER database. *Lung Cancer.* 2021;161:18–25.
- Pathak R, Goldberg SB, Canavan M, Herrin J, Hoag JR, Salazar MC, et al. Association of survival with adjuvant chemotherapy among patients with early-stage non-small cell lung cancer with vs without high-risk clinicopathologic features. *JAMA Oncol.* 2020;6:1741–50.
- Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol.* 2016;11:39–51.
- Brechot JM, Chevret S, Charpentier MC, Appere de Vecchi C, Capron F, Prudent J, et al. Blood vessel and lymphatic vessel invasion in resected nonsmall cell lung carcinoma correlation with TNM stage and disease free and overall survival. *Cancer.* 1996;78:2111–8.
- Noma D, Inamura K, Matsuura Y, Hirata Y, Nakajima T, Yamazaki H, et al. Prognostic effect of lymphovascular invasion on TNM staging in stage I non-small-cell lung cancer. *Clin Lung Cancer.* 2018;19:e109–e22.
- Kudo Y, Saji H, Shimada Y, Matsubayashi J, Nagao T, Kakhana M, et al. Proposal on incorporating blood vessel invasion into the T classification parts as a practical staging system for stage I non-small cell lung cancer. *Lung Cancer.* 2013;81:187–93.
- Guglielmetti LC, Schneider D, Hillinger S, Opitz I, Caviezel C, Weder W, et al. Lymphovascular invasion is an independent prognostic factor for survival in pathologically proven N2 non-small cell lung cancer. *Swiss Med Wkly.* 2021;151:w20385.
- Yun JK, Lee GD, Choi S, Kim HR, Kim YH, Kim DK, et al. Comparison of prognostic impact of lymphovascular invasion in stage IA non-small cell lung cancer after lobectomy versus sublobar resection: a propensity score-matched analysis. *Lung Cancer.* 2020;146:105–11.
- Wang C, Wu Y, Shao J, Liu D, Li W. Clinicopathological variables influencing overall survival, recurrence and post-recurrence survival in resected stage I non-small-cell lung cancer. *BMC Cancer.* 2020;20:150.
- Wang S, Zhang B, Qian J, Qiao R, Xu J, Zhang L, et al. Proposal on incorporating lymphovascular invasion as a T-descriptor for stage I lung cancer. *Lung Cancer.* 2018;125:245–52.
- Okiror L, Harling L, Toufektzian L, King J, Routledge T, Harrison-Phipps K, et al. Prognostic factors including lymphovascular invasion on survival for resected non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2018;156:785–93.
- Hamanaka R, Yokose T, Sakuma Y, Tsuboi M, Ito H, Nakayama H, et al. Prognostic impact of vascular invasion and standardization of its evaluation in stage I non-small cell lung cancer. *Diagn Pathol.* 2015;10:17.
- Tibshirani R. The lasso method for variable selection in the Cox model. *Stat Med.* 1997;16:385–95.
- Fontanini G, Bigini D, Vignati S, Basolo F, Mussi A, Lucchi M, et al. Microvessel count predicts metastatic disease and survival in non-small cell lung cancer. *J Pathol.* 1995;177:57–63.
- Kang DY, Lee S. Lymphatic vessel invasion and lymph node metastasis in patients with clinical stage I non-small cell lung cancer. *Thorac Cardiovasc Surg.* 2014;62:521–4.
- Liotta LA, Kleinerman J, Saidel GM. Quantitative relationships of intravascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. *Cancer Res.* 1974;34:997–1004.
- Sung SY, Kwak YK, Lee SW, Jo IY, Park JK, Kim KS, et al. Lymphovascular invasion increases the risk of nodal and distant recurrence in node-negative stage I-IIA non-small-cell lung cancer. *Oncology.* 2018;95:156–62.
- Henderson JM, Sherman M, Tavill A, Abecassis M, Chejfec G, Gramlich T. AHPBA/AJCC consensus conference on staging of hepatocellular carcinoma: consensus statement. *HPB (Oxford).* 2003;5:243–50.
- Lobo J, Costa AL, Vilela-Salgueiro B, Rodrigues A, Guimaraes R, Cantante M, et al. Testicular germ cell tumors: revisiting a series in light of the new WHO classification and AJCC staging systems, focusing on challenges for pathologists. *Hum Pathol.* 2018;82:113–24.
- Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. *Eur Urol.* 2018;73:560–9.
- Tsuchiya T, Hashizume S, Akamine S, Muraoka M, Honda S, Tsuji K, et al. Upstaging by vessel invasion improves the pathology staging system of non-small cell lung cancer. *Chest.* 2007;132:170–7.
- National Comprehensive Cancer Network. Non-Small Cell Lung Cancer (Version 4.2021). Available online at: [https://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf) (accessed March 5, 2021). 2021.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Cai J-S, Wang X, Yang F, Li Y, Qiu M-T. Lymphovascular invasion: A non-sized T descriptor for stage IA non-small cell lung cancer. *Thorac Cancer.* 2022;13(17):2413–20. <https://doi.org/10.1111/1759-7714.14530>