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ORIGINAL REPORT

Development and Validation of a Nomogram for Predicting Survival in Patients With Resected Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
A nomogram is a useful and convenient tool for individualized cancer prognoses. We sought to develop a clinical nomogram for predicting survival of patients with resected non–small-cell lung cancer (NSCLC).

Patients and Methods
On the basis of data from a multi-institutional registry of 6,111 patients with resected NSCLC in China, we identified and integrated significant prognostic factors for survival to build a nomogram. The model was subjected to bootstrap internal validation and to external validation with a separate cohort of 2,148 patients from the International Association for the Study of Lung Cancer (IASLC) database. The predictive accuracy and discriminative ability were measured by concordance index (C-index) and risk group stratification.

Results
A total of 5,261 patients were included for analysis. Six independent prognostic factors were identified and entered into the nomogram. The calibration curves for probability of 1-, 3-, and 5-year overall survival (OS) showed optimal agreement between nomogram prediction and actual observation. The C-index of the nomogram was higher than that of the seventh edition American Joint Committee on Cancer TNM staging system for predicting OS (primary cohort, 0.71 *v* 0.68, respectively; $P < .01$; IASLC cohort, 0.67 *v* 0.64, respectively; $P = .06$). The stratification into different risk groups allowed significant distinction between survival curves within respective TNM categories.

Conclusion
We established and validated a novel nomogram that can provide individual prediction of OS for patients with resected NSCLC. This practical prognostic model may help clinicians in decision making and design of clinical studies.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths worldwide, with non–small-cell lung cancer (NSCLC) accounting for approximately 85% of all diagnosed patients.[1] For early-stage NSCLC, including stage I and II and a subset of stage III disease, the standard and potentially curative treatment is radical resection.[2] The seventh edition of the American Joint Committee on Cancer TNM classification represents the most widely used staging system, in which patients with nonmetastatic NSCLC are stratified based on tumor size and invasion, as well as extent of lymph node involvement.[3] However, survival of patients with the same stage varies widely.[4-6] It is believed that other independent prognostic factors such as sex, age, histology, and treatment-related factors could significantly contribute to individualized prediction of survival.[4-6]

Nomograms have been accepted as reliable tools to quantify risk by incorporating and illustrating important factors for oncologic prognoses.[7-9] By creating an intuitive graph of a statistical predictive model, a nomogram gives rise to a numerical probability of a clinical event, such as overall survival (OS). In several types of cancers, nomograms have been proved to generate more precise prediction when compared with the traditional TNM staging systems.[10,11] However, nomograms for predicting long-term survival outcome after surgery in NSCLC

Table 1. Demographics and Clinicopathologic Characteristics of the Primary Cohort (training set) and IASLC Cohort (validation set)

Demographic or Clinicopathologic Characteristic	Training Set (N = 5,261)				IASLC Validation Set (N = 2,148)							
					China		Europe		North America		Overall	
			OS (months)									
	No. of Patients	%	Median	95% CI	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Sex												
Male	3,657	69.5	85.8	77.5 to 94.1	145	69.4	572	83.7	560	44.6	1,277	59.5
Female	1,604	30.5	90.2	78.6 to 101.8	64	30.6	111	16.3	696	55.4	871	40.5
Age, years												
< 60	2,597	49.4	101.6	87.4 to 115.7	99	47.4	209	30.6	252	20.1	560	26.1
60-70	1,891	35.9	88.3	76.3 to 100.3	64	30.6	256	37.5	436	34.7	756	35.2
> 70	773	14.7	65.0	49.8 to 80.2	46	22.0	218	31.9	568	45.2	832	38.7
ECOG PS												
0	1,788	34.0	91.6	81.4 to 101.9								
1	3,473	66.0	88.1	79.6 to 96.6								
Histology												
BAC	269	5.1	101	NA	7	3.3	26	3.8	130	10.4	163	7.6
SC	1,651	31.4	90.4	75.2 to 105.6	50	23.9	268	39.2	208	16.6	526	24.5
ADC	2,886	54.9	87.1	76.6 to 97.6	126	60.3	276	40.4	628	50.0	1,030	48.0
ADSC	282	5.4	56.8	38.2 to 75.3	8	3.8	19	2.8	11	0.9	38	1.8
LC	104	1.9	NA		16	7.7	53	7.8	6	0.5	75	3.5
Others	69	1.3	44.4	25.1 to 63.7	2	1.0	41	6.0	273	21.7	316	14.7
Operation type												
Complete VATS	1,673	31.8	102.9	91.5 to 114.3								
Assisted VATS	764	14.5	80.6	67.4 to 93.7								
Open surgery	2,824	53.7	87.1	76.6 to 97.7								
Resection type												
Lobectomy	4,733	94.6	90.4	81.1 to 99.7								
Sleeve resection	146	2.8	NA									
Wedge resection	96	1.8	88.2	46.3 to 130.1								
Pneumonectomy	286	5.4	40.3	32.6 to 48.1								
Tumor location												
Right upper lobe	1,490	28.3	102.6	NA								
Right middle lobe	383	7.3	73.6	54.5 to 92.7								
Right lower lobe	982	18.7	98.8	81.7 to 116.0								
Left upper lobe	518	9.9	87.4	72.3 to 102.4								
Left lower lobe	379	7.2	88.1	NA								
Undefined	1,509	28.7	78.3	62.6 to 94.0								
Pathologic T category												
T1a	696	13.2	Not reached		25	12.0	139	20.4	414	33.0	578	26.9
T1b	717	13.6	Not reached		25	12.0	82	12.0	206	16.4	313	14.6
T2a	2,498	47.5	99.4	84.9 to 113.9	104	49.8	233	34.1	343	27.3	680	31.7
T2b	642	12.2	54.3	40.8 to 67.8	19	9.1	75	11.0	73	5.8	167	7.8
T3	625	11.9	35.6	30.5 to 40.7	25	12.0	125	18.3	150	11.9	300	14.0
T4	83	1.6	41.7	16.4 to 67.1	11	5.3	29	4.2	70	5.6	110	5.1
Pathologic N category					115	55.0	474	69.4	897	71.4	1,486	69.2
N0	3,141	59.7	129.3	NA	21	10.0	131	19.2	153	12.2	305	14.2
N1	857	16.3	53.0	46.4 to 59.7	73	34.9	78	11.4	206	16.4	357	16.6
N2	1,263	24.0	33.0	30.1 to 35.9	115	55.0	474	69.4	897	71.4	1,486	69.2
Pathologic TNM stage												
IA	993	18.9	Not reached		32	15.3	172	25.2	505	40.2	709	33.0
IB	1,479	28.1	Not reached		59	28.2	162	23.7	213	17.0	434	20.2
IIA	878	16.7	76.2	62.7 to 89.7	24	11.5	124	18.2	133	10.6	281	13.1
IIB	429	8.2	40.5	27.9 to 53.1	11	5.3	93	13.6	122	9.7	226	10.5
IIIA	1,482	28.2	33.7	30.9 to 36.5	77	36.8	129	18.9	263	20.9	469	21.8
T4N2	NA		NA		6	2.9	3	0.4	20	1.6	29	1.4
No. of harvested LNs												
0-14	2,755	52.4	77.5	68.1 to 86.9	54	25.8	505	73.9	1155	92.0	1,714	79.8
≥ 15	2,506	47.6	101.7	97.3 to 106.1	155	74.2	178	26.1	101	8.0	434	20.2

(continued on following page)

Table 1. Demographics and Clinicopathologic Characteristics of the Primary Cohort (training set) and IASLC Cohort (validation set) (continued)

Demographic or Clinicopathologic Characteristic	Training Set (N = 5,261)				IASLC Validation Set (N = 2,148)							
			OS (months)		China		Europe		North America		Overall	
	No. of Patients	%	Median	95% CI	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Stations of sampled LNs												
1-6	2,129	40.5	78.7	68.0 to 89.3								
7-10	3,109	59.1	97.7	89.0 to 106.4								
Blood loss volume, mL												
0-150	2,324	44.2	99.4	87.5 to 111.4								
> 150	2,937	55.8	76.2	66.0 to 86.4								
Comorbidity												
Yes	4,755	90.4	88.3	81.2 to 95.4								
No	270	5.1	71.9	46.2 to 97.6								
Postoperative complications												
Yes	4,956	94.2	89.0	82.3 to 95.7								
No	305	5.8	71.9	NA								

Abbreviations: ADC, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchioloalveolar carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IASLC, International Association for the Study of Lung Cancer; LC, large-cell carcinoma; LN, lymph node; NA, not available; SC, squamous carcinoma; VATS, video-assisted thoracic surgery.

are scarce. In this study, we aimed to build a nomogram for resected NSCLC by combining known clinicopathologic variables based on the data from a multi-institutional registry in China. In addition, we used a separate cohort from the International Association for the Study of Lung Cancer (IASLC) database to externally validate it.

PATIENTS AND METHODS

Patient Population and Data Processing

A multi-institutional registry consisting of 6,111 patients who received treatment between January 2001 and December 2008 from the departments of cardiothoracic surgery of seven institutions in the People's Republic of China (The First Affiliated Hospital of Guangzhou Medical University, Guangzhou; Shanghai Pulmonary Hospital of Tongji University, Shanghai; Shanghai Zhongshan Hospital of Fudan University, Shanghai; West China Hospital, Sichuan University, Chengdu; China and Japan Friendship Hospital, Beijing; Shenzhen People's Hospital, Shenzhen; and Cancer Center of Sun Yat-Sen University, Guangzhou) was established. Ethical approval was obtained from participating institutions through their respective institutional review boards or the chairperson of their ethics committee who waived the need for patient consent for this study when individual patient consents were not identified.

A standardized data form was created to retrieve all relevant information on sociodemographic data (age, sex, Eastern Cooperative Oncology Group performance status, smoking history [yes or no], forced expiratory volume in 1 second [FEV_1], and FEV_1/forced vital capacity [FEV1%]); pathologic data (histologic type; pathologic tumor, node, and metastasis status; tumor location: central [starting within tertiary bronchi] *v* peripheral [starting beyond tertiary bronchi], or specific lobes; number and station of obtained lymph nodes; and presence of viscera invasion); treatment-related data, including type of resection (lobectomy, sleeve resection, wedge resection, or pneumonectomy) and type of operation (complete video-assisted thoracic surgery [VATS; non–rib-spreading approach], assisted VATS [mini-thoracotomy approach with rib spreading], or open surgery); and presence of any comorbidity (including all diseases described in the International Classification of Diseases, Ninth Revision, Clinical Modification[12]) or complications (including bronchopleural fistula, chylothorax, hemothorax, transfusion, respiratory failure, arrhythmia, myocardial infarct, cardiovascular complications, prolonged air leak of > 5 days, pneumonia lung embolism, empyema, and wound infection). Standardized clinical data for consecutive patients treated in each of the seven institutions were entered into an independent central database at the Baird Institute for Applied Heart and Lung Surgical Research in Sydney, Australia. Follow-up data for all patients were obtained from their most recent medical review, which consisted of a clinical examination and an assessment of chest x-rays or computed tomography scans. Patients' survival time was calculated from the surgery date to the date of death or last contact. Pathologic staging was characterized according to the seventh edition of the American Joint Committee on Cancer TNM staging system. An independent biostatistician managed and maintained the collected data.

Only patients diagnosed with NSCLC who underwent radical resection were included in the study. Patients who underwent resection for local advanced or metastatic disease (TNM stage IIIB or stage IV) were excluded. Variables with more than 10% missing values were not eligible for analysis. In addition, patients with any missing value on the eligible variables were excluded from subsequent processing. Continuous variables were transformed into categorical variables based on recognized cutoff values (for age) or median number (for blood loss volume, number of obtained lymph nodes, and lymph node station).[13]

To examine the generalizability of the model, an external validation cohort was provided by the IASLC lung cancer database. The cohort is composed of 2,148 patients with stage I to III NSCLC diagnosed between 1999 and 2010 in China, Europe, and North America. It should be noted that patients in this cohort from China were treated at the Guangdong General Hospital and Shanghai Lung Tumor Medical Center and are completely distinct from the patients in the primary multi-institutional registry. Only patients with surgically resected, nonmetastatic disease were included, and all patients were required to have sufficient information to score all variables in the established nomogram. Patients with N3 disease were excluded because they could not be scored according to the nomogram. Although we did not include patients with T4N2 disease when building the nomogram, the statisticians from the IASLC included these patients according to the principle of validation because these patients could be scored by the nomogram. Including these patients tested the validity of the nomogram in a wider set of patients.

Construction of the Nomogram

In the training set, survival curves for different variable values were generated using the Kaplan-Meier estimates and were compared using the log-rank test. Variables that achieved significance at $P < .05$ were entered into the multivariable analyses via the Cox regression model. Statistical analyses to

Table 2. Univariable Analysis and Cox Proportional Hazards Regression Analysis

Variable	Univariable Analysis *P*	Multivariable Analysis			Selected Factors for Building the Model		
		Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Sex	< .001			.002			< .001
Female		Reference			Reference		
Male		1.196	1.068 to 1.340	.002	1.222	1.092 to 1.367	< .001
Age, years	< .001			< .001			< .001
< 60		Reference			Reference		
60-70		1.223	1.100 to 1.360	< .001	1.212	1.092 to 1.346	< .001
> 70		1.695	1.477 to 1.945	< .001	1.658	1.448 to 1.898	< .001
Histology	< .001			< .001			< .001
BAC		Reference			Reference		
SC		1.107	0.846 to 1.448	.458	1.168	0.895 to 1.523	.252
ADC		1.306	1.008 to 1.692	.043	1.351	1.046 to 1.745	.021
ADSC		1.784	1.310 to 2.430	.000	1.854	1.363 to 2.521	< .001
LC		1.441	0.951 to 2.184	.085	1.524	1.009 to 2.301	.045
Others		2.049	1.323 to 3.175	.001	2.060	1.335 to 3.179	.001
VATS type	< .001			.165			
Complete VATS		Reference					
Assisted VATS		1.143	0.996 to 1.313	.058			
Open surgery		1.056	0.905 to 1.232	.491			
Resection type	< .001			.143			
Lobectomy		Reference					
Sleeve resection		1.081	0.808 to 1.445	.599			
Wedge resection		1.294	0.926 to 1.808	.132			
Pneumonectomy		1.337	0.865 to 2.064	.191			
Tumor location	.005			.227			
Right upper lobe		Reference					
Right middle lobe		1.093	0.895 to 1.335	.384			
Right lower lobe		1.085	0.938 to 1.255	.270			
Left upper lobe		1.081	0.901 to 1.297	.400			
Left lower lobe		0.963	0.780 to 1.187	.721			
Undefined		1.164	1.023 to 1.324	.021			
Pathologic T category	< .001			< .001			< .001
T1a		Reference			Reference		
T1b		1.249	0.997 to 1.566	.054	1.246	0.994 to 1.562	.056
T2a		1.590	1.312 to 1.926	< .001	1.568	1.295 to 1.897	< .001
T2b		2.386	1.915 to 2.974	< .001	2.354	1.898 to 2.919	< .001
T3		3.059	2.460 to 3.806	< .001	2.974	2.406 to 3.676	< .001
T4		3.670	2.560 to 5.260	< .001	3.669	2.573 to 5.233	< .001
Pathologic N category	< .001			< .001			
N0		Reference			Reference		
N1		2.066	1.816 to 2.350	< .001	2.092	1.842 to 2.376	< .001
N2		3.265	2.918 to 3.653	< .001	3.250	2.911 to 3.630	< .001
No. of harvested LNs	< .001			< .001			< .001
0-14		Reference			Reference		
≥ 15		0.741	0.671 to 0.818	< .001	0.734	0.667 to 0.809	< .001
Blood loss volume, mL	< .001			< .001			
0-150		Reference					
> 150		1.296	1.159 to 1.449	< .001			
ECOG PS	.486						
Stations of sampled LNs	.182						
Comorbidity	.194						
Postoperative complications	.081						

Abbreviations: ADC, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchioloalveolar carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; LC, large-cell carcinoma; LN, lymph node; SC, squamous carcinoma; VATS, video-assisted thoracic surgery.

identify independent prognostic factors were conducted in SPSS 17.0 for Windows (SPSS, Chicago, IL). On the basis of the results of the multivariable analysis, a nomogram was formulated by R 2.14.1 (http://www.r-project.org) with the survival and rms package.[14] A final model was selected using a backward step-down process, which used the Akaike information criterion as a stopping rule.[15]

Validation and Calibration of the Nomogram

The nomogram was subjected to 1,000 bootstrap resamples for internal validation of the primary training cohort and external validation with the IASLC cohort. The model performance for predicting outcome was evaluated by calculating the concordance index (C-index).[16] The value of the C-index ranges from 0.5 to 1.0, with 0.5 indicating a random chance and 1.0 indicating

a perfect ability to correctly discriminate the outcome with the model. Comparison of the C-index of two different models was based on methods previously described.[17] Calibration of the nomogram for 1-, 3-, and 5-year OS was performed by comparing the predicted survival with the observed survival after bias correction.

Risk Group Stratification Based on the Nomogram Beyond TNM Staging

In addition to numerically comparing the discrimination ability by C-index, we sought to illustrate the independent discrimination ability of the nomogram beyond standard TNM staging. By grouping the patients evenly into different risk groups within a certain TN category according to the total risk scores (from highest to lowest) in the training cohort, we determined the cutoff values. These values were then applied to the IASLC validation cohort, and the respective Kaplan-Meier survival curves were delineated.

RESULTS

Screening Process and Clinicopathologic Characteristics of Patients

Among the collected variables in the primary database, FEV_1, FEV_1%, tumor location (central *v* peripheral), presence of viscera invasion, and smoking history were not suitable for analysis because of a rate of missing values of greater than 10%. Of the 6,111 patients in the primary database, patients without documented staging information (n = 83) and patients who had stage IIIB or IV disease (n = 255) were excluded. In addition, patients who had missing values on any of the examined variables, including histology (n = 140), tumor location (n = 373), resection type (n = 21), sampled lymph nodes (n = 28), sampled lymph node station (n = 27), blood loss volume (n = 292), presence of comorbidity (n = 266), presence of postoperative complications (n = 280), and survival outcome (n = 4), were excluded. Thus, a total of 5,261 patients were included according to the screening criteria. There were 1,746 events (deaths) over a median follow-up time of 3.1 years (range, 3 days to 10.6 years). The median survival time was 7.3 years (95% CI, 6.7 to 7.8 years). The IASLC cohort consisted of the entire 2,148 patients with stage I to III NSCLC diagnosed between 1999 and 2010, which included 209 patients from China, 683 patients from Europe, and 1,256 patients from North America. There were 762 events (deaths) over a median follow-up time of 2.6 years (range, 0 to 9.1 years). The median survival time was 5.6 years (95% CI, 5.1 to 6.2 years). The clinicopathologic characteristics of patients in the primary and IASLC validation cohorts are listed in Table 1.

Independent Prognostic Factors in the Training Set

The results of the univariable analysis are listed in Table 2. Female sex (*v* male; $P < .001$) and younger age (< 60 *v* 60 to 70 *v* > 70; $P < .001$) were associated with better prognosis. Among all cell types, bronchioloalveolar carcinoma subtype had the most favorable survival, followed by squamous cell carcinoma, adenocarcinoma, large-cell carcinoma/adenosquamous carcinoma, and others ($P < .001$). Pathologic T ($P < .001$) and N categories ($P < .001$) were also factors that had an impact on survival. With respect to factors associated with surgery, we found that patients who underwent pneumonectomy experienced less favorable survival compared with patients who underwent lobectomy, sleeve resection, or wedge resection ($P < .001$). Patients who received and successfully finished a complete VATS resection had superior survival than patients who did not receive or complete a minimally invasive surgery ($P < .001$). Interestingly, there was no significant survival difference between Eastern Cooperative Oncology Group performance status of 0 and 1 ($P = .486$). Some parameters obtained from the perioperative period, including number of lymph nodes obtained ($P < .001$) and volume of blood loss ($P < .001$), were significant, but other parameters, including the stations of sampled lymph nodes ($P = .182$), presence of any comorbidity ($P = .194$), and presence of postoperative complications ($P = .081$), were not. All significant factors in the univariable analysis were entered into the multivariable analysis based on the Cox regression. Age ($P < .001$), sex ($P = .002$), histology ($P < .001$), number of obtained lymph nodes ($P < .001$), blood loss volume ($P < .001$), T category ($P < .001$), and N category ($P < .001$) remained independent prognostic factors in the Cox model (Table 2).

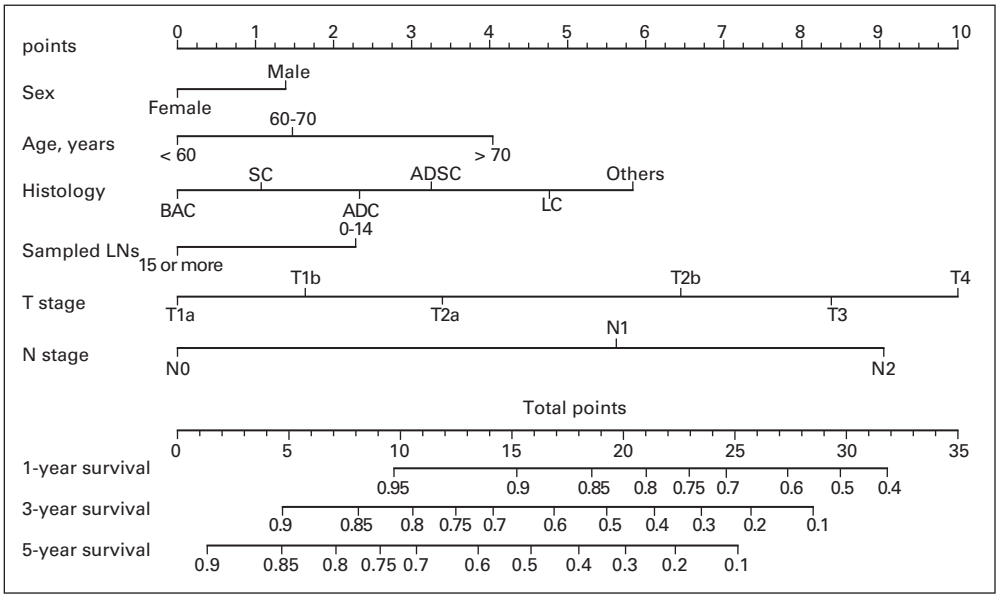

Fig 1. Postoperative prognostic nomogram for patients with resected non–small-cell lung cancer. ADC, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchioloalveolar carcinoma (fits adenocarcinoma in situ and minimally invasive adenocarcinoma); LC, large-cell carcinoma; LN, lymph node; SC, squamous carcinoma.

Prognostic Nomogram for OS

A nomogram that incorporated the significant prognostic factors was established (Fig 1 and Table 3). Considering the availability of information on blood loss volume in the IASLC validation set, we excluded blood loss volume in the final nomogram without compromising the discriminative ability of the model. The nomogram illustrated T category and N category as sharing the largest contribution to prognosis, followed by the histologic type and age. Number of obtained lymph nodes and sex showed a moderate impact on the survival. Each subtype within these variable was assigned a score on the point scale. By adding up the total score and locating it on the total point scale, we were easily able to draw a straight line down to determine the estimated probability of survival at each time point.

Calibration and Validation of the Nomogram

The calibration plots presented an excellent agreement in the primary cohort and an acceptable agreement in the IASLC validation cohort between the nomogram prediction and actual observation for 1-, 3-, and 5-year OS (Fig 2). In the primary cohort, the Harrell's C-index for the established nomogram to predict OS (0.71; 95% CI, 0.70 to 0.72) was significantly higher than that of the TNM staging system (0.68; 95% CI, 0.67 to 0.69; $P < .01$). In the IASLC cohort, the C-index was also greater for the nomogram prediction (0.67; 95% CI, 0.65 to 0.69) than for the TNM category prediction (0.64; 95% CI, 0.62 to 0.66), although this difference was not statistically significant ($P = .06$).

Table 3. Point Assignment and Prognostic Score

Variable and Prognostic Score	Score	Estimated 5-Year Overall Survival (%)
Age, years		
< 60	0	
60-70	1.5	
> 70	4	
Histology		
BAC	0	
SC	1.1	
AD	2.3	
LC	3.2	
ADSC	4.8	
Others	5.8	
No. of sampled LNs		
> 14	0	
0-14	2.3	
Sex		
Male	1.4	
Female	0	
T stage		
T1a	0	
T1b	1.6	
T2a	3.3	
T2b	6.4	
T3	8.4	
T4	10	
N stage		
N0	0	
N1	5.6	
N2	9	
Total prognostic score*		
0-7		82
7.1-9.6		72
9.7-13.3		63
13.4-16.9		45
≥ 17		29

Abbreviations: AD, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchioloalveolar carcinoma; LC, large-cell carcinoma; LN, lymph node; SC, squamous carcinoma.
*For score-projected estimation, please see Figure 1.

Performance of the Nomogram in Stratifying Risk of Patients

We determined the cutoff values by grouping the patients in the training cohort evenly into five subgroups after sorting by total score (score: 0 to 7, 7.1 to 9.6, 9.7 to 13.3, 13.4 to 16.9, and ≥ 17); each group represented a distinct prognosis (Table 3 and Appendix Fig A1, online only). After applying the cutoff values to group patients in the IASLC cohort, stratification into different risk subgroups allowed significant distinction between Kaplan-Meier curves for survival outcomes within each TN category (Fig 3).

DISCUSSION

Because NSCLC is remarkably heterogeneous in regard to survival of individual patients,[18] prediction of survival using the TNM staging system is imprecise. Despite several previously reported prognostic models,[6,19] a nomogram has not been developed for early-stage NSCLC. Thus, we sought to develop a postoperative nomogram to predict long-term survival of operable patients.

The primary cohort was obtained from a multi-institutional registry of seven institutions from China. These institutions are all leading medical centers and represent the standard and advanced technical or medical care in China. The wide geographic distribution of patients and large sample size in this cohort guaranteed its representativeness and generalizability for Chinese patients with NSCLC. Through univariable analysis and subsequent multivariable analysis, we identified age, sex, histology, number of obtained lymph nodes, blood loss volume, T category, and N category as independent prognostic factors. These findings were in high concordance with previous reports on risk factors for NSCLC.[20-23] Notably, the number of obtained lymph nodes was an important factor that has been established in many cancers,[24-26] and some similar studies also support the relationship between higher number of examined lymph nodes and better survival.[27,28] One of the possible reasons is that with more extensive sampling of lymph nodes, potential metastasized lymph nodes will be cleared out. Moreover, complete sampling of lymph nodes results in precise staging and, therefore, appropriate adjuvant treatments for patients.

It should be noted that, since 2011, the term bronchioloalveolar carcinoma is no longer used in the current IASLC/American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma.[29] We encourage users to assign the current terms of adenocarcinoma in situ and minimally invasive adenocarcinoma to the score of the bronchioloalveolar carcinoma category in this nomogram, which indicates the lowest risk for disease-specific death among all histologic subtypes, whereas other adenocarcinoma subtypes should be assigned according to the adenocarcinoma category. In addition, adjuvant chemotherapy and adjuvant radiotherapy were not selected as candidate factors because adjuvant therapies are recommended only for a proportion of

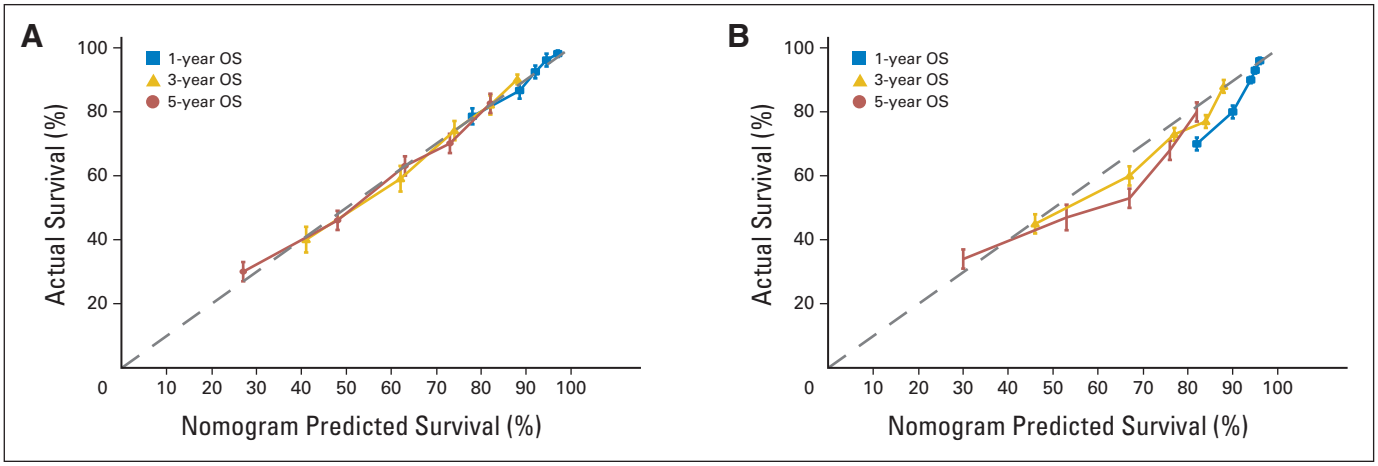

Fig 2. The calibration curves for predicting patient survival at each time point in the (A) primary cohort and (B) International Association for the Study of Lung Cancer cohort. Nomogram-predicted overall survival (OS) is plotted on the *x*-axis; actual OS is plotted on the *y*-axis. A plot along the 45-degree line would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes.

patients who had potentially high risk for disease recurrence, such as patients with residual cancer, lymph node involvement, or more aggressive malignancy. The adjuvant therapies, when introduced into the nomogram, have contradictory impact on targeted and nontargeted populations, causing the wrong score to be assigned to nontargeted patients. In addition, a high proportion of missing data and a time bias would be introduced because adjuvant chemotherapy was not a routine treatment in China until 2006. The blood loss volume was a significant factor in the primary cohort, but it was not recorded in the IASLC database. We cautiously decided not to include this factor in the final nomogram because the C-index improved by only 0.004 after adding it to the current model. In addition, we also tested an altered model by putting age and obtained lymph node count into the nomogram as a continuous variable, but discrimination was slightly impaired (C-index, 0.70).

Validation of the nomogram is essential to avoid overfitting of the model and determine generalizability.[30] In the current study, calibration plots showed optimal agreement between prediction and actual observation, which guaranteed the repeatability and reliability of the established nomogram. More importantly, the model also fit the IASLC cohort, which consisted of patients from China, North America, and Europe; this supported the worldwide use of this nomogram, regardless of race and health care disparities. Discrimination was revealed by the significantly higher C-index of the nomogram compared with the TNM staging system in the training cohort. In the external validation cohort, the discriminative ability was only slightly reduced. In addition, by stratifying patients with disease in the same TNM category into five risk groups using the cutoff values from the training cohort, we separated patients in the IASLC cohort with distinct survival outcomes. Although the magnitudes of discrimination ability of the primary cohort (C-index, 0.71 for nomogram *v* 0.68 for TNM staging system; 0.03 difference) and external validation cohort (0.67 for nomogram *v* 0.64 for TNM staging system; 0.03 difference) were similar, significance was not reached ($P = .06$) and some tangles of survival curves were observed in stage IIB patients. We believe the sample size to be the main contributor to this insignificance. Another reason for this might be that patients with T4N2 disease were included in the validation cohort, whereas such patients were not included when building the nomogram.

To the best of our knowledge, this is the first nomogram for predicting survival of patients with resected NSCLC that is based on a large database with long-term follow-up. Both physicians and patients could perform an individualized survival prediction after surgery through this easy-to-use scoring system. Identifying subgroups of patients at different risk for poor survival might have an impact on the treatment or care option. Selection of patients who need additional therapy or intensive follow-up remains controversial.[31] This scoring system should help physicians to address such issues. In addition, this tool could provide information for patient stratification in the design of clinical study, gaining better equivalence between study arms. We believe that the established nomogram represents a more precise prognostic model compared with the TNM staging system and some previous prognostic models.[4,6] Still, our nomogram is limited by the retrospective nature of data collection and the failure to incorporate some recognized prognostic parameters (eg, tumor cell differentiation, lymphatic permeation, vascular invasion perineural invasion[32-35]), and some important molecular factors (eg, *EGFR* mutation, *ALK-EML4* fusion). Further efforts on prospective data collection and patient follow-up, wider geographic recruitment, and incorporation of some other factors are encouraged to improve this model.

In conclusion, we established and validated a novel nomogram for predicting survival of patients with resected NSCLC. Through this model, clinicians could more precisely estimate the survival of individual patients after surgery and identify subgroups of patients who are in need of a specific treatment strategy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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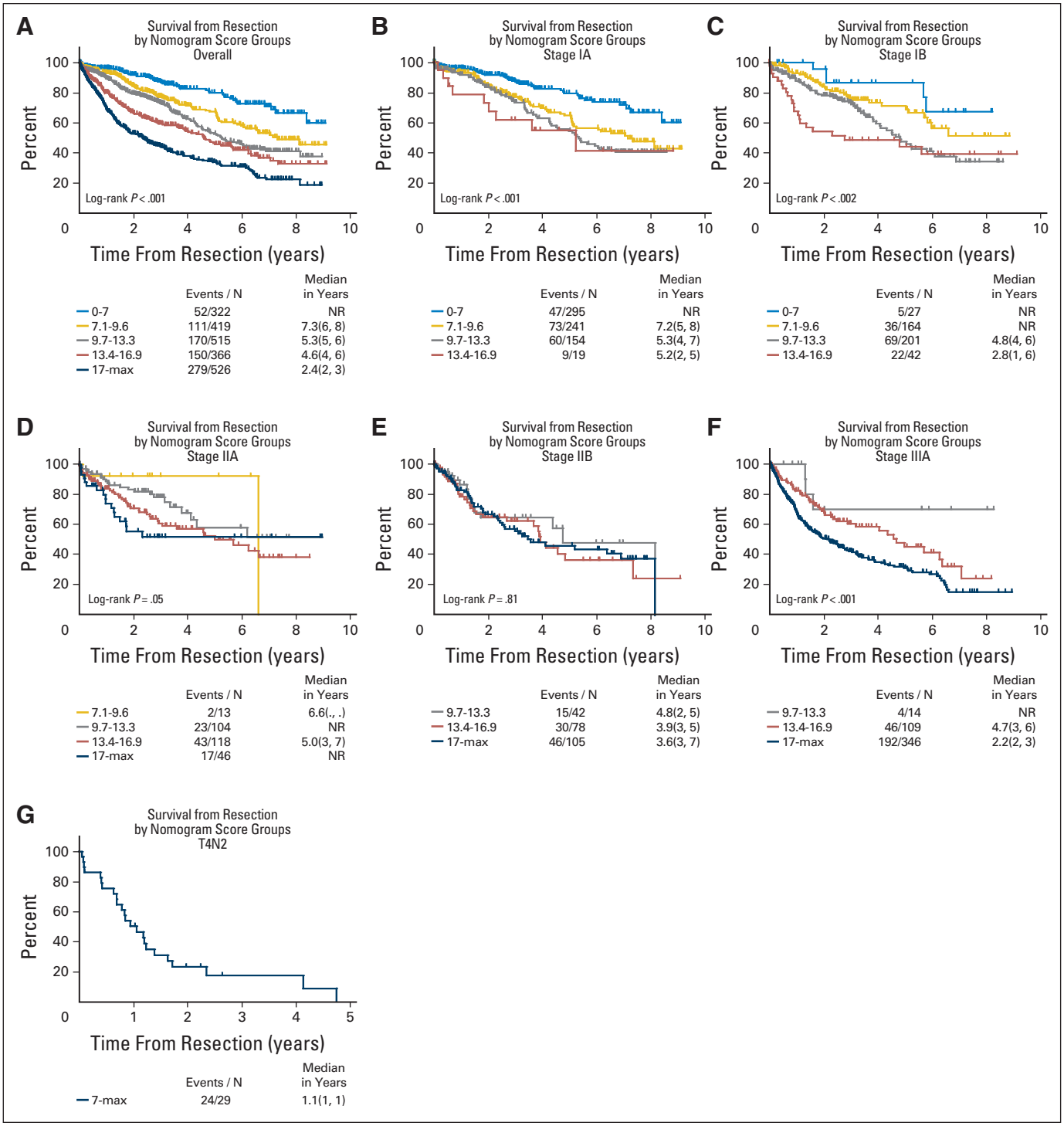

Fig 3. Risk group stratification within each TNM stage (A, all patients; B-G, stages) in the International Association for the Study of Lung Cancer cohort. Subgroups with fewer than 10 patients were omitted from the graphs. NR, not reached.

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Data analysis and interpretation: Wenhua Liang, Jianxing He

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Final approval of manuscript: All authors

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GLOSSARY TERMS

nomogram: a prediction tool based on the Cox proportional hazards regression model that incorporates factors included in any staging system. It can also add other clinical and pathologic factors known to have an impact on outcome.

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

risk score: a simplified version of a prognostic model, in which scores are assigned to each risk factor (eg, on the basis of rounded regression coefficients).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Development and Validation of a Nomogram for Predicting Survival in Patients With Resected Non–Small-Cell Lung Cancer

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Appendix

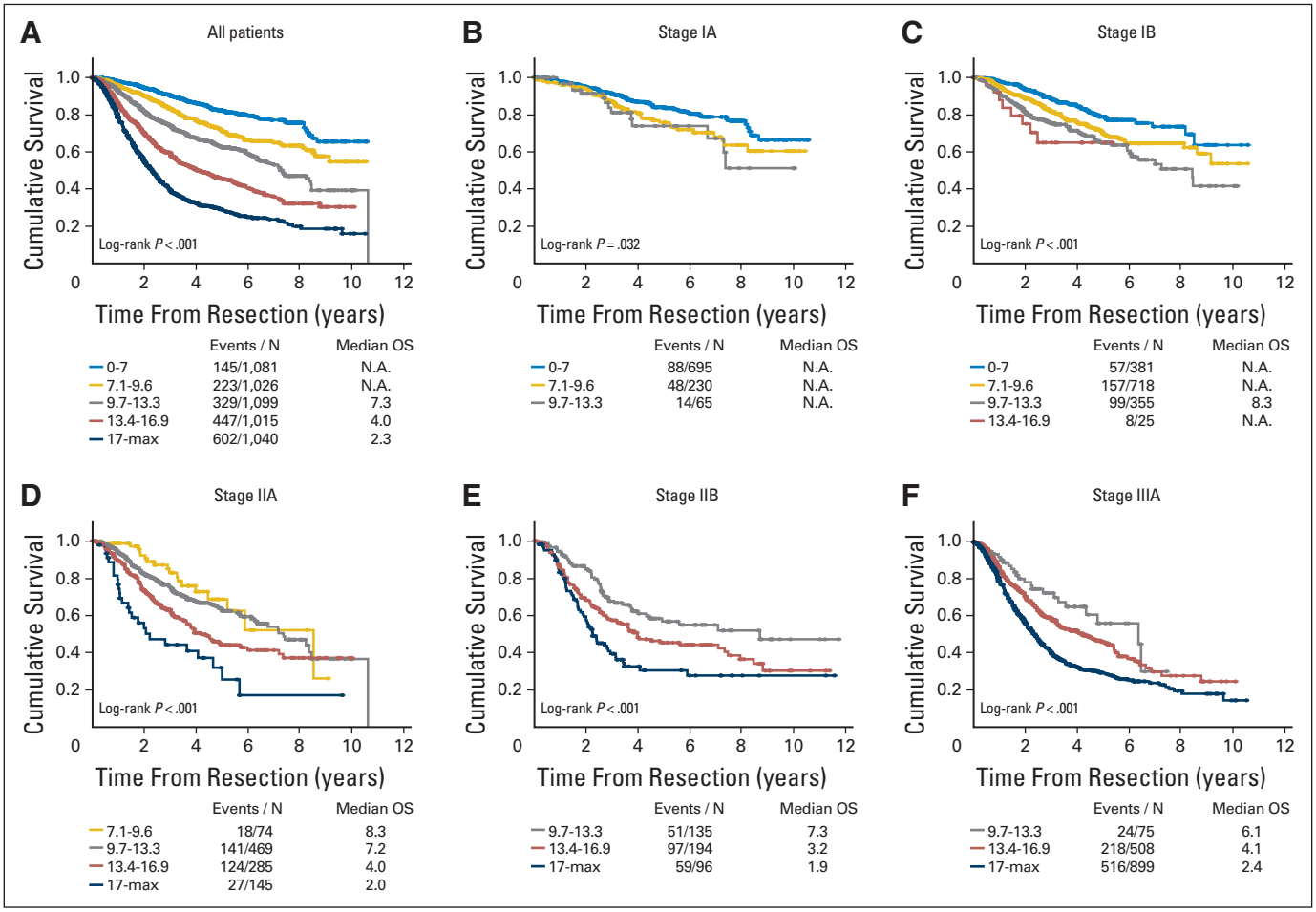

Fig A1. Determination of cutoff values based on the training cohort and the respective delineation of survival curves. (A) All patients; (B-F) stages. Subgroups with fewer than 10 patients were omitted from the graphs. NA, not available; OS, overall survival.