Cancer Management and Research

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ORIGINAL RESEARCH

Prediction of Overall Survival of Patients with Completely Resected Non-Small Cell Lung Cancer: Analyses of Preoperative Spirometry, Preoperative Blood Tests, and Other Clinicopathological Data

This article was published in the following Dove Press journal:
Cancer Management and Research

Cancer Management and Research downloaded from https://www.dovepress.com/
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Purpose: Risk stratification of patients with non-small cell lung cancer (NSCLC) is crucial to select the appropriate treatments, but available models for patients with complete resection are unsatisfactory. The purpose of this study was to determine a prediction model based on clinical information, routine physical and blood tests, and molecular markers.

Patients and Methods: This was a retrospective cohort study of patients who underwent surgical resection for lung cancer between 2009 to 2013. Potential prognostic factors were used to build a full prediction model based on a multivariable Cox regression analysis. A nomogram was constructed. The risk stratification cutoffs for clinical use were determined based on the model.

Results: A total of 368 NSCLC patients with R0 resection were included. The final multivariable model indicated that low diffusing capacity of the lung for carbon monoxide (HR=1.66, 95% CI: 1.18–2.34), high platelet-to-lymphocyte ratio (HR=1.42, 95% CI: 1.04–1.95), histology type of squamous cell carcinoma and others (squamous cell carcinoma vs adenocarcinoma, HR=1.40, 95% CI: 1.01–1.96; others vs adenocarcinoma, HR=2.36, 95% CI: 1.15–4.84; *P* trend=0.001), N>0 status (HR=1.96, 95% CI: 1.42–2.70), high serum carcinoembryonic antigen levels (HR=1.61, 95% CI: 1.13–2.27), and postoperative chemotherapy (HR=0.53, 95% CI: 0.33–0.87) were independently associated with poor OS. The patients were classified into four risk groups according to the nomogram, and the OS was different among the four groups (P<0.05).

Conclusion: A nomogram was successfully constructed based on a multivariable analysis, and the nomogram can discriminate the OS of patients with NSCLC based on risk categories, but external validation is still necessary.

Keywords: non-small cell lung cancer, survival, prognosis, spirometry, biochemistry

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Introduction

Lung cancer is the leading cause of cancer death in the world.[1] In China, the incidence and mortality of lung cancer are high, with 733,300 incident cases and 610,200 deaths in 2015.[2] Lung cancer can be histologically classified as small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC), and the prognosis differs significantly between the two diseases. NSCLC accounts for about 85% of

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http://doi.org/10.2147/CMAR.S232219

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all lung cancers,[1] and the 5-year overall survival (OS) ranges from 73% for stage IA to 24% for stage IIIA.[3]

Surgical resection is the primary treatment strategy for patients with resectable NSCLC. Many factors were suggested to contribute to the OS of patients with NSCLC, including age, clinical stage,[4] histological type,[5] chemotherapy,[6,7] preoperative spirometry parameters such as forced expiratory volume in the first second (FEV1)[8] and diffusing capacity of the lung for carbon monoxide (DLCO),[9] systematic inflammation markers such as the Glasgow Prognostic Score (GPS),[10] neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR),[11] and molecular markers such as carcinoembryonic antigen (CEA) levels, cancer antigen (CA)-125, CA-199, Ki-67, and interleukins.[12–14]

Although prognostic factors have been identified, there is limited literature on prognostic models based, especially in China. Risk stratification of patients is crucial to guide the application of potentially harmful treatments only to the patients who are the most likely to benefit from them, and because it can help the surgeons select patients eligible for complete resection since surgery implies risks.

Hence, this study aimed to build a prediction model based on clinical information, routine physical and blood tests, and molecular markers. We also constructed a nomogram based on the model parameters. Risk stratification cutoffs for patient OS were suggested based on this nomogram.

Methods

Patients

Patients who underwent surgical resection for lung cancer at the Thoracic Surgery Department of Zhongshan Hospital, Fudan University, from 2009 to 2013, were retrospectively analyzed.

The inclusion criteria were: 1) patients confirmed with first-ever NSCLC by postoperative pathology; and 2) underwent radical resection. The exclusion criteria were: 1) history of any cancer (including lung cancer); 2) patients with metastasis before surgery; 3) preoperative radiotherapy or chemotherapy; 4) incomplete data; or 5) ≤6 months of follow-up.

The institutional review board of Zhongshan Hospital (Fudan University China) approved the study (B2018-083). The study was carried out according to the accepted guidelines and the Declaration of Helsinki. The review board waived the need for informed consent.

Data Collection

Clinical information (age, sex, smoking history, family history of cancer, symptoms [cough, hemoptysis, and chest pain], duration of symptoms, surgical type, tumor grade, clinical stage, and postoperative chemoradiotherapy) were collected from the medical charts. The histological type was confirmed by postoperative pathological examination, according to the classification of the World Health Organization.[15] The pathological stage was determined according to the eighth edition of the TNM classification system from the American Joint Committee of Cancer (AJCC).[16] Histopathological analysis was performed using the 2015 World Health Organization (WHO) classification of tumors of the lung, pleura, thymus, and heart.[17]

Information on preoperative spirometry parameters, preoperative blood tests, and molecular markers (including forced vital capacity FEV1%, DLCO, creatinine clearance rate [CCR], PLR, CEA, CA19-9, and Cyfra21-1) were extracted from a customer-designed computer-aided software, which is prospectively maintained by research staff. The data were double-entered and stored in the software within 48 h of examination. A unique identifier matched the patients included in the present study, and the corresponding data were exported from the database.

Postoperative Treatment and Follow-Up

Patients were routinely followed every 2–3 months during the first year after surgery, and every 3–6 months after that. At each postoperative hospital visit, chest computed tomography (CT) was routinely performed. OS was calculated from the time of surgery to the date of death. The first-grade relatives of the patients identified deaths and date of death. The patients still alive by June 30th, 2017, were censored.

Statistical Analysis

Statistical analyses were performed using STATA 11.2 (StataCorp, Houston, TX, USA) and R 3.4.3 (R Foundation for Statistical Computing). Univariable and multivariable Cox proportional hazards regression analyses were used, with backward variable selection at $P<0.10$ to identify the variables retained in the final multivariable model. Prediction models for OS were constructed based on all the retained variables. The Akaike information criterion (AIC) was used to determine the structure of the final prediction model. The Harrell's C index (also called area under curve (AUC)[18] was used to evaluate the model's performance in terms of

discriminative ability. Comparisons were made using the approach by Kang et al[19] and using the decision curve analysis (DCA) between the full multivariable model and the clinical model, including clinical stage and histological type. The calibration curves for the full multivariable model were generated at 3 and 5 years after surgery. The observed vs the expected probabilities of survival were determined using the bootstrapping method with 1000 replicates in the "rms" R package.

A nomogram was established based on the coefficients of the full multivariable model. To use the nomogram, a patient's clinical values are located on each axis of each variable, and a line is drawn upwards to determine the number of points received for each variable value. The sum of these numbers is located on the total points axis, and the patient is stratified according to the summed score. The Kaplan-Meier method was used to generate the survival curves, and the log rank test was used for analysis.

All tests were two-sided, and the significance level was set to P<0.05 unless otherwise specified.

Results

Characteristics of the Patients

A total of 1951 pathologically-diagnosed NSCLC patients underwent surgical resection between 2009 to 2013. Of these patients, 88 had metastatic lesions, R1 or R2 resection was achieved in 463 patients, 768 patients had incomplete clinical information or test results, 262 patients had <6 months of follow-up, and two were finally diagnosed with adenocarcinoma in situ. Therefore, 368 NSCLC patients with R0 resection were included (Figure 1).

The characteristics of the included patients are shown in Table 1. The median follow-up was 51.0 months (interquartile range, 27.0–67.0 months). A total of 188 (50.7%) patients died during follow-up. The 1-, 3-, and 5-year survival rates were 95.7%, 68.2%, and 51.2%, respectively (Table 2).

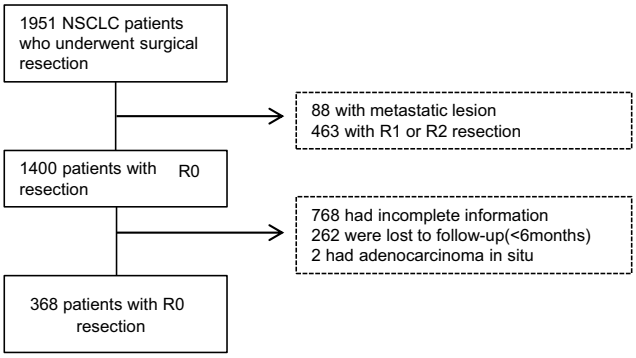

Figure 1 Patient flowchart.

Risk Factor Analysis

The final multivariable model indicated that low DLCO (HR=1.66, 95% CI: 1.18–2.34, *P*=0.004), high PLR (HR=1.42, 95% CI: 1.04–1.95, *P*=0.028), histology type of squamous cell carcinoma and others (squamous cell carcinoma vs adenocarcinoma, HR=1.40, 95% CI: 1.01–1.96, *P*=0.046; others vs adenocarcinoma, HR=2.36, 95% CI: 1.15–4.84, *P*=0.019), N>0 status (HR=1.96, 95% CI: 1.42–2.70, *P*<0.001), high serum level of CEA (HR=1.61, 95% CI: 1.13–2.27, *P*=0.008) and postoperative chemotherapy (HR=0.53, 95% CI: 0.33–0.87, *P*=0.012) were independently associated with poor OS of NSCLC patients (Table 3).

Prediction Model Building, Validation, and Calibration

For the discrimination of patient survival at 3 years, the final multivariable Cox model (full model) reached an AUC of 0.720 (95% CI: 0.658–0.782), which was similar to the clinical model with only clinical stage and histological type (AUC=0.670, 95% CI: 0.607–0.733, Figure 2A). For the discrimination of patient survival at 5 years, the full model reached an AUC of 0.712 (95% CI: 0.649–0.775), which was also similar to the clinical model (AUC=0.647, 95% CI: 0.582–0.711, Figure 2B). The decision curve analysis showed that the full prediction model had a higher net benefit compared with the clinical model for OS at 3 or 5 years (Figure 3).

The calibration analysis for the full model was performed using the bootstrapping method, and the calibration curves showed that the observed proportion of OS and model-predicted OS at 3 and 5 years after surgery were consistent (Figure 4).

Nomogram for the Full Model and Risk Stratification

We constructed a nomogram based on the structure and coefficients of the prediction model. The total nomogram score of each of the 368 patients was calculated. Score 0–99 was classified as low risk, 100–199 was moderate risk, 200–299 was moderate-high risk, and ≥300 was high risk (Figure 5). The Kaplan-Meier survival analysis showed that the OS was significantly different among these four groups of patients (P<0.001) (Figure 6).

Table 1 Characteristics of 368 NSCLC Patients, 2009–2013

Variables	n (%)
Age, n (%)	
<65 years	244 (66.3)
≥65 years	124 (33.7)
Sex, n (%)	
Female	138 (37.5)
Male	230 (62.5)
Smoking history, n (%)	102 (27.7)
Family history of cancer, n (%)	2 (0.5)
Duration of symptoms, n (%)	
<1 year	172 (46.7)
≥1 year	196 (53.3)
Kidney dysfunction (CCR ≤60 mL/min), n (%)	10 (2.7)
FEV1%, n (%)	
≥80%	237 (64.4)
<80%	131 (35.6)
DLCO, n (%)	
≥20	133 (36.1)
<20	235 (63.9)
Platelet-lymphocyte ratio (PLR), n (%)	
<150	227 (61.7)
≥150	141 (38.3)
CEA, n (%)	
<5 μL/mL	260 (71)
≥5 μL/mL	106 (29)
CA19-9, n (%)	
<37 U/mL	297 (80.7)
≥37 U/mL	24 (6.5)
Missing data	47 (12.5)
Cyfra21-1, n (%)	
<30 ng/mL	315 (85.6)
≥30 ng/mL	3 (0.8)
Missing data	50 (13.6)
Surgery, n (%)	
Pneumonectomy & Partial pneumonectomy	27 (7.3)
Lobectomy	341 (92.7)
Pathology, n (%)	
Adenocarcinoma	226 (61.4)
Squamous cell carcinoma	130 (35.3)
Others*	12 (3.3)
Tumor grade, n (%)	
I	3 (0.8)
II	196 (53.4)
III	168 (45.8)
Pathological stage, n (%)	
I	202 (54.9)
II	59 (16.0)
III & IV	107 (29.1)
T status, n (%)	
1	55 (14.9)
2	262 (71.2)
3	19 (5.2)
4	32 (8.7)
N status, n (%)	
0	224 (60.9)
1	65 (17.7)
2	79 (21.5)
M status, n (%)	
0	361 (98.1)
1	7 (1.9)
Postoperative radiotherapy, n (%)	
No	348 (94.6)
Yes	20 (5.4)
Postoperative chemotherapy, n (%)	
No	305 (82.9)
Yes	63 (17.1)

Notes: *Others: five adenosquamous carcinomas, one sarcomatoid carcinoma, one carcinoid, three large cell carcinoma, and two mucinous epidermoid carcinomas.
Abbreviations: CCR, creatinine clearance rate; FEV1%, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; CEA, carcinoembryonic antigen; CA19.9, cancer antigen 19.9; Cyfra21-1, cytokeratin 21-fragment.

Discussion

In this study, we established a nomogram for the OS of NSCLC patients with R0 resection in China. The nomogram was based on an internal validated and calibrated prediction model built using the data from 368 NSCLC patients treated in 2009–2013. The nomogram showed a higher discrimination ability and higher net benefit than the commonly used clinical stage and histological type. To our knowledge, this is the first study evaluating the integrated prediction ability of previously identified prognostic factors on the OS of NSCLC patients with R0 resection in China.

Table 2 Overall Survival of 368 NSCLC Patients with R0 Resection, 2009–2013

	Overall Survival
1-year	95.7%
3-year	68.2%
5-year	51.2%

Table 3 Factors Associated with the Survival of 368 NSCLC Patients, 2009–2013

Variables	Univariable Cox Regression Analysis			Multivariable Cox Regression Analysis[a]		
	Hazard Ratio	95% CI	*p*-value	Hazard Ratio	95% CI	*p*-value
Age						
<65 years	Ref	–	–			
≥65 years	1.39	1.04,1.86	0.029			
Sex						
Female	Ref	–	–			
Male	1.36	1.01,1.85	0.047			
Duration of symptoms						
<1 year	Ref	–	–	Ref	–	–
≥1 year	1.44	1.08,1.93	0.014	1.35	0.98,1.86	0.063
Kidney dysfunction (CCR ≤60 mL/min)						
No	Ref	–	–			
Yes	1.885	0.93,3.83	0.080			
FEV1%						
≥80%	Ref	–				
<80%	1.37	1.02,1.83	0.034			
DLCO						
≥20	Ref	–	–	Ref	–	–
<20	1.39	1.02,1.89	0.039	1.66	1.18,2.34	0.004
Platelet-lymphocyte ratio (PLR)						
<150	Ref	–	–	Ref	–	–
≥150	1.44	1.08,1.93	0.013	1.42	1.04,1.95	0.028
Pathology						
Adenocarcinoma	Ref	–	–	Ref	–	–
Squamous cell carcinoma	1.36	1.01,1.84	0.041	1.40	1.01,1.96	0.046
Others*	2.83	1.48,5.43	0.002	2.36	1.15,4.84	0.019
Pathological stage						
I	Ref	–	–			
II	1.47	0.99,2.2	0.057			
III & IV	2.06	1.5,2.84	<0.001			
P trend			<0.001			
Tumor status						
T1/T2	Ref	–	–			
T3/T4	1.19	0.8,1.76	0.401			
Nodal status						
N0	Ref	–	–	Ref	–	–
N>0	1.95	1.47,2.6	<0.001	1.96	1.42,2.7	<0.001
Distant metastases						
M0	Ref					
M1	0.44	0.11,1.78	0.252			
Serum level of CEA						
<5 μL/mL	Ref	–	–	Ref	–	–
≥5 μL/mL	1.7	1.26,2.29	0.001	1.61	1.13,2.27	0.008

(*Continued*)

Table 3 (Continued).

Variables	Univariable Cox Regression Analysis			Multivariable Cox Regression Analysis[a]		
	Hazard Ratio	95% CI	*p*-value	Hazard Ratio	95% CI	*p*-value
CA19-9						
<37 U/mL	Ref	–	–			
≥37 U/mL	1.58	0.96,2.62	0.074			
Cyfra21-1						
<30 ng/mL	Ref	–	–			
≥30 ng/mL	1.73	0.43,6.98	0.443			
Postoperative chemotherapy						
No	Ref	–	–	Ref	–	–
Yes	0.65	0.42,0.99	0.045	0.53	0.33,0.87	0.012
Postoperative radiotherapy						
No	Ref	–	–			
Yes	1.01	0.55,1.85	0.987			

Notes: [a]Backward-selection method with a significance threshold of 0.1 was used to identify variables included in the final multivariate model.
Abbreviations: CCR, creatinine clearance rate; FEV1%, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; CEA, carcinoembryonic antigen; CA19.9, cancer antigen 19.9; Cyfra21-1, cytokeratin 21-fragment.

Despite the rapid development of surgical techniques in the last decade, distinct heterogeneities are still observed among NSCLC patients with R0 resection. Observational studies showed that recurrence might occur as early as 10 months after R0 resection, even with stage IA disease,[20] indicating a poor prognosis.[21] Nevertheless, R0 resection is curative for about 50% of patients with NSCLC, achieving long-term survival.[22] Patients with the same stages of NSCLC or the same histological types may recur or not after complete resection.[23] The most commonly used predictors for patients' prognosis are the TNM staging system and histological type, but they may have reached the limit of their usefulness to meet the needs for personalized evaluation in the context of precision medicine.[24]

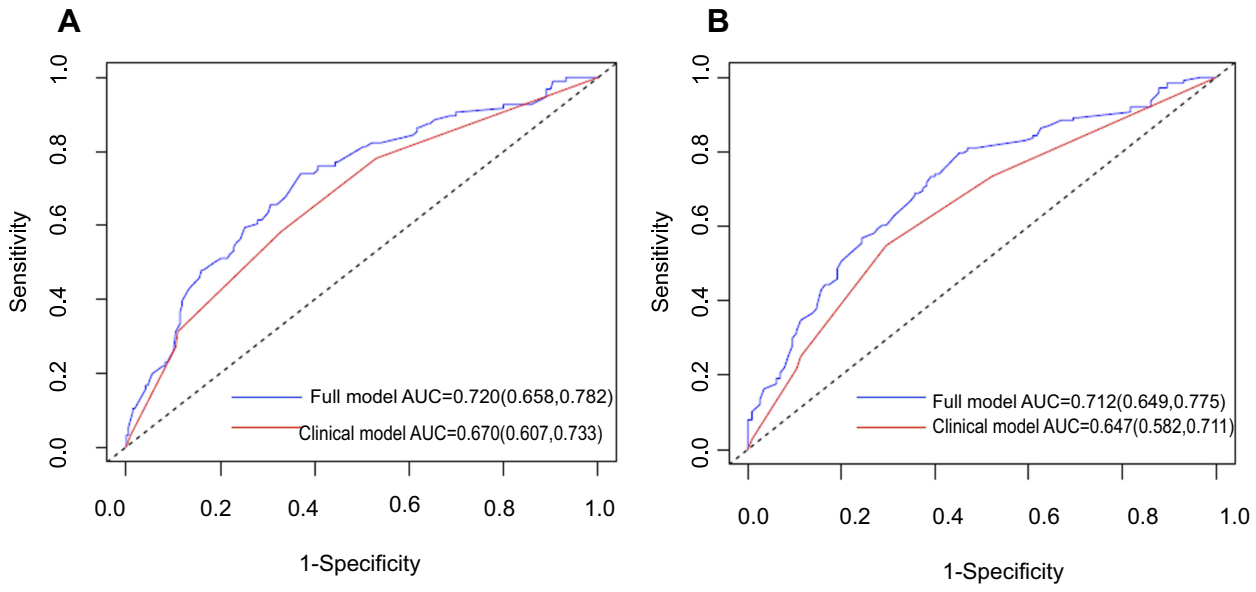

Figure 2 Performance of prediction models generated from 368 NSCLC patients with R0 resection, 2009–2013. (**A**) Receiver-operating characteristics (ROC) analysis of the full prediction model (the variables in the full prediction model included duration of symptoms, diffusing capacity of the lung for carbon monoxide, platelet-lymphocyte ratio, serum level of carcinoembryonic antigen, pathology diagnosis, nodal status, and chemotherapy) and simple clinical model (variables in the clinical model included pathology diagnosis and nodal status) for predicting 3-year overall survival. (**B**) ROC of the full prediction model and simple clinical model for predicting 5-year overall survival.

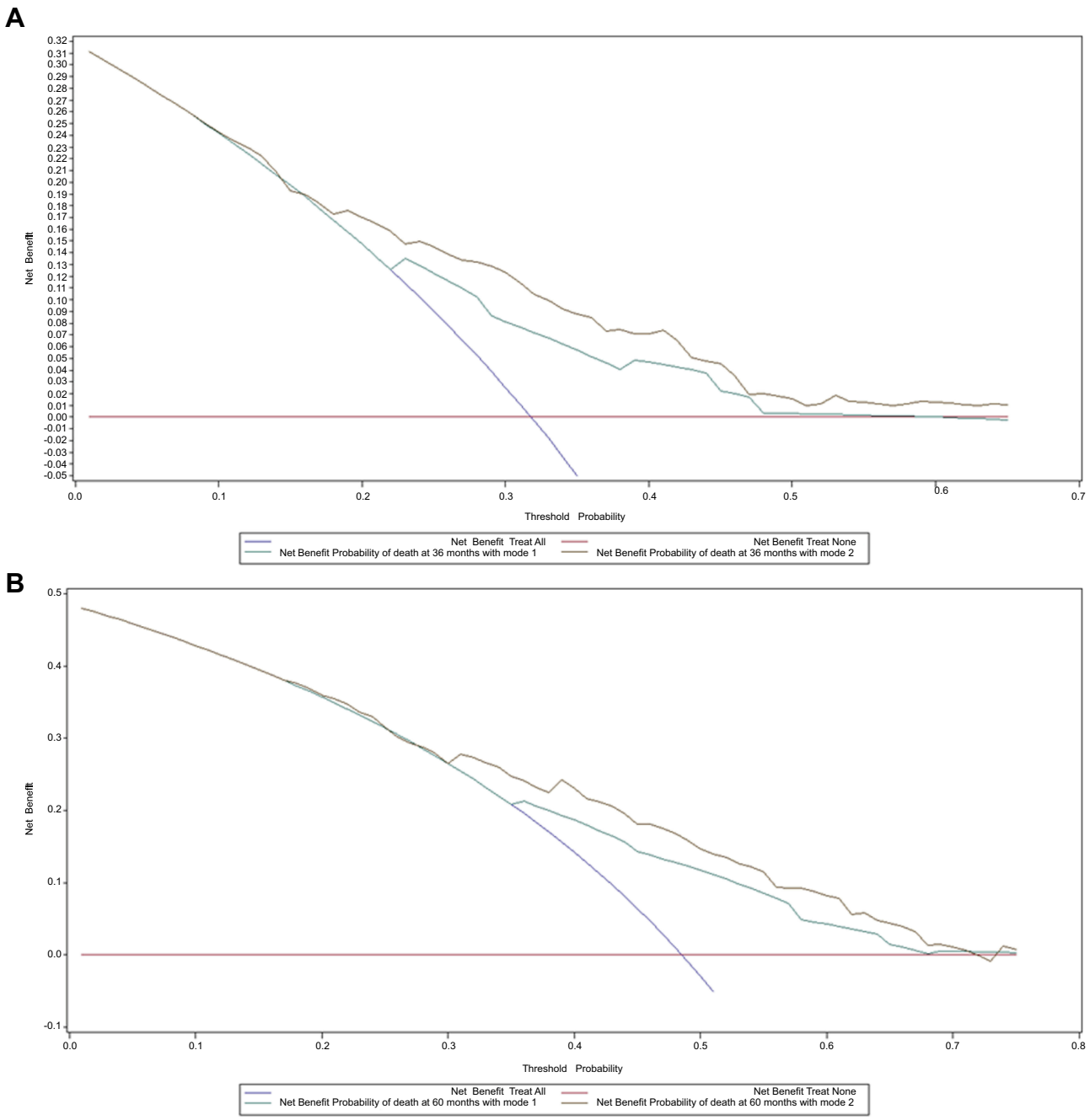

Figure 3 Decision curves for the net benefit of the full prediction model (model 2) and clinical model (model 1). (**A**) Assessment of 3-year overall survival. (**B**) Assessment of 5-year overall survival.

Previous prediction models were mainly designed from western populations and focused on one or two candidate prognostic factors. Moreover, most prediction models of the survival of patients with NSCLC are presented in the form of receiver operating characteristic (ROC) curves or mathematical formulas, which are not straightforward to the physicians, impairing their application in clinical practice. For example, Dehing-Oberije et al established a prognostic model using blood biomarkers to predict the OS of NSCLC patients and reported that the AUC of the full model consisting of clinical information, CEA levels, and interleukin-6 reached 0.81.[25] Another study in China with 320 NSCLC patients showed that the AUCs of PLR and NLR were 0.531 (95% CI: 0.468–0.595) and 0.632 (95% CI: 0.571–0.693), respectively.[26] Therefore, it is necessary to establish an accurate, reliable, and easy-to-use prediction model that

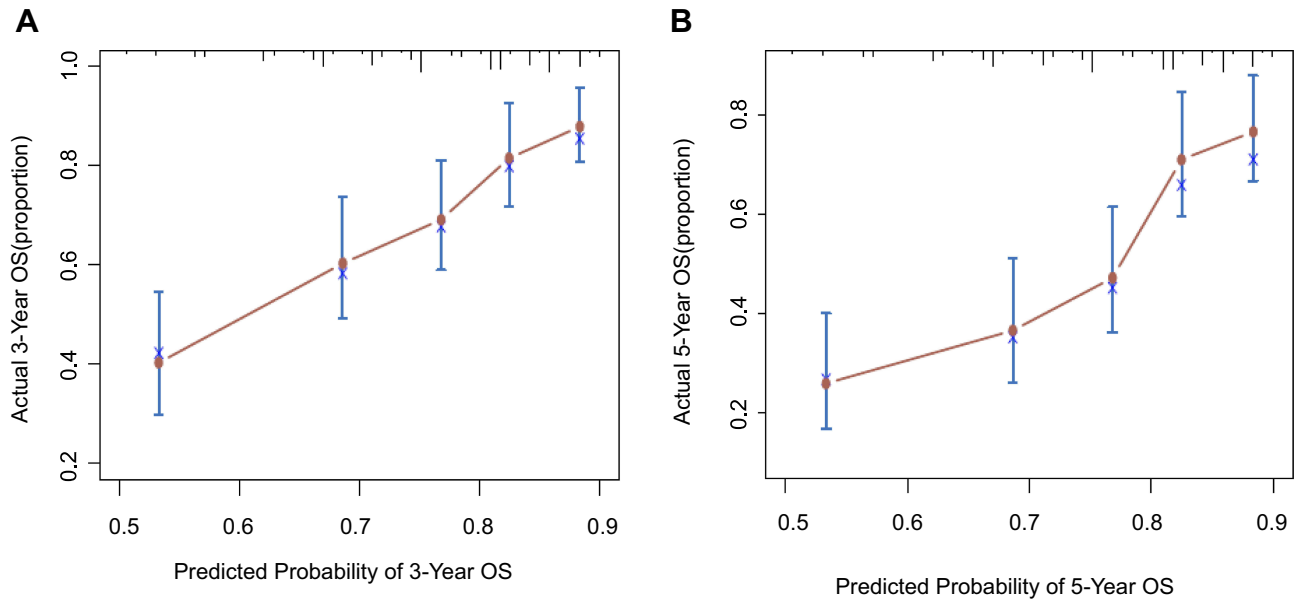

Figure 4 Calibration plot of the full prediction model that included duration of symptoms, diffusing capacity of the lung for carbon monoxide, platelet-lymphocyte ratio, serum level of carcinoembryonic antigen, pathological diagnosis, nodal status, and chemotherapy) generated from 368 NSCLC patients with R0 resection, 2009–2013. (**A**) Comparison of predicted and actual 3-year survival of patients generated by bootstrap resampling (n=368, replicates=1000). (**B**) Comparison of predicted and actual 5-year survival of patients generated by bootstrap resampling (n=368, replicates=1000).

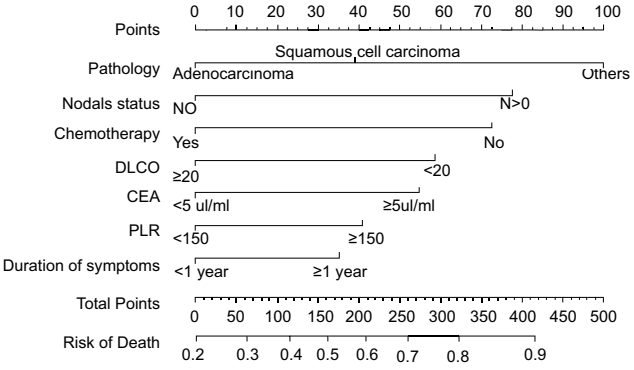

Figure 5 Nomogram for risk stratification of NSCLC patients with R0 resection.

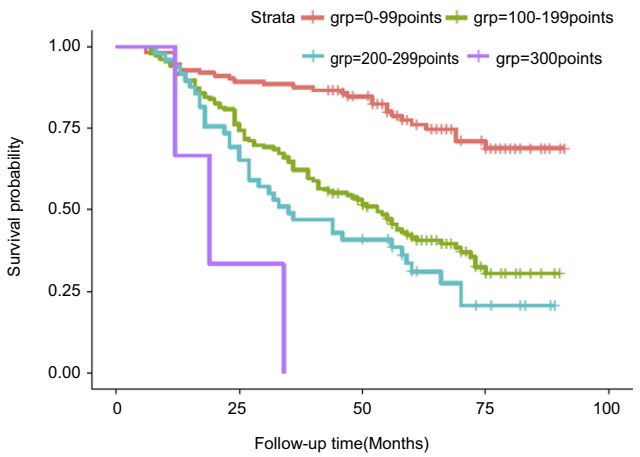

Figure 6 Survival of 368 NSCLC patients with R0 resection during 2009–2013, stratified by risk groups as defined by the nomogram.

systematically combines the prediction ability of previously reported factors for the survival of patients with NSCLC.

Here, we present an easy-to-use nomogram for risk stratification of NSCLC patients with R0 resection. The patients were classified into four risk categories, namely low risk (0–99 points), moderate risk (100–199 points), moderate-high risk (200–299 points), and high risk (≥300 points). The 5-year survival for these four groups of patients was 77.7%, 56.5%, 34.9%, and 0%, respectively. The OS of the "low risk" and "moderate risk" groups is better than the average OS, and it could be suggested that these patients should take priority for surgical treatment since they are most likely to benefit from the operation and achieve long-term survival. Caution should be considered for patients who are classified as "moderate-high risk" since they might have a relatively high risk of recurrence. Thus, it is recommended that these patients should have shorter intervals between postoperative follow-up examinations. For "high risk" patients, conservative therapy might be an alternative solution, since no patient achieved long-term survival despite successful operation. Importantly, there was no external validation nor control cohort, and these results have to be taken with caution in the meantime and cannot be used, for now, to modify or guide the clinical practice.

One strength of this study is that we used the decision curve analysis in addition to the AUC to compare the performance between the full multivariable model and the classical clinical model. The AUC focuses on the accuracy of discrimination (i.e., sensitivity and specificity), while the decision curve analysis seeks to maximize the net benefit, which solves the clinical effect problem. In this study, we found that the full prediction model showed a higher net benefit compared with the clinical model across a wide range of threshold probabilities. Additional studies could be performed to verify the value of the full model over the clinical stage and histological type.

We identified a series of previously reported prognostic factors for NSCLC in the 368 patients with R0 resection. The commonly used prognostic variables in clinical settings, the clinical stage, and histological type, demonstrated some degree of prediction ability for OS, but their performance was not robust within the training sample because the internal validation produced an AUC of 0.518, which is very close to a random guess. The additional prognostic factors suggested include the duration of symptoms, DLCO, PLR, serum level of CEA, and CCR. Those variables had additive value for the discrimination of patient OS. Importantly, only a slightly decreased AUC was obtained by the internal validation, suggesting that the increase in model performance is robust within our sample. It should be noted that the selection of predictors in this study was mainly based on statistical association, which does not always mean biological relevance. Besides, potential prognostic factors identified by previous studies were not necessarily observed here. For example, CEA and CCR were included in the final model, but other serum markers such as CA-199 and prognostic factors such as liver dysfunction were excluded.

Lung spirometry was recognized as a critical factor of acute mortality after lung resection in the 1980s and is identified to be a determinant of all-cause mortality in the general population.[27] For NSCLC patients, several studies have reported that FEV1 is an independent risk factor of OS.[8,28] DLCO is associated with an increased risk of acute morbidity after significant lung resection,[29] but the association between DLCO and OS is controversial. Liptay et al showed that the DLCO is associated with long-term survival after curative lung resection for lung cancer.[30] On the other hand, Wang et al failed to observe such an association.[31] In the present study, DLCO was an independent prognostic factor for the OS of NSCLC patients with R0 resection, which supports the critical role DLCO plays in determining the prognosis of NSCLC patients.

It is well accepted that systemic inflammation plays a crucial role in the carcinogenic process.[32] Convenient systemic inflammatory response indicators such as the GPS (calculated based on the concentrations of C-reactive protein and albumin) have been identified to predict the OS of patients in a variety of cancer types.[33–35] The NLR and the PLR can be easily estimated based on blood routine examination results and have been proposed to be useful for predicting the prognosis of lung cancer patients.[36] In the present study, we found that PLR ≥150 predicted poor survival among NSCLC patients with R0 resection. The mechanisms explaining this association include: 1) platelets release several kinds of cytokines and growth factors that might affect cell proliferation, migration, and angiogenic activity;[37] 2) tumor cells produce cytokines (e.g., interleukin-6) and expedite the differentiation of bone marrow-derived megakaryocytes to platelets;[38] and 3) the immune evasion process of tumor cells may lead to platelet aggregation.[39]

The CEA is a diagnostic and prognostic marker for cancer.[40] It is widely expressed in a variety of tumors (digestive tract cancers, breast cancer, and urogenital tract cancers), but up-regulation of CEA is not cancer-specific, and high levels of CEA can be detected in non-cancer (e.g., pneumonia) patients.[12] The relatively low sensitivity and specificity of CEA alone in predicting cancer occurrence or patient survival limited its clinical use. Serum CEA levels have been reported to be a prognostic factor and an indicator of recurrence after surgical resection of NSCLC.[41,42] In the present study, serum CEA ≥5 μL/mL was also found to be an independent risk factor for OS in NSCLC patients with R0 resection. Thus, we think that CEA levels should be used as an adjunct to other predictors to achieve better discrimination in NSCLC patients with R0 resection.

This study has limitations. First, external validation of our prediction model in an independent cohort of patients is needed since we only performed internal validation in the current study. Second, this is a single-center study, and the cutoff values for predictors and risk stratification need to be verified by large-scale multicenter studies.

Conclusions

In conclusion, a nomogram was successfully constructed based on a multivariable analysis, and the nomogram can discriminate the OS of patients with NSCLC based on the nomogram's risk categories. Nevertheless, external validation is still necessary, but external validation is still required.

Abbreviations

NSCLC, non-small cell lung cancer; OS, overall survival; FEV1, forced expiratory volume in the first second; GPS, Glasgow Prognostic Score; CEA, carcinoembryonic antigen; AJCC, American Joint Committee of Cancer; WHO, World Health Organization; CT, computed tomography; AIC, Akaike information criterion; AUC, area under curve; DCA, decision curve analysis.

Disclosure

The authors report no conflicts of interest in this work.

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