Development and Validation of a Nomogram to Predict the Overall Survival of Patients with Stage I Non-Small Cell Lung Cancer After Surgery

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Abstract

Background: This study aimed to establish an effective prognostic nomogram for stage I non-small cell lung cancer (NSCLC) patients receiving surgery.

Methods: Stage I NSCLC patients at Taizhou Hospital of Zhejiang Province from October 2010 to June 2014 were included. Clinical, pathological and laboratory variables ascertained before surgery were selected through least absolute shrinkage and selection operator and Cox regression analysis, and a nomogram model was established. The nomogram model was validated using stage I NSCLC patients from the same institution between July 2014 and December 2015.

Results: Training cohort included 274 patients. From 46 potential predictors, the independent risk factors for Overall survival (OS) of patients with stage I NSCLC were age, CA125, and tumor diameter. The C index of the nomogram model was 0.759(95% confidence interval (CI) 0.666–0.852). The area under the ROC curve of the nomogram was 0.776. The patients in the low-risk subgroup had significantly better survival than those in the high-risk subgroup (logrank, $p < 0.001$). The AUC in the validation cohort was 0.809, and the C index was 0.707(95% CI, 0.572-0.842).

Conclusion: We developed a nomogram model that includes clinical, pathological and laboratory variables to predict the OS of stage I NSCLC patients.

Introduction

Lung cancer is the most common cause of cancer death in the world, and 85% of patients have non-small cell lung cancer (NSCLC)[1]. With the increasing use of high-resolution computed tomography (CT) and low-dose CT in high-risk groups of lung cancer screening, an increasing number of early lung cancers have been diagnosed. Surgical treatment is still the most effective means of treatment for early NSCLC patients [2].

Nomograms have been widely used to predict the prognosis of cancer patients because they can integrate all prognostic factors into a model and thus better stratify cancer patients[3–5]. Although there are many nomograms for the prognosis of NSCLC patients after surgery, there are still few nomograms for the prognosis of stage I NSCLC patients. The five-year survival rate for stage I NSCLC patients generally ranges 73–90% [6, 7], and their survival after surgery is still difficult to assess. Therefore, we need nomograms to help clinicians find high-risk groups and carry out effective long-term follow-up and treatment.

Our goal was to establish a nomogram containing clinical and pathological data and laboratory indicators to predict survival of stage I NSCLC patients.

Materials And Methods

Patient selection

Training cohort: NSCLC patients at Taizhou Hospital of Zhejiang Province from October 2010 to June 2014 were selected as the training cohort. Inclusion criteria: Stage I patients reclassified according to American Joint Committee on Cancer (AJCC) eighth edition; complete clinical, pathological and laboratory data; standard lobectomy and mediastinal lymph node dissection with microscopically radical resection (R0); histopathologically confirmed NSCLC. Exclusion criteria: second primary tumor; history of malignant tumors before NSCLC surgery; patients with tumor-node-metastasis (TNM) staging systems from stage 2 to stage 4; Radiotherapy after surgery.

Validation cohort: We selected patients from July 2014 to December 2015 as the validation cohort according to the same selection criteria and exclusion criteria.

The study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province.

All patients provided a complete medical history. Clinical laboratory test results including biochemical indices, routine blood results, and tumor markers were collected within 2 weeks before the operation. Routine examinations also included electrocardiogram, chest X-ray, magnetic resonance imaging, chest and upper abdominal CT.

Potential Predictive Variables

Potential predictive variables include the following: age, sex, vascular invasion, pleural invasion, smoking status, drinking status, tumor size (the diameter of the solid part of the tumor), pathological type, tumor location, postoperative chemotherapy, white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, red blood cell count, hemoglobin, red blood cell distribution width, platelet count, prothrombin time, thromboplastin time, partial thromboplastin time, fibrinogen, alanine aminotransferase, aspartate transaminase, direct bilirubin, indirect bilirubin, triglycerides, total cholesterol, alkaline phosphatase, total bilirubin, total protein, albumin, total bile acids, γ -glutamyl transferase, prealbumin, creatinine, blood urea nitrogen, uric acid, low- and high-density lipoprotein cholesterol, Apolipoprotein B, Lipoprotein a, creatine kinase, Apolipoprotein A, lactate dehydrogenase, carcinoembryonic antigen (CEA), and carbohydrate antigen 125 (CA125).

Follow-up and outcome

After surgery, patients were followed up every 3 months for 1 year, 6 months for 2-3 years, and once a year thereafter. In April 2017, the survival status of patients in the training cohort was confirmed. The validation cohort patients was verified again in August 2018. Overall survival (OS) was calculated from the date of surgery to the date of death or the last day of follow-up. A total of 274 patients were included in the training cohort, and the validation cohort had 122 patients.

Statistical analysis

Continuous variables were expressed as the mean (standard deviation) or median (interquartile range). Nonparametric tests (Mann-Whitney U) were used for continuous variables. Percentages were used to describe categorical variables. The comparison of categorical variables was performed by the X² test. A two-sided *p*-value of < 0.05 was considered statistically significant. Forty-eight variables were selected by least absolute shrinkage and selection operator (LASSO) regression. The most predictive covariates were selected by the minimum (λ min). The selected variables were analyzed by multivariate Cox regression. The most meaningful variables were selected into the nomogram model[8, 9]. The performance of the nomogram was compared by discrimination (Harrell's concordance index) and calibration (calibration plots). The application of the nomogram model in the training cohort and the validation cohort was compared with the receiver operating characteristic curve (ROC curve). The total score of each patient was calculated through the established nomogram model, and then risk stratification was performed by X-TILE software. The log-rank test was used to compare the survival time for categorical variables, and survival curves were depicted using the Kaplan-Meier method. R software version 4.0.2 was used to develop the nomogram and perform the decision curve and LASSO regression analyses.

Results

Characteristics of the Validation Cohort

We collected 274 stage I NSCLC patients who had undergone surgery. The median survival time was 45.3 months (range 2.0-78.5). A total of 28 patients died, and the overall mortality rate was 10.2%. The 1-, 3-, 5-year survival rate respectively was 96.72%, 92.34%, 89.78%. A total of 151 (55.1%) patients were male, only 8% had vascular invasion, and 15% had pleural invasion. There were 119 smoking patients, accounting for 43.4%. The tumor size was 2.0±0.9 cm. There were 58 patients with squamous cell carcinoma (21.2%). There were 112 patients (40.9%) with tumors located in the left lung, and 87 patients (31.8%) who underwent postoperative chemotherapy (Table 1). Laboratory findings of the training cohort are presented in Table 2.

Variable selection

Forty-six variables in the training cohort were included in the LASSO regression. Five variables remained significant predictors of survival of stage I NSCLC patients after surgery, including age, CA125, pathological type, vascular invasion and tumor size (Supplement Figure 1). Through Cox regression analysis, it was found that these three variables were independent risk factors for predicting the OS of stage I NSCLC patients. These variables included age (HR=3.849; 95% confidence interval (CI), 1.454-10.185; P=0.007), tumor size (HR=1.716; 95% CI, 1.125-2.617; P=0.012) and CA125 (HR=1.021; 95% CI, 1.010-1.032; P=0.000) (Table 3).

Nomogram construction

Three independent risk factors for predicting the OS of patients were found, and a nomogram was constructed (Figure 1A). The C-index of the nomogram was 0.759[95% CI, 0.666–0.852]. The calibration

curves showed that the nomogram predicted the survival rate of stage I NSCLC patients at 1, 3, and 5 years, and there was good agreement between the actual observations (Figure 2A/2B/2C). We also compared the predictive ability for OS between tumor size, CA125, the nomogram and TNM staging systems. The C-index was 0.759, which was significantly higher ($P < 0.001$) than that of the CA125 (0.503), tumor size (0.665), and TNM staging system (0.709). Decision curve analysis (DCA) and clinical impact curve analysis showed that the nomogram had better overall net income than tumor size, and TNM staging (Figure 1B, 1C).

Validation of the Nomogram for OS

The validation cohort had 122 patients. The median survival time was 40.2 months (range 4.7-49.7), and 9 patients died. The 1-year, 3-year survival rate respectively was 98.36%, 92.62%. Comparing the predicted values and observed values of 1-, 3-, and 4- survival rates, the calibration curve showed good agreement (Figure 2D, 2E, 2F). The C-index of the validation cohort was 0.707 (95% CL, 0.572-0.842) and was lower than the C-index of the training cohort (0.759, $P < 0.001$). The area under the ROC curve (AUC) in the training cohort was 0.776, and AUC in the validation cohort was 0.809 (Figure 3A, 3B).

Risk stratification of the nomogram in predicting OS

Through the nomogram, we calculated the total score of each patient in the training cohort. The patients were divided into two groups by X-tile software: the low-risk group (< 98.8) and the high-risk group (≥ 98.8) (Supplementary Figure 2). In the training cohort, the survival time of the low-risk group was 47.1 ± 11.7 months, and the survival time of the high-risk group was 41.9 ± 20.7 months ($P = 0.027$) (Figure 3C). The patients in the low-risk subgroup had significantly better survival than those in the high-risk subgroup (logrank, $p < 0.001$). In the verification group, the low-risk survival time was 41.4 ± 5.7 months, and the high-risk group was 37.6 ± 9.9 months ($P = 0.008$) (Figure 3D). In the validation group, the high-risk group had a worse survival rate than the low-risk group (logrank, $p < 0.001$).

Discussion

In this study, we established a nomogram model for the postoperative survival of patients with stage I NSCLC. The nomogram model incorporated three variables: CA125, age and tumor size. The nomogram model had good discrimination ability, the C-index of the training cohort was 0.759, and the C-index of the validation cohort was 0.707. The analysis of DCA and ROC curves also further showed that the nomogram model had better net clinical benefits. We also divided patients into low-risk groups and high-risk groups, which can better guide clinicians in the follow-up and treatment of stage I NSCLC patients after surgery.

In recent years, there have been a large number of nomogram studies on tumor prognosis, including breast cancer [10, 11], colorectal cancer [12], gastric cancer [5] and so on. These studies showed that the nomogram model had a better predictive value for the prognosis of tumors than the traditional TNM

staging system. There are many nomogram models for the prognosis of lung cancer. For example, a nomogram was established to predict brain metastasis in NSCLC patients after radical surgery [13]. There are also many nomogram models for predicting disease-free survival after surgery for early NSCLC (pathological stage I and stage II) [14–16]. However, there are still few nomogram models for predicting the survival rate of stage I NSCLC patients that include clinical data, pathological data, and laboratory indicators.

In this study, 48 variables, including clinical and pathological data and laboratory indicators, were selected through LASSO regression. Cox regression analysis found that there were three independent risk factors for postoperative survival in stage I NSCLC patients: age, tumor size, CA125. Many research reports have shown that age is a risk factor for poor postoperative prognosis in lung cancer patients, whether in early or advanced lung cancer [17–19]. Tumor size was an major factor for the prognosis of NSCLC patients, especially stage I NSCLC patients[20]. TNM staging system also fully considered the tumor size, but the TNM staging system only analyzed the tumor size according to 1 cm, 2 cm, and 3 cm sizes. We believe that the actual tumor size will have a great influence on OS of stage I NSCLC patients. Therefore, this paper analyzed tumor size as a continuous variable, which may have better predictive value for the prognosis of with stage I NSCLC patients, which was also consistent with the study of Cao et al. [21]. Laboratory indicators are generally not included in other nomogram. But laboratory indicators are easy to obtain and easy to monitor, So the nomogram also includes laboratory indices such as serum tumor markers. CA125, as common tumor markers, have great value in predicting the prognosis of tumors. In some studies, it has also been shown that elevated CA125 is an independent risk factor for the survival of NSCLC patients [22, 23].

This study combined clinical, pathological and laboratory variables to establish a nomogram model to predict the postoperative survival of stage I NSCLC patients. The calibration curve showed that there was good agreement between the predicted survival rates of stage I NSCLC patients at 1, 3, and 5 years after surgery and actual observations. The C-index also showed the good predictive ability of the nomogram model (0.759for the training cohort and 0.707 for the validation cohort). Both DCA and the clinical impact curve indicated that the nomogram model had better overall net benefits than the TNM staging system. The 5-year survival rate of patients with stage I NSCLC was relatively high. Therefore, not all patients need additional treatment and frequent follow-up.

.In this study, the risk stratification of patients with stage I NSCLC was based on the score of the nomogram model. Not all patients with stage I NSCLC need adjuvant therapy .For stage I NSCLC patients in the low-risk group, regular follow-up is enough, while for patients in the high-risk group, more careful follow-up examination and adjuvant therapy may be required. This could also help clinicians make individualized treatment decisions.

This study also had some shortcomings, as follows: 1. This study was a single-center study, and there may be regional biases. 2. A relatively small sample size will limit statistical analysis. Although the nomogram model had been verified internally and externally to verify the accuracy of the model, data

from different regions still needed to be further verified. 3. This study failed to include some important genetic factors, such as EGFR mutations.

Conclusions

In summary, we developed and verified a nomogram model of postoperative survival of stage Ⅲ NSCLC patients, including clinical, pathological and laboratory indicators. Through this model, clinicians could better identify patients with poor prognosis and help them provide more personalized treatment decisions.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province.

Consent for publication

In cases where images are entirely unidentifiable and there are no details on individuals reported within the manuscript, consent for publication of images may not be required.

Availability of data and materials

The authors declare that the data supporting the findings of this study are available within the article and additional supporting files.

Competing interests

The authors declare that they have no competing interests

Funding

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Authors' contributions

YX, WL, and LH contributed to conception and design of the study. CL organized the database. CS performed the statistical analysis. YX wrote the first draft of the manuscript. WL and CS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version

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24. Table1. Demographics and Clinical Characteristics Among stage I NSCLC Patients In the study Cohort

Tables

Table1. Demographics and Clinical Characteristics Among stage I NSCLC Patients In the study Cohort

Characteristic	Total N=396	training cohort N=274	validation cohort N=122	P
Gender				0.275
Male	211 (53.3)	151(55.1)	60(49.2)	
Female	185 (46.7)	123(44.9)	62(50.8)	
Age				0.663
≤60	185(46.7)	130(47.4)	55(45.1)	
>60	211(53.3)	144(52.6)	67(54.9)	
Vascular invasion				0.078
Positive	26(6.6)	22(8.0)	4(3.3)	
Negative	370(93.4)	252(92.0)	118(96.7)	
Pleural invasion				0.876
Positive	60(15.2)	41(15.0)	19(15.6)	
Negative	336(84.8)	233(85.0)	103(84.4)	
Smoking status				0.066
Yes	160(40.4)	119(43.4)	41(33.6)	
No	236(59.6)	155(56.6)	81(66.4)	
Drinking status				0.340
Yes	83(21.0)	61(22.3)	22(18.0)	
No	313(79.0)	213(77.7)	100(82.0)	
Tumor size(cm)	1.9±0.9	2.0±0.9	1.9±1.0	0.582
Pathological type				0.042
Adenocarcinoma	313(79.0)	208(75.9)	105(86.1)	
Squamous cell carcinoma	71(17.9)	58(21.2)	13(10.7)	
others	12(3.0)	8(2.9)	4(3.3)	
Tumor site				0.774
Left	160(40.4)	112(40.9)	48(39.3)	
Right	236(59.6)	162(59.1)	74(60.7)	

Postoperative chemotherapy				0.000
Yes	101(25.5)	87(31.8)	14(11.5)	
No	295(74.5)	187(68.2)	108(88.5)	

Table2 Laboratory Findings Among stage I NSCLC Patients In the study Cohort

Variable	Total, median (25%-75%)	training cohort [̂%̂]	validation cohort [̂%̂]	P
WBC,×10 ⁹ /L	6.1(5.1-7.3)	6.2(5.2-7.3)	6.0(4.9-7.1)	0.181
Neutrophil cell,×10 ⁹ /L	3.7(2.9-4.5)	3.7(2.9-4.6)	3.5(2.8-4.4)	0.327
Lymphocyte count,×10 ⁹ /L	1.8(1.5-2.2)	1.9(1.5-2.3)	1.8(1.5-2.1)	0.277
Monocyte count,×10 ⁹ /L	0.36(0.30-0.46)	0.37(0.30-0.48)	0.30(0.30-0.40)	0.075
Red blood cell,×10 ¹² /L	4.5(4.2-4.8)	4.5(4.2-4.8)	4.5(4.3-4.8)	0.732
Hemoglobin, g/L	137(128-146)	137(128-147)	136(129-144)	0.973
RDW,%	12.9(12.5-13.4)	12.9(12.5-13.4)	12.8(12.5-13.3)	0.203
Plateletcrit,%	216(181-256)	215(182-257)	218(180-252)	0.897
Fibrinogen,g/L	3.4(3.0-3.9)	3.4(3.0-3.9)	3.3(2.9-4.0)	0.473
PT,s	12.8(12.4-13.3)	12.7(12.3-13.1)	13.2(12.7-13.5)	0.000
APTT,s	36.0(33.6-38.6)	35.7(33.4-38.1)	37.1(35.2-40.2)	0.000
ALT,U/L	18.0(13.0-26.0)	18.0(13.0-26.0)	18.0(13.0-27.2)	0.870
AST, U/L	22.0(18.0-26.0)	22.0(17.0-26.0)	22.0(18.0-27.0)	0.780
ALP,U/L	84.0(71.0-101.0)	82.0(70.0-97.0)	89.0(74.8-112.0)	0.006
GGT, U/L	22.0(16.0-33.0)	22.0(16.0-34.0)	21.0(15.8-32.0)	0.567
Total bilirubin,μmol/L	10.0(8.0-12.9)	9.7(8.0-12.9)	10.6(8.2-13.6)	0.280
Direct bilirubin,μmol/L	3.2(2.5-4.3)	3.1(2.5-4.1)	3.4(2.7-4.5)	0.027
Indirect bilirubin,μmol/L	6.9(5.2-8.8)	6.8(5.3-8.6)	7.2(5.1-8.9)	0.560
TP,g/L	71.5(67.0-75.3)	71.5(67.1-76.0)	71.5(66.9-75.0)	0.589
Albumin,g/L	43.9(40.5-46.4)	43.5(40.4-46.4)	44.3(41.2-46.5)	0.350
TBA,μmol/L	3.8(2.3-6.6)	3.8(2.3-6.3)	3.9(2.3-7.2)	0.832
Prealbumin,mg/dl	27.7(24.3-31.7)	27.9(24.6-32.5)	27.2(23.7-30.3)	0.114
<i>Creatinine</i> ,μmol/L	74.0(59.0-86.0)	78.0(65.0-90.0)	63.0(54.0-71.3)	0.000
<i>Urea</i> ,mmol/L	5.0(4.3-6.1)	5.2(4.4-6.2)	4.8(4.2-5.7)	0.072
<i>Uric acid</i> ,μmol/L	284(231-338)	286(237-339)	276(213-333)	0.440
Triglycerides ,mmol/L	1.36(1.00-2.07)	1.31(0.98-1.97)	1.54(1.02-2.30)	0.087

TC,mmol/L	4.8(4.2-5.5)	4.8(4.2-5.6)	4.8(4.2-5.5)	0.793
HDL, mmol/L	1.3(1.2-1.6)	1.3(1.2-1.6)	1.3 (1.2-1.5)	0.892
LDL, mmol/L	2.6(2.2-3.2)	2.7(2.2-3.2)	2.6(2.2-3.1)	0.244
Apolipoprotein A,g/L	1.5(1.3-1.7)	1.4(1.2-1.7)	1.5(1.3-1.7)	0.007
Apolipoprotein B,g/L	0.98(0.82-1.15)	0.98(0.82-1.17)	0.98(0.82-1.15)	0.916
Lipoprotein (a),mg/L	168(96-276)	169(103-272)	160(82-286)	0.926
CK,U/L	87(63-120.0)	86(64-118)	89.5(59.8-126.3)	0.755
LDH,U/L	163(142-182)	161(142-180)	168(143-185)	0.240
CEA ,ng/ml	2.5(1.6-3.9)	2.5(1.6-4.0)	2.5(1.6-3.4)	0.414
CA 125,U/ml	10.8(7.7-15.2)	10.7(7.7-15.3)	10.9(8.2-15.1)	0.575

Abbreviations:WBC, White blood cell count;RDW, Red blood cell distribution width;

APTT, activated partial thromboplastin time;PT, Prothrombin time;TT, thrombin time;ALP, alkaline phosphatase;TP, Total protein;TBA, total bile acid;TC, *total cholesterol*;CK, creatine kinase;ALT, Alanine aminotransferase; AST,aspartate aminotransferase;GGT, Glutamyl transpeptidase;HDL, High-density lipoprotein;LDL, *low-density lipoprotein*;LDH, Lactate dehydrogenase;CEA, carcinoembryonic antigen;CA125, carbohydrate antigen 125;

Table3 Multivariable cox Regression Model for Predicting Development of OS in stage I NSCLC Patients

Variable	Univariate analysis		Ptrend	Multivariate analysis	
	HR	P		HR	P
Overall survival					
Age ≤60 VS >60	4.459 [1.694-11.732]	0.002		3.849 [1.454-10.185]	0.007
Tumor diameter	1.821 [1.240-2.676]	0.002		1.716 [1.125-2.617]	0.012
CA125	1.020 [1.009-1.030]	0.000		1.021 [1.010-1.032]	0.000
Pathological type			0.019		0.120
Adenocarcinoma	1			1	
Squamous cell carcinoma	2.960 [1.385-6.328]	0.005		2.332 [1.038-5.194]	0.040
Others*	2.061 [0.272-15.628]	0.484		1.777 [0.232-13.646]	0.580
Vascular invasion Yes VS No	2.472 [0.937-6.522]	0.067			

*included: Large cell carcinoma, Carcinosarcoma

Figures

Figure 1

Nomogram and decision curve for overall survival (OS) in patients with stage I non-small cell lung cancer (NSCLC). To use the nomogram, the value of an individual patient is first located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the total point axis, and a line is drawn downward to the survival axes to determine the likelihood of 1-, 3-, or 5-year OS. (A) Nomogram for 1-, 3-, and 5-year overall survival (OS) in

patients with stage I non-small cell lung cancer (NSCLC). (B) Decision curve depicts the clinical net benefit in pairwise comparisons between the nomogram (red line) and the TNM staging system (green line), tumor size (blue line), and pathological type (purple line). (C) The clinical impact curve of the nomogram plotted the number of stage I NSCLC patients classified as high-risk and the number of cases classified as truly high-risk at each high-risk threshold.

Figure 2

The calibration curve for predicting patient survival at (A) 1 year, (B) 3 years and (C) 5 years in the training cohort and at (D) 1 year, (E) 3 years and (F) 4 years in the validation cohort. The nomogram-predicted probability of overall survival was plotted on the x-axis; actual overall survival was plotted on the y-axis.

Figure 3

The ROC curves and Kaplan-Meier survival curves of the nomogram ROC curve used to distinguish the survival of stage I NSCLC patients in the training cohort (A) and validation cohort (B). Kaplan-Meier survival curves of the nomogram in the training cohort (C) and validation cohort (D).

Supplementary Files

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