



Development and validation of a dynamic survival nomogram for metastatic non-small cell lung cancer based on the SEER database and an external validation cohort

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Background: Limited efficacy and poor prognosis are common in patients with metastatic non-small cell lung cancer (NSCLC). An accurate and useful nomogram helps the clinician predict the prognosis of the patients. However, there has been no previous report on the nomogram specially for predicting the overall survival (OS) of metastatic NSCLC patients.

Methods: A total of 18,343 patients diagnosed with metastatic NSCLC in the Surveillance, Epidemiology, and End Results (SEER) database were included and divided into the training cohort (n=12,840) and the internal validation cohort (n=5,503), and 242 patients in Renji Hospital were additionally enrolled as the external validation cohort. Demographical, clinical, and OS data were collected. A Cox proportional hazards regression model was used to develop a nomogram based on the training cohort. To validate the nomogram, we applied C-indexes, calibration curves, receiver operating characteristic (ROC) curve, decision curve analysis (DCA), and a Kaplan-Meier survival curve.

Results: The multivariate Cox regression model found that there were a total of 16 independent risk factors for OS of the patients (all 16 factors showed $P < 0.001$), which were integrated into the nomogram with a C-index of 0.702 [95% confidence interval (CI): 0.684–0.720]. The nomogram also exhibited good prognostic value in the internal validation cohort (C-index = 0.699, 95% CI: 0.673–0.725) and external validation cohort (C-index = 0.695, 95% CI: 0.653–0.737). The ROC and Kaplan-Meier survival curve analyses demonstrated a high discriminative ability. High-risk patients had significantly less favorable OS than low-risk patients in the SEER population and external validation cohort (both $P < 0.001$). The DCA analysis showed that the nomogram provided better prognosis prediction than the tumor-node-metastasis (TNM) staging system.

Conclusions: We constructed and validated a dynamic nomogram with 16 variables based on a large-scale population of SEER database to predict the prognosis of metastatic NSCLC patients. The nomogram is expected to provide higher predictive ability and accuracy than the TNM staging system.

Keywords: Non-small cell lung cancer (NSCLC); metastasis; prognosis; nomogram; overall survival (OS)

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Introduction

In recent years, there have been sharp declines in the incidence and mortality, and significant improvement of survival of lung cancer patients, especially those with non-small cell lung cancer (NSCLC). It is estimated that the 2-year relative survival of NSCLC has been improved from 34% (diagnosed from 2009 through 2010) to 42% (diagnosed from 2015 through 2016), including absolute improvement of 5–6% for patients at all stages (1). However, lung cancer is at present the second common cancer and the leading cause of cancer death, with an estimated 2.3 million newly diagnosed cases and 1.8 million deaths in 2020 of the USA alone (2). According to the American Joint Committee on Cancer (AJCC) 8th edition tumor-node-metastasis (TNM) staging system, metastatic lung cancer is defined as stages M1 and IV, including M1a (separate tumor nodule/s in a contralateral lobe; pleural nodules, or malignant pleural or pericardial effusion), M1b [single extrathoracic metastasis or involvement of a single distant (non-regional) node], and M1c (multiple extrathoracic metastases in 1 or multiple organs) (3). Patients with stage IV account for about 35% of all patients, while the 2- and 5-year survival rates have been reported at only 23% and 10% for stage IVA, and 10% and 0% for stage IVB, respectively (4). Despite the novel molecular-targeted therapies and immunotherapies have been developed, stage IV patients still have a very poor prognosis (5).

A predictive model helps the clinicians estimate disease progression and predict patients' survival according to their baseline characteristics and clinical data. Based on a Cox hazard regression model, a nomogram is a widely applied tool for predicting the survival of patients with malignant tumors (6). Many studies have reported the creation of a nomogram for lung cancer. Liang *et al.* developed a nomogram based on a Chinese multi-institutional registry of 6,111 patients with resected NSCLC and validated by a separate cohort of 2,148 patients from the International Association for the Study of Lung Cancer (IASLC) database. The nomogram included 6 independent prognostic factors and reached a C-index of 0.71, higher than the TNM staging system for predicting overall survival (OS) (7).

The TNM staging system is the most-widely used tool for guiding clinical treatments and predicting the prognosis (8). Wankhede *et al.* evaluated the 8th AJCC TNM stage for NSCLC by meta-analysis, indicating that the C-index of the 8th and 7th editions were 0.690 and 0.688, respectively (9). For the purpose of convenient use and easy prediction, the

TNM staging system only includes three key factor, lacking some essential information for survival analysis, such as age, gender, histology, and treatments. Therefore, numerous nomograms have been developed to predict the prognosis of lung cancer. A study published a nomogram for stage IB NSCLC, with age, gender, histology, differentiation grade, the extent of surgery, and lymph nodes resected entered. The authors found that the nomogram demonstrated good prognostic applicability and clinical accuracy, with the C-index values of 0.637 (95% CI: 0.634–0.641) for the training cohort and 0.667 (95% CI: 0.656–0.678) for the external validation cohort (10). The nomogram demonstrates better performance in prognosis prediction with much more factors requested. However, there has been no previous report of a nomogram for patients with metastatic NSCLC. In this study, we developed a nomogram for patients with metastatic NSCLC based on the Surveillance, Epidemiology, and End Results (SEER) database. We validated the nomogram with an internal validation cohort from the SEER database and an external validation cohort from a single center. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-544/rc>).

Methods

Patient selection

We selected the patients from 18 population-based cancer registries (with additional treatments fields) of the SEER database (<http://seer.cancer.gov/>). The SEER*Stat program (v 8.3.9; seer.cancer.gov/seerstat) was used to extract the information of patients with lung cancer. The extraction conditions were as follows: “the location of the disease: Lung and Bronchus” and “diagnosis year: 2004–2016”.

Following variables were extracted: “Age recode with <1 year old”, “Race recode (White, Black, Other)”, “Sex”, “Marital status at diagnosis”, “Primary Site – labeled”, “Histologic Type ICD-O-3”, “Grade”, “Laterality”, “Derived AJCC Stage Group, 7th ed (2010–2015)”, “Derived AJCC T, 7th ed (2010–2015)”, “Derived AJCC N, 7th ed (2010–2015)”, “Derived AJCC M, 7th ed (2010–2015)”, “Derived AJCC Stage Group, 6th ed (2004–2015)”, “Derived AJCC T, 6th ed (2004–2015)”, “Derived AJCC N, 6th ed (2004–2015)”, “Derived AJCC M, 6th ed (2004–2015)”, “RX Summ--Surg Prim Site (1998+)”, “RX Summ--Scope Reg LN Sur (2003+)”, “RX Summ--Surg Oth Reg/

Dis (2003+)”, “Chemotherapy recode”, “Radiation recode”, “SEER Combined Mets at DX-bone (2010+)”, “SEER Combined Mets at DX-brain (2010+)”, “SEER Combined Mets at DX-liver (2010+)”, “SEER Combined Mets at DX-lung (2010+)”, “Survival months”, “Vital status recode”, “First malignant primary indicator”, “Total number of in situ/malignant tumors for patient”. We screened the selected patients according to the following exclusion criteria: (I) patients diagnosed with small cell lung cancer (SCLC); (II) patients with M0 stage, MX, or unknown M stage; (III) age <18 years; (IV) patients in whom lung cancer was the first primary tumor; (V) patients with more than 1 malignant tumor; (VI) patients without information about the survival months; (VII) patients with unknown race, marital status, tumor site, grade, T stage, N stage, and metastatic sites. The patients’ T stage and N stage were transformed into the AJCC 8th TNM stage, while the M stage was not changed. In the 7th AJCC TNM stage, M1b stands for distant metastasis, divided into M1b (single extrathoracic metastasis) and M1c (multiple extrathoracic metastases) in the 8th TNM staging system.

The selected patients from the SEER database were randomly assigned to the training and internal validation cohorts with a bootstrapping technique and a proportion of 7:3. We selected patients with metastatic NSCLC diagnosed from 2015 to 2020 in Renji Hospital as the external validation cohort. At last, a total of 242 patients with metastatic NSCLC at Renji Hospital were enrolled as the external validation cohort, who had complete baseline characteristics and follow-up data. Clinical and pathological data were retrieved retrospectively from the hospital database, and follow-up information was collected by telephone interview. Patients without follow-up data and other essential clinical data were excluded.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China) (No. RA-2020-572), and informed consent was taken from all the patients.

Nomogram development

We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk factors for the OS of the training

cohort by applying the univariate Cox proportional hazards regression model when the risk factors with a P value less than 0.05 were included in the multivariate regression model. The independent risk factors were integrated into the nomogram model (P<0.05 in the multivariate Cox proportional hazards regression analysis). The probability of OS less than 3, 6, and 12 months could be estimated with the nomogram.

Nomogram validation

The training, internal, and external validation cohorts were used to validate the discriminative ability and calibration of the nomogram. Harrell’s C-statistic (C-index) was adopted as the primary indicator of discriminative power. Ranging from 0.5 to 1, the C-index values means that the discrimination ranges from none to perfect. A predicting model with C-index higher than 0.7 is usually considered as useful and predicative. Time-dependent receiver operating characteristic (ROC) curves with area under the curve (AUC) at 3, 6, and 12 months were also applied to demonstrate discriminative power. We used the calibration plot which to calibrate the relationship between observations and predicted probabilities. A standard curve of the calibration plot is a straight line through the origin of the axes with a slope of 1. when the prediction line falls on the 45-degree diagonal more, the model is more accurate. Finally, we applied decision curve analysis (DCA) to compare the accuracy of the nomogram and the TNM staging system.

Statistical analysis

We used R software (version 4.0.2; The R Foundation for Statistical Computing, Vienna, Austria) to construct the nomogram. All tests were two-sided and the statistical result was considered statistically significant when the P value was less than 0.05. We presented categorical variables as proportions and used Chi-square tests or Fisher’s precision probability test to compare the difference of categorical variables. According to the previous report (11), we also calculated the sum score of each patient based on the Cox hazards proportional regression model. We divided the patients into the low-risk and high-risk groups with the cut-off point for the risk stratification, which was calculated by the “surv_cutpoint” function of the “survminer” of the R packages. Survival analysis between the low-risk and high-risk groups was conducted with a Kaplan–Meier survival curve and the log-rank test.

Results

Demographic and clinicopathological characteristics

We listed all analyzed variables of the included patients in the SEER database (*Table 1*). A total of 18,343 patients in the SEER database were randomly divided into the training cohort (n=12,840) and the internal validation cohort (n=5,503). There was no statistically-significant difference between the training cohort and the internal validation cohort in all analyzed variables, including age, race, gender, marital status, primary site, histology, grade, laterality, T stage, N stage, M stage, surgery, chemotherapy, radiation therapy, bone metastasis, liver metastasis, brain metastasis, and lung metastasis.

In addition, we enrolled a total of 242 patients with metastatic NSCLC at Renji Hospital as the external validation cohort. We compared the demographic and clinicopathological characteristics of the SEER cohort and the external validation cohort (*Table 2*). All patients in the external validation cohort were Chinese that corresponded ‘others’ in the SEER database and the age of the external validation cohort was higher than that of the SEER cohort ($P<0.001$). The external validation cohort had a significantly higher proportion of T4 stage, M1a stage, surgery, and liver metastasis, and that showed a significantly lower proportion of chemotherapy than the SEER cohort (all $P<0.05$). However, there was no statistically-significant difference between the 2 cohorts regarding gender, marital status, primary site, histology, grade, laterality, N stage, radiation therapy, bone metastasis, brain metastasis, and lung metastasis (all $P>0.05$). The significant differences between the 2 cohorts helped to highlight the efficacy of the validation. *Figure 1* shows the flowchart of the study design.

Univariate and multivariate analysis in the training cohort

We conducted the univariate and multivariate analysis using the Cox proportional hazards regression model in the training cohort (n=12,840), with a total of 11,446 events recorded (*Table 3*). In terms of OS, in terms of OS, the univariate analysis showed that the vast majority of the variables including age, race, gender, marital status, primary site, histology, grade, T stage, N stage, M stage, surgery, chemotherapy, radiation therapy, bone metastasis, liver metastasis, and brain metastasis was significantly associated with the OS of the patients (all $P<0.05$), with the exceptions of laterality and lung metastasis ($P>0.05$). When

incorporated into the multivariate model, all included variables remained statistically significant after a stepwise regression (all $P<0.05$).

Development of the nomogram

We established the nomogram based on the established multivariate model (*Figure 2*). A total of 16 risk factors were included: age, race, gender, marital status, primary site, histology, grade, T stage, N stage, M stage, surgery, chemotherapy, radiation therapy, bone metastasis, liver metastasis, and brain metastasis. Since most patients survived less than 1 year, we built the nomogram predicting the survival probability at 3, 6, and 12 months. The C-index of the nomogram was 0.702 (95% CI: 0.684–0.720). For example, in the case of a 40-year-old white patient who was divorced and had been diagnosed with a grade III lung adenocarcinoma in the left upper lobe, the TNM stage was T1N1M1b (bone metastasis) and stage IV. He had received no surgery, no chemotherapy, and no radiation. This patient would be scored 1,100 points according to the nomogram, with the survival probabilities of 0.386 for less than 3 months, 0.6 for less than 6 months, and 0.813 for less than 12 months. The nomogram was published online at <https://pillawang.shinyapps.io/dynnomapp/>.

Validation of the nomogram

We applied an internal validation cohort from the SEER database (n=5,503) and an external validation cohort (n=242) to validate the nomogram, indicating that the nomogram also exhibited good prognostic value in the internal validation cohort (C-index =0.699, 95% CI: 0.673–0.725) and external validation cohort (C-index =0.695, 95% CI: 0.653–0.737). We also plotted the calibration plots of the nomogram in the training cohort, internal validation cohort, and external validation cohort (*Figure 3*) by 1,000 bootstrap resamples. The calibration plots showed that there was a good concordance between the predicted and observed 3-, 6-, and 12-month OS probability in internal and external validations. However, we noticed that the 12-month OS rate of the external validation group was higher than those of the training cohort and the internal validation cohort.

The ROC analysis showed that the nomogram had a high discriminative ability in all cohorts (*Figure 4*). The training cohort’s 3-, 6-, and 12-month AUCs were 0.781, 0.762, and 0.754, respectively. The internal validation cohort’s 3-, 6-, and 12-month AUCs were 0.777, 0.754, and 0.747,

Table 1 Demographics and clinicopathological characteristics of the training and internal validation cohort

Variables	Training set (N=12,840)	Test set (N=5,503)	P value
Age			0.065
20–54 years	1,745 (13.6%)	818 (14.9%)	
55–64 years	3,565 (27.8%)	1,543 (28.0%)	
65–74 years	4,308 (33.6%)	1,745 (31.7%)	
75–84 years	2,654 (20.7%)	1,158 (21.0%)	
85+ years	568 (4.4%)	239 (4.3%)	
Race			0.431
White	9,899 (77.1%)	4,267 (77.5%)	
Black	1,794 (14.0%)	731 (13.3%)	
Other	1,147 (8.9%)	505 (9.2%)	
Gender			0.427
Female	5,713 (44.5%)	2,484 (45.1%)	
Male	7,127 (55.5%)	3,019 (54.9%)	
Marital status			0.34
Married	6,954 (54.2%)	3,023 (54.9%)	
Others	5,886 (45.8%)	2,480 (45.1%)	
Primary site			0.799
Main bronchus	627 (4.9%)	256 (4.7%)	
Upper lobe	7,695 (59.9%)	3,341 (60.7%)	
Middle lobe	579 (4.5%)	246 (4.5%)	
Lower lobe	3,784 (29.5%)	1,588 (28.9%)	
Overlapping lesion of lung	155 (1.2%)	72 (1.3%)	
Histology			0.466
Adenocarcinoma	6,758 (52.6%)	2,950 (53.6%)	
Squamous	3,152 (24.5%)	1,315 (23.9%)	
Others	2,930 (22.8%)	1,238 (22.5%)	
Grade			0.541
Grade I	701 (5.5%)	289 (5.3%)	
Grade II	3,595 (28.0%)	1,504 (27.3%)	
Grade III	8,127 (63.3%)	3,543 (64.4%)	
Grade IV	417 (3.2%)	167 (3.0%)	
Laterality			0.905
Bilateral	46 (0.4%)	21 (0.4%)	
Left	5,331 (41.5%)	2,269 (41.2%)	
Right	7,463 (58.1%)	3,213 (58.4%)	

Table 1 (continued)**Table 1** (continued)

Variables	Training set (N=12,840)	Test set (N=5,503)	P value
T stage			0.989
T0	4 (0.0%)	2 (0.0%)	
T1	1,206 (9.4%)	519 (9.4%)	
T2	2,101 (16.4%)	903 (16.4%)	
T3	1,137 (8.9%)	498 (9.0%)	
T4	8,392 (65.4%)	3,581 (65.1%)	
N stage			0.394
N0	3,093 (24.1%)	1,289 (23.4%)	
N1	1,158 (9.0%)	483 (8.8%)	
N2	5,958 (46.4%)	2,546 (46.3%)	
N3	2,631 (20.5%)	1,185 (21.5%)	
M stage			0.268
M1a	2,551 (19.9%)	1,109 (20.2%)	
M1b	10,091 (78.6%)	4,326 (78.6%)	
M1NOS	198 (1.5%)	68 (1.2%)	
Surgery			0.898
No	11,967 (93.2%)	5,132 (93.3%)	
Yes	873 (6.8%)	371 (6.7%)	
Chemotherapy			0.0807
No/unknown	4,873 (38.0%)	2,013 (36.6%)	
Yes	7,967 (62.0%)	3,490 (63.4%)	
Radiation			0.341
No	11,495 (89.5%)	4,953 (90.0%)	
Yes	1,345 (10.5%)	550 (10.0%)	
Bone metastasis			0.227
No	7,946 (61.9%)	3,353 (60.9%)	
Yes	4,894 (38.1%)	2,150 (39.1%)	
Liver metastasis			0.365
No	10,790 (84.0%)	4,654 (84.6%)	
Yes	2,050 (16.0%)	849 (15.4%)	
Lung metastasis			0.932
No	8,535 (66.5%)	3,654 (66.4%)	
Yes	4,305 (33.5%)	1,849 (33.6%)	
Brain metastasis			0.297
No	8,858 (69.0%)	3,753 (68.2%)	
Yes	3,982 (31.0%)	1,750 (31.8%)	

Table 2 Demographics and clinicopathological characteristics of the SEER and External validation cohort

Variables	External cohort (N=242)	SEER cohort (N=18,343)	P value
Age			<0.001
20–54 years	26 (10.7%)	2,563 (14.0%)	
55–64 years	60 (24.8%)	5,108 (27.8%)	
65–74 years	66 (27.3%)	6,053 (33.0%)	
75–84 years	53 (21.9%)	3,812 (20.8%)	
85+ years	37 (15.3%)	807 (4.4%)	
Race			<0.001
White	0 (0%)	14,166 (77.2%)	
Black	0 (0%)	2,525 (13.8%)	
Other	242 (100%)	1,652 (9.0%)	
Gender			0.912
Female	109 (45.0%)	8,197 (44.7%)	
Male	133 (55.0%)	10,146 (55.3%)	
Marital status			0.061
Married	117 (48.3%)	9,977 (54.4%)	
Others	125 (51.7%)	8,366 (45.6%)	
Primary site			0.359
Main bronchus	8 (3.3%)	883 (4.8%)	
Upper lobe	138 (57.0%)	11,036 (60.2%)	
Middle lobe	15 (6.2%)	825 (4.5%)	
Lower lobe	76 (31.4%)	5,372 (29.3%)	
Overlapping lesion of lung	5 (2.1%)	227 (1.2%)	
Histology			0.160
Adenocarcinoma	120 (49.6%)	9,708 (52.9%)	
Squamous	72 (29.8%)	4,467 (24.4%)	
Others	50 (20.7%)	4,168 (22.7%)	
Grade			0.329
Grade I	8 (3.3%)	990 (5.4%)	
Grade II	66 (27.3%)	5,099 (27.8%)	
Grade III	163 (67.4%)	11,670 (63.6%)	
Grade IV	5 (2.1%)	584 (3.2%)	
Laterality			0.504
Bilateral	0 (0%)	67 (0.4%)	
Left	106 (43.8%)	7,600 (41.4%)	
Right	136 (56.2%)	10,676 (58.2%)	

Table 2 (continued)

Table 2 (continued)

Variables	External cohort (N=242)	SEER cohort (N=18,343)	P value
T stage			0.012
T0 + T1	19 (7.9%)	1,731 (9.4%)	
T2	22 (9.1%)	3,004 (16.4%)	
T3	25 (10.3%)	1,635 (8.9%)	
T4	176 (72.7%)	11,973 (65.3%)	
N stage			0.177
N0	51 (21.1%)	4,382 (23.9%)	
N1	17 (7.0%)	1,641 (8.9%)	
N2	111 (45.9%)	8,504 (46.4%)	
N3	63 (26.0%)	3,816 (20.8%)	
M stage			0.002
M1a	68 (28.1%)	3,660 (20.0%)	
M1b	168 (69.4%)	14,417 (78.6%)	
M1NOS	6 (2.5%)	266 (1.5%)	
Surgery			0.007
No	215 (88.8%)	17,099 (93.2%)	
Yes	27 (11.2%)	1,244 (6.8%)	
Chemotherapy			0.024
No/unknown	108 (44.6%)	6,886 (37.5%)	
Yes	134 (55.4%)	11,457 (62.5%)	
Radiation			0.093
No	225 (93.0%)	16,448 (89.7%)	
Yes	17 (7.0%)	1,895 (10.3%)	
Bone metastasis			0.290
No	141 (58.3%)	11,299 (61.6%)	
Yes	101 (41.7%)	7,044 (38.4%)	
Liver metastasis			0.040
No	192 (79.3%)	15,444 (84.2%)	
Yes	50 (20.7%)	2,899 (15.8%)	
Lung metastasis			0.110
No	149 (61.6%)	12,189 (66.5%)	
Yes	93 (38.4%)	6,154 (33.5%)	
Brain metastasis			0.459
No	161 (66.5%)	12,611 (68.8%)	
Yes	81 (33.5%)	5,732 (31.2%)	

SEER, Surveillance, Epidemiology, and End Results.

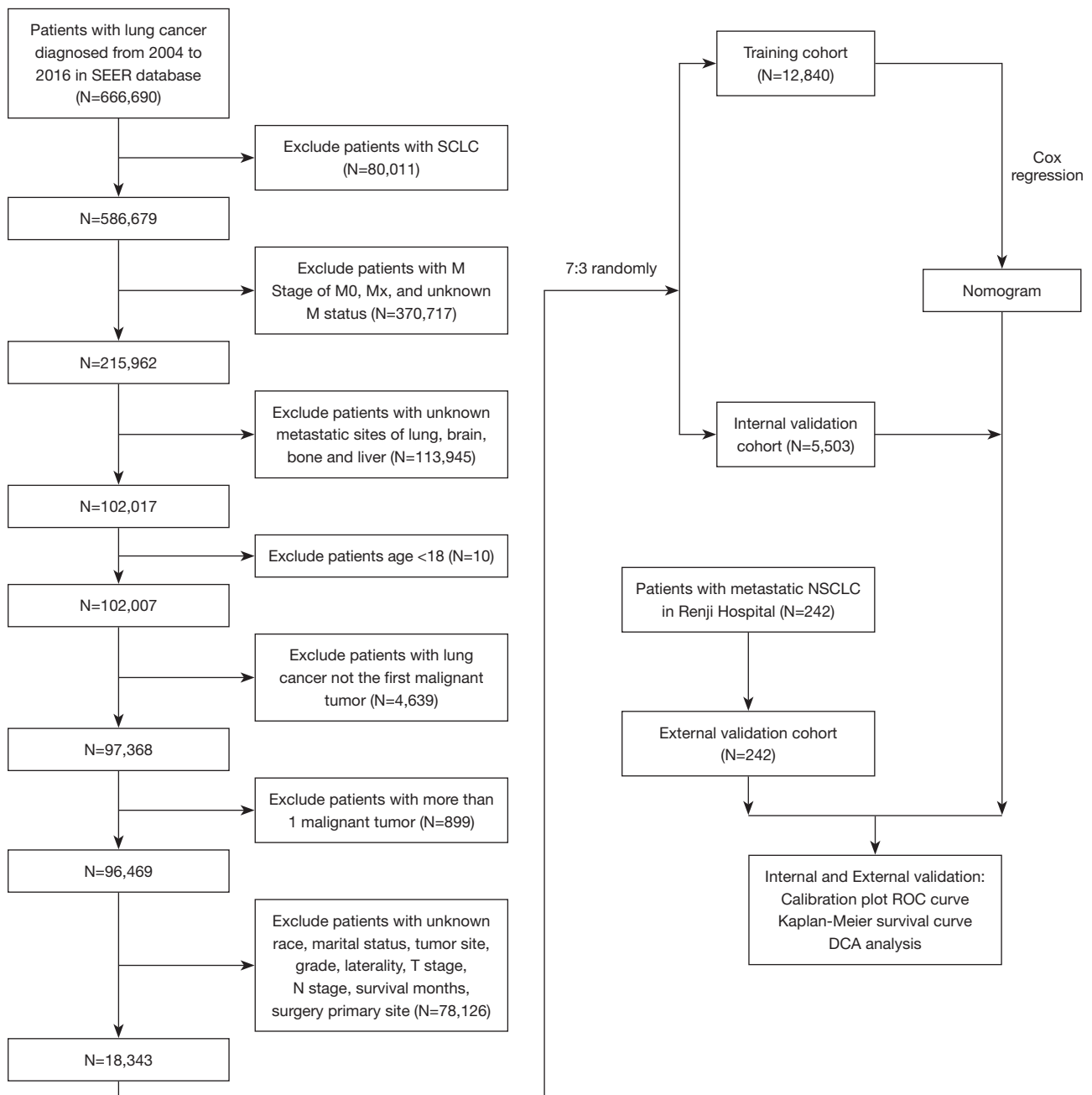


Figure 1 Flowchart of patient screening and study design. SEER, Surveillance, Epidemiology, and End Results; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; ROC, receiver operating curve; DCA, decision curve analysis.

respectively. The external validation cohort's 3-, 6-, and 12-month AUCs were 0.793, 0.753, and 0.759, respectively.

Survival and DCA analysis

The Cox hazard proportional regression model's cut-off

point was set at 1.05, dividing the patients into the high- and low-risk groups. We compared the survival between the high- and low-risk groups using Kaplan–Meier survival curve (Figure 5), indicating a significant difference between the high- and low-risk groups in the training, internal, and external validation cohort (all $P < 0.001$). We also completed

Table 3 Univariate and multivariate Cox regression analysis of each factor's ability for predicting OS in the training cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
20–54 years	Reference		Reference	
55–64 years	1.182 (1.111–1.258)	<0.001	1.150 (1.080–1.224)	<0.001
65–74 years	1.356 (1.277–1.441)	<0.001	1.301 (1.224–1.383)	<0.001
75–84 years	1.540 (1.443–1.643)	<0.001	1.401 (1.309–1.498)	<0.001
85+ years	1.736 (1.573–1.917)	<0.001	1.351 (1.219–1.497)	<0.001
Race				
Black	Reference		Reference	
White	0.954 (0.905–1.005)	0.081	1.351 (0.981–1.092)	0.205
Other	0.684 (0.631–0.741)	<0.001	0.757 (0.698–0.822)	<0.001
Gender				
Female	Reference		Reference	
Male	1.287 (1.24–1.335)	<0.001	1.237 (1.191–1.285)	<0.001
Marital status				
Married	Reference		Reference	
Others	1.211 (1.167–1.256)	<0.001	1.151 (1.108–1.196)	<0.001
Primary site				
Main bronchus	Reference		Reference	
Upper lobe	0.761 (0.700–0.828)	<0.001	0.843 (0.774–0.918)	<0.001
Middle lobe	0.699 (0.620–0.788)	<0.001	0.794 (0.704–0.896)	<0.001
Lower lobe	0.789 (0.723–0.861)	<0.001	0.877 (0.803–0.958)	0.003
Overlapping lesion of lung	0.714 (0.591–0.863)	<0.001	0.815 (0.674–0.984)	0.034
Histology				
Adenocarcinoma	Reference		Reference	
Squamous	1.341 (1.282–1.402)	<0.001	1.198 (1.143–1.255)	<0.001
Others	1.229 (1.173–1.286)	<0.001	1.167 (1.113–1.224)	<0.001
Grade				
Grade I	Reference		Reference	
Grade II	1.288 (1.178–1.409)	<0.001	1.185 (1.082–1.298)	<0.001
Grade III	1.668 (1.531–1.817)	<0.001	1.448 (1.327–1.580)	<0.001
Grade IV	1.961 (1.724–2.232)	<0.001	1.643 (1.440–1.875)	<0.001
Laterality				
Bilateral	Reference		NA	
Left	0.914 (0.672–1.244)	0.570	NA	
Right	0.926 (0.681–1.260)	0.627	NA	

Table 3 (continued)

Table 3 (continued)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
T stage				
T0 + T1	Reference		Reference	
T2	1.200 (1.112–1.296)	<0.001	1.218 (1.128–1.315)	<0.001
T3	1.408 (1.292–1.535)	<0.001	1.300 (1.191–1.419)	<0.001
T4	1.379 (1.291–1.472)	<0.001	1.427 (1.335–1.526)	<0.001
N stage				
N0	Reference		Reference	
N1	1.171 (1.089–1.259)	<0.001	1.173 (1.090–1.261)	<0.001
N2	1.318 (1.258–1.381)	<0.001	1.299 (1.238–1.364)	<0.001
N3	1.328 (1.256–1.404)	<0.001	1.409 (1.329–1.493)	<0.001
M stage				
M1a	Reference		Reference	
M1b	1.403 (1.338–1.471)	<0.001	1.228 (1.161–1.300)	<0.001
M1NOS	1.296 (1.112–1.510)	<0.001	1.124 (0.961–1.313)	0.142
Surgery				
No	Reference		Reference	
Yes	0.444 (0.409–0.481)	<0.001	0.535 (0.490–0.584)	<0.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.462 (0.445–0.480)	<0.001	0.426 (0.410–0.444)	<0.001
Radiation				
No	Reference		Reference	
Yes	0.7095 (0.667–0.7547)	<0.001	0.892 (0.835–0.954)	<0.001
Bone metastasis				
No	Reference		Reference	
Yes	1.252 (1.206–1.3)	<0.001	1.248 (1.197–1.301)	<0.001
Liver metastasis				
No	Reference		Reference	
Yes	1.434 (1.365–1.506)	<0.001	1.299 (1.234–1.366)	<0.001
Lung metastasis				
No	Reference		NA	
Yes	0.9835 (0.946–1.022)	0.4014	NA	
Brain metastasis				
No	Reference		Reference	
Yes	1.171 (1.126–1.218)	<0.001	1.332 (1.274–1.393)	<0.001

OS, overall survival; CI, confidence interval; HR, hazard ratio; NA, not available.

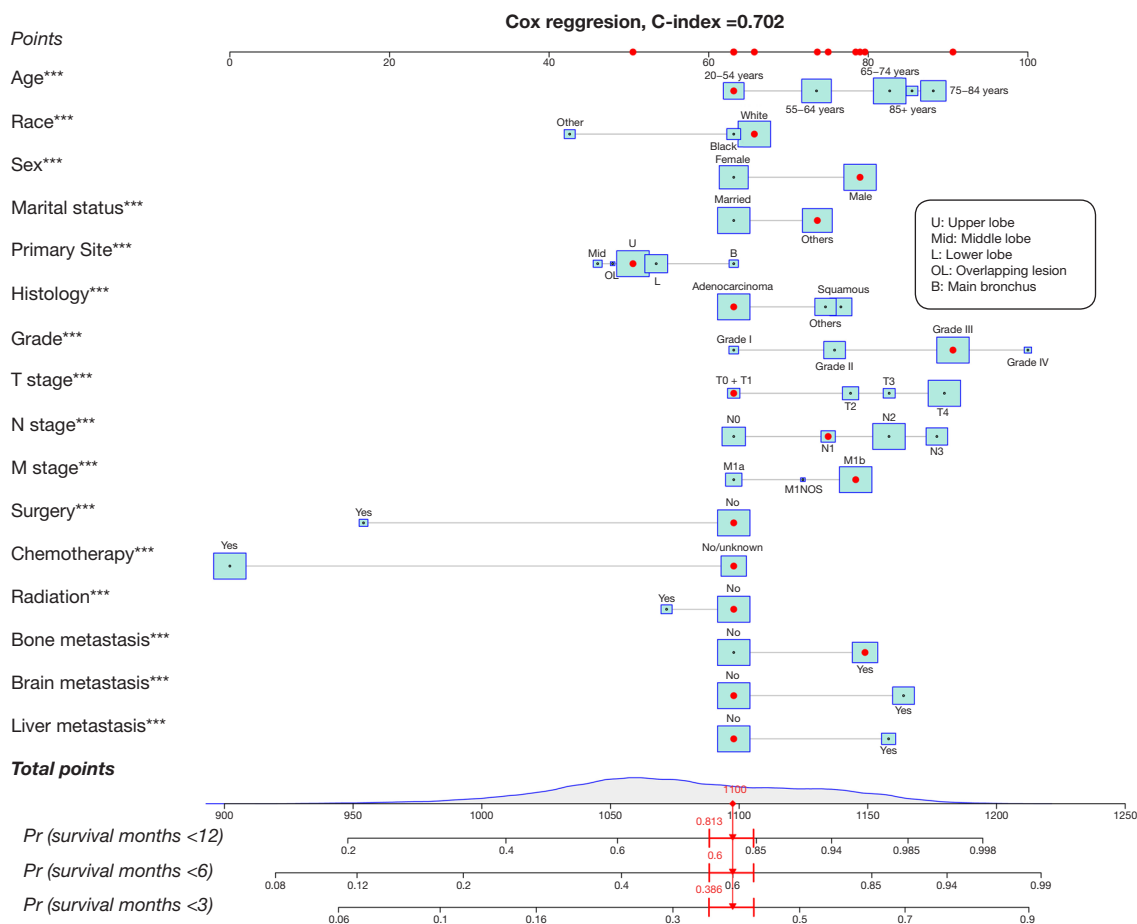


Figure 2 Nomogram for predicting the probability of 3-, 6-, and 12-month OS in patients with metastatic NSCLC. NSCLC, non-small cell lung cancer; OS, overall survival. ***, P<0.001.

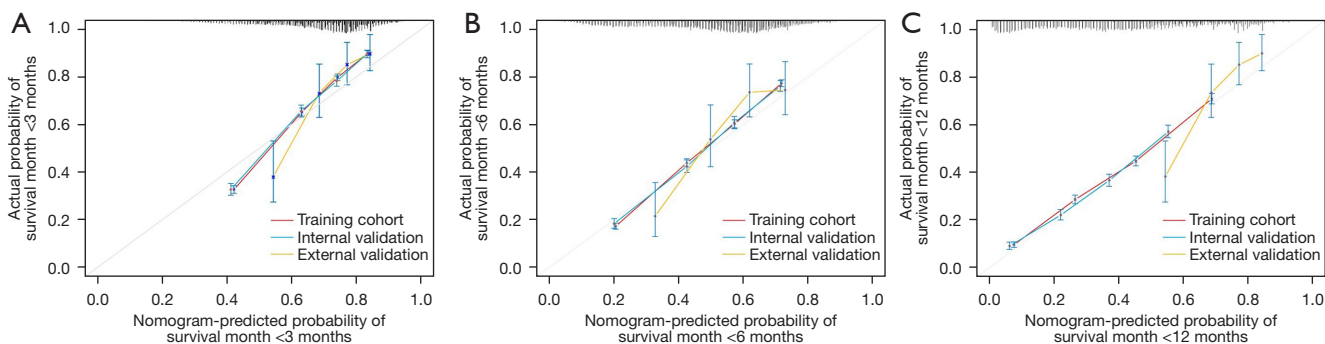


Figure 3 Calibration curves predicting the survival probability less than 3 (A), 6 (B), and 12 (C) months in the training, internal, and external cohorts.

the DCA analysis to compare the nomogram and the TNM staging system in the prediction performance (Figure 6). The results demonstrated that the nomogram was better

than the TNM staging system in predicting 3-, 6-, and 12-month OS. The C-index of the TNM staging system was 0.563 (95% CI: 0.560–0.565).

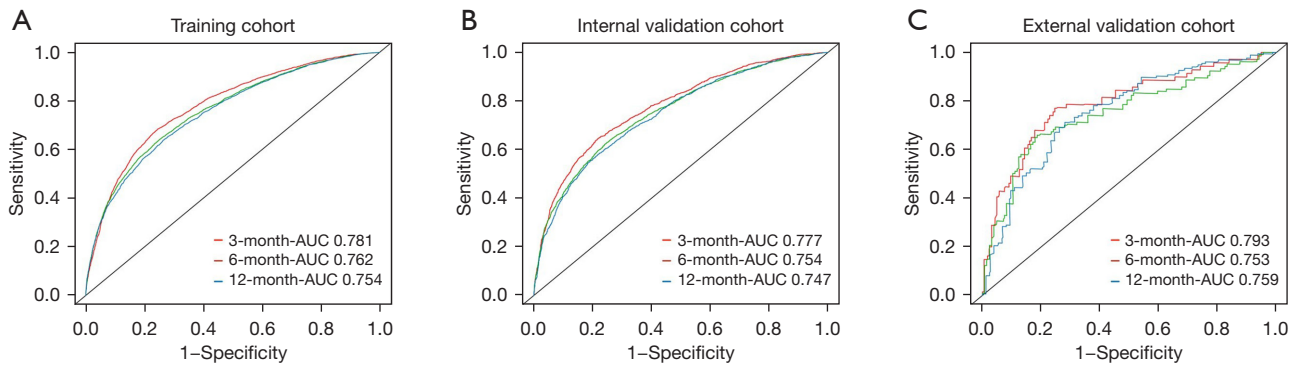


Figure 4 ROC curves and AUCs at 3-, 6-, and 12-month in the training cohort (A), internal validation cohort (B), and the external validation cohort (C). ROC, receiver operating characteristic; AUC, area under the curve.

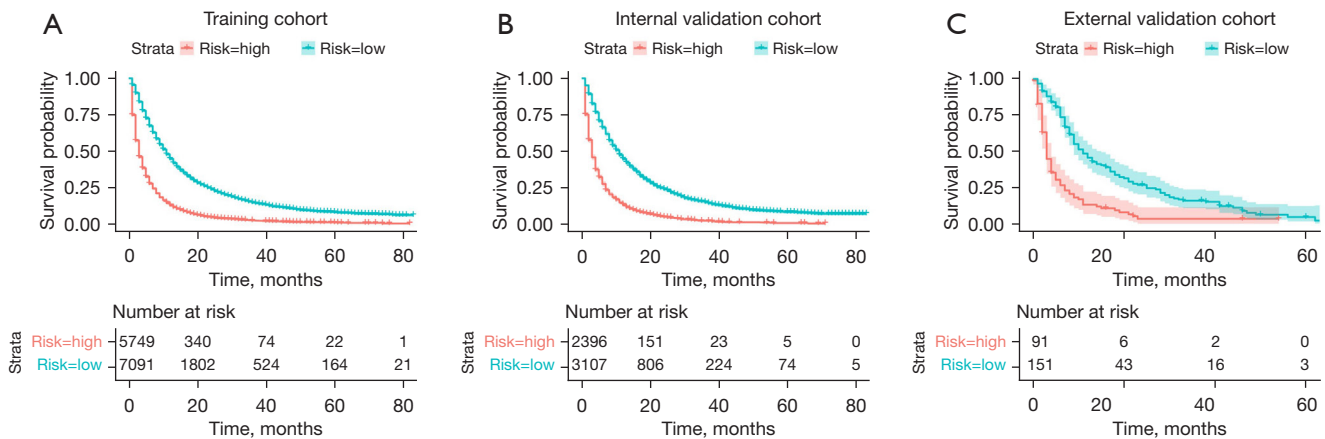


Figure 5 Kaplan-Meier curves of OS for risk stratification in the training cohort (A), internal validation cohort (B), and the external validation cohort (C). OS, overall survival.

Discussion

According to the latest reports in the US, the incidence of NSCLC per 100,000 has dropped from 46.4 in 2010 to 40.9 in 2017 overall, and that of stage IV at diagnosis has decreased slightly from 21.7 to 19.6 (12). Nevertheless, the 5-year survival probability decreases sharply according to the stages, from 50–65% for stage I to 2–3% for stage IV (13). In this study, we attempted to build a nomogram for stage IV patients based on the SEER database and then to validate the nomogram with internal and external validation cohorts.

A total of 16 independent risk factors, which was significantly higher than those in previous reports, were identified in this study. The entered risk factors could be attributed to 3 aspects. Firstly, the demographic characteristics including age, gender, marital status, and race were chosen for the nomogram. The earlier

nomogram for stage IB NSCLC only contained the age and gender without marital status and race because the authors did not input the race into the univariate analysis. The sample size was far less than in our study; hence the marital status was not statistically significant (10). Secondly, the tumor information including primary site, histology, grade, T stage, N stage, and M stage was entered into the nomogram. Zheng *et al.* investigated lung cancer incidence, survival, and prognostic factors with bone metastasis and developed a nomogram (14). The factors of age, gender, the total number of sites, histological types, grade, tumor size, and treatment were enrolled into the model, which was quite different from our study. The total number of sites was limited to 1 in our study, and the tumor size equaled the T stage in our model. Wang *et al.* compared different N descriptor numbers of positive

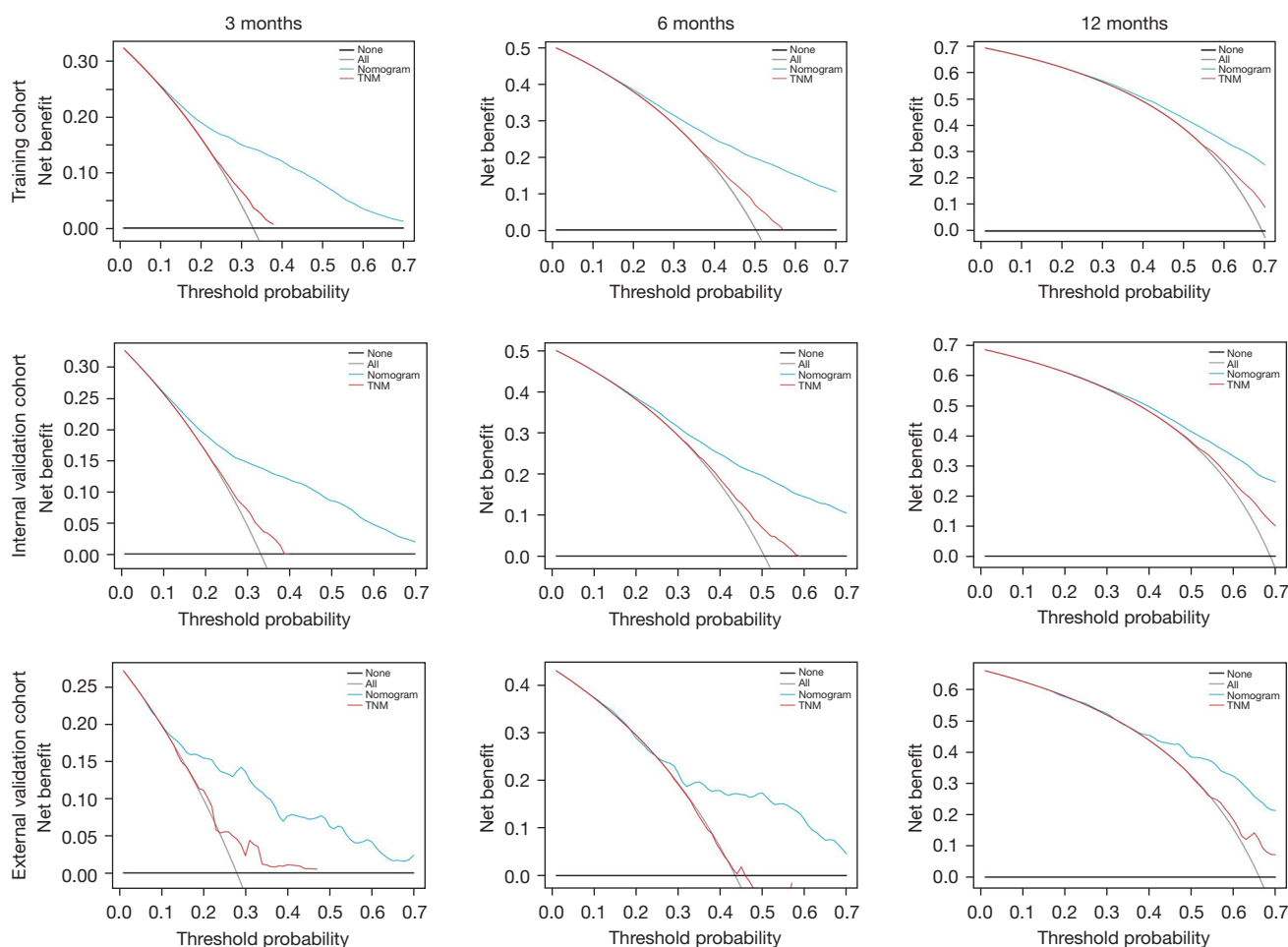


Figure 6 DCA of AJCC 8th TNM stage and nomogram for 3-, 6-, and 12-month OS of the training (A), internal (B), and external cohorts (C). DCA, decision curve analysis; AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis; OS, overall survival.

lymph nodes (NPLN), log odds of positive lymph nodes (LODDS), and lymph node ratio (LNR) in their prognostic roles for lung adenocarcinoma. They found that LODDS + LNR demonstrated the highest prediction accuracy, and developed a nomogram based on the findings (11). All of the nomograms above did not include the M stage since the studies were limited to the M0 stage or metastasis to bone. Thirdly, the treatment modalities, including surgery, chemotherapy, and radiation, were vital in the model. All treatments were important protecting factors for OS, with a significantly lowered hazard ratio (HR) of 0.535 (95% CI: 0.490–0.584) for the surgery, 0.426 (95% CI: 0.410–0.444) for the chemotherapy, and 0.892 (95% CI: 0.835–0.954) for the radiation. Surprisingly, the surgery was a significantly-improving factor for OS. Chao *et al.* compared the OS of patients with stage IV extrathoracic metastatic NSCLC

receiving surgery or not. They demonstrated that surgery could improve the survival of patients with single organ metastasis, while surgery showed no significant survival benefits in patients with multiple organ metastases (15). Lastly, the metastasis sites were included in the multivariate model. We have transformed the 7th AJCC TNM staging into the 8th edition, although the M stage was not changed because the number of sites of the metastasis was unknown in the SEER database.

A nomogram with a C-index higher than 0.70 is usually considered accurate and useful. Liang's nomogram had a C-index higher than the 7th AJCC TNM staging system in both the primary cohort (0.71 *vs.* 0.68, respectively; $P < 0.01$) and IASLC cohort (0.67 *vs.* 0.64, respectively; $P = 0.06$). We also calculated the C-index of the TNM staging system in metastatic NSCLC patients, which was lower than that of

the nomogram (0.563 vs. 0.702, $P < 0.001$). The DCA analysis also demonstrated that the nomogram performed better than the TNM staging system. The calibration plot and Kaplan–Meier survival curve were constructed to validate the nomogram in the internal and external validation cohorts, indicating that the nomogram was as accurate and discriminative as in the internal validation cohort. We noticed that the OS of the external cohort was better than that of the SEER cohort. We supposed that the diagnosis year of the external validation cohort was 2015–2020, when novel therapies had improved the OS of stage IV.

To the best of our knowledge, this is the first nomogram for predicting the survival of patients with metastatic NSCLC based on an extensive database with long-term follow-up and validated by a single-center retrospective cohort. We have also provided an online tool of the nomogram for prognosis prediction. However, several limitations of this study must be noted. Firstly, our nomogram was more complex than the TNM classification, when 16 items must be considered and analyzed. It is hard to make an accurate grading of the pathological results. Since metastatic NSCLC cases are the main subjects, the pathological specimens were likely to be biopsy specimens, and the entire tumors have not been evaluated. Secondly, although we have transformed the T stage and N stage from the 7th AJCC TNM stage to the 8th AJCC TNM stage, the M stage could not be transformed due to the lack of information about the number of the metastatic sites in the SEER database. In our nomogram, the M1b and M1c stage in the 8th AJCC TNM must be allocated into the M1b stage. Thirdly, molecular or genetic information is now becoming an important aspect affecting the prognosis, which was absent from the nomogram and should be considered in future models. Lastly, only traditional treatments were included in the model without novel therapies, such as targeted therapy and immunotherapy.

Conclusions

We have developed a novel dynamic nomogram for predicting the survival of metastatic NSCLC patients. The internal and external cohort validations demonstrated that the nomogram had good accuracy and discriminative ability. This tool provides a practical tool for clinicians to evaluate the stage and predict the prognosis for patients with stage IV NSCLC.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-544/rc>

Data Sharing Statement: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-544/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-544/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Ethics Committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China) (No. RA-2020-572), and informed consent was taken from all the patients.

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