Original Article

Development and validation of a nomogram for predicting overall survival in patients with stage III-N2 lung adenocarcinoma based on the SEER database

Shengchao Zhang^, Xiangzhi Xiao, Xuan Qin, Hongwei Xia

Department of Thoracic Surgery, Zhongshan Hospital Qingpu Branch, Fudan University, Shanghai, China

Contributions: (I) Conception and design: S Zhang, H Xia; (II) Administrative support: H Xia; (III) Provision of study materials or patients: S Zhang; (IV) Collection and assembly of data: S Zhang, X Qin; (V) Data analysis and interpretation: S Zhang, X Xiao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shengchao Zhang, MD. Department of Thoracic Surgery, Zhongshan Hospital Qingpu Branch, Fudan University, 1158 East Parkway, Shanghai 201700, China. Email: zhang.shengchao@qphospital.com.

Background: There is variability in the prognosis of stage III-N2 lung adenocarcinoma (LUAD) patients. The current tumor-node-metastasis (TNM) staging is not sufficient to precisely estimate the prognosis of stage III-N2 LUAD patients. The Surveillance, Epidemiology, and End Results (SEER) database collected first-hand information from a large number of LUAD patients. Based on the SEER database, this study aimed to determine the prognostic factors that affect overall survival (OS) in stage III-N2 LUAD patients and then establish a nomogram for predicting OS in this type of cancer to identify the high-risk population that may require more frequent surveillance or intensive care.

Methods: Data for 1,844 stage III-N2 primary LUAD patients who were registered between 2010 and 2015 were obtained from the SEER database. These patients were randomly assigned to either training (n=1,290) or validation (n=554) cohorts at a 7:3 ratio. The univariate and multivariate Cox regression (UCR and MCR) analyses were performed to find the relevant independent prognostic factors. To predict the OS based on these prognostic factors, a nomogram was then developed. The performance of the nomogram was examined based on the calibration curves, and receiver operating characteristic (ROC) curves. The ability of nomogram to stratify patient risk was validated by Kaplan-Meier survival analysis.

Results: Age, gender, tumor location, T-stage and treatment modality (chemotherapy, radiation therapy, surgery and scope of lymph node dissection) of stage III-N2 LUAD patients were significantly associated with prognosis. The area under the curve (AUC) values of OS predicted by the nomogram constructed with these factors at 12-, 36- and 60-month were 0.784, 0.762 and 0.763 in the training cohort, whereas 0.707, 0.685 and 0.705 in the validation cohort, respectively. Additionally, calibration curves demonstrated concordance between predicted and observed outcomes. Nomogram risk stratification provides a meaningful distinction between patients with various survival risks.

Conclusions: A survival prediction model that may be useful for risk stratification and decision-making is developed and validated for stage III-N2 LUAD patients. A high-risk patient predicted by the prediction model may require more frequent surveillance or intensive care.

Keywords: Stage III-N2 lung adenocarcinoma (stage III-N2 LUAD); nomograms; overall survival (OS); prognosis; Surveillance, Epidemiology, and End Results database (SEER database)

Submitted Dec 07, 2022. Accepted for publication Sep 13, 2023. Published online Oct 24, 2023.
doi: 10.21037/tcr-22-2757
View this article at: https://dx.doi.org/10.21037/tcr-22-2757

^ ORCID: 0000-0002-0641-7857.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, with more than half manifesting histologically as lung adenocarcinoma (LUAD) (1,2). Prognostic factors for LUAD are essential for developing prognostic assessments that might potentially identify patients who will benefit most from aggressive treatment choices while protecting others from the toxicity (3). The International Union Against Cancer (UICC) released the 8th edition of the tumor-node-metastasis (TNM) staging of lung cancer on January 1, 2018, with several revisions and additions to the 7th version. It is currently routinely applied to predict the prognosis of LUAD patients (4). With the recognition that mediastinal lymph node metastases (N2 staging) are closely connected with therapy and prognosis, the effective implementation of stage III-N2 LUAD patients remains unknown (5). Aside from TNM stage, additional factors effecting LUAD prognosis include gender, age, histological grade, smoking status, the type of lung resection and so on (6). A study utilizing the surveillance, epidemiology, and end results (SEER) database demonstrated that among stage III-N2 NSCLC patients after surgery, those with squamous cell cancer had a worse overall survival (OS) than those with adenocarcinoma (7). Xie *et al.* developed a model for predicting prognosis for patients with LUAD using the SEER database. The area under the curve (AUC) for the 3- and 5-year OS demonstrated excellent prognostic accuracy in both the training and validation cohorts (8). The SEER database contained a wealth of information on patients with LUAD and was widely used for prognostic modeling of LUAD at different stages or in different populations (9-11). However, to date, no study has been conducted on the construction of prediction model for OS in stage III-N2 LUAD patients.

A visual calculator called a nomogram has been extensively used in clinical investigations to predict prognosis according to significant factors. Nomogram, which consists of scales for each factor, gives clinical professionals a practical and efficient approach to calculate risk and make judgments (12).

Therefore, our research aimed to determine the prognostic factors that are associated with stage III-N2 LUAD patients' OS by analyzing relevant information from the SEER database and to develop and validate a novel nomogram model to predict the 12-, 36- and 60-month OS in these patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2757/rc).

Highlight box

Key findings

- The overall survival (OS) of stage III-N2 lung adenocarcinoma (LUAD) is not only related to tumor stage, but also affected by various factors such as the patient's age, gender, treatment modality, and so on.
- The Nomogram based on multivariate Cox regression analyses can more accurately predict the OS of patients with stage III-N2 LUAD.

What is known and what is new?

- There is variability in the prognosis of stage III-N2 lung LUAD patients. The current tumor-node-metastasis (TNM) staging is not sufficient to precisely estimate the OS of stage III-N2 LUAD patients.
- The OS of stage III-N2 LUAD patients can be predicted by the Nomogram developed, which may aid in decision-making and risk stratification.

What is the implication, and what should change now?

- A high-risk patient predicted by the Nomogram may require more frequent surveillance.

Methods

Data source and patient selection

The information of patients with stage III-N2 LUAD was extracted from the SEER database using the SEER*Stat v8.4.0.1 (National Cancer Institute, USA). The inclusion criteria were: (I) patients who were histologically diagnosed with LUAD between 2010 and 2015; (II) patients without distant metastases at the time of diagnosis; and (III) patients in the N2 stage. The exclusion criteria were: (I) patients with more than one malignant tumor; (II) patients whose T stage was T0 or Tx; (III) whether the patient underwent surgical treatment was unknown. Overall, 1,844 eligible patients were ultimately enrolled in this study after screening. *Figure 1* depicts the data-processing procedure. The patients were assigned to two sets randomly: training set (70%) and validation set (30%). Because SEER is a publicly accessible database, investigations that use it do not need ethics board permission or patient consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

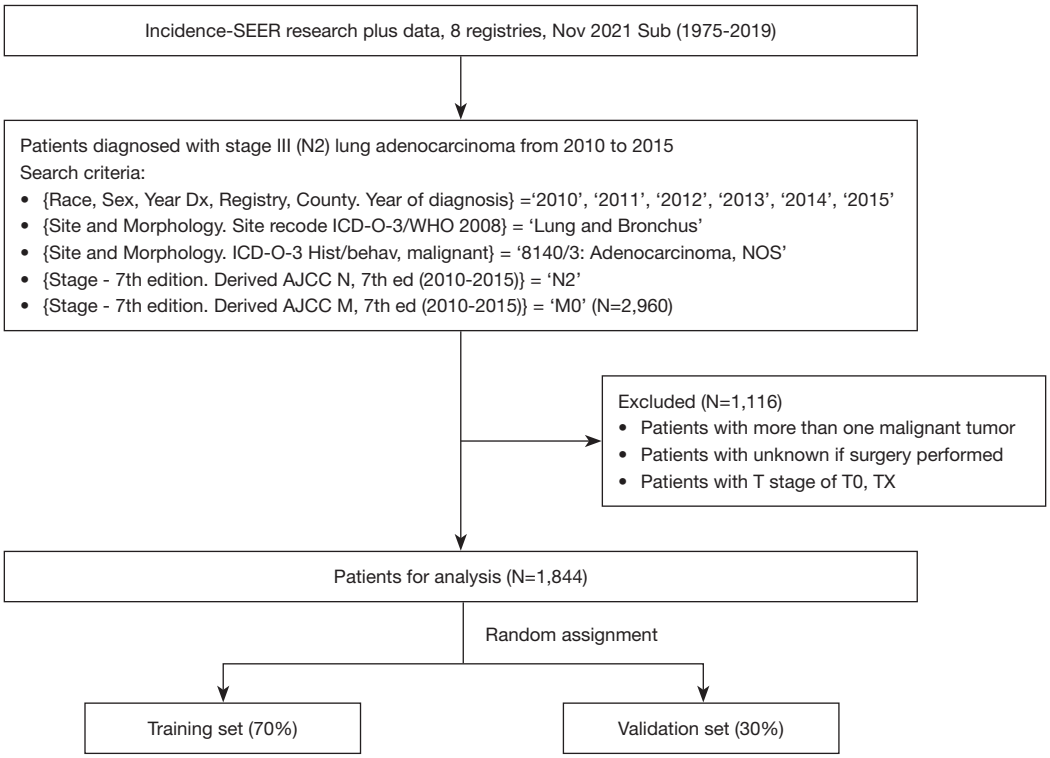

Figure 1 Flowchart of patient screening.

Study variables

Herein, ten variables were used to determine independent prognostic factors in stage III-N2 LUAD patients. The demographic variables included gender (female or male), race (white, black, or other) and age (<60, 60–69, 70–79 or ≥80 years). The clinicopathological features of LUAD included T stage (T1, T2, T3, or T4), tumor grade (I, II, III, IV or unknown), primary location (right upper lobe, right middle lobe, right lower lobe, left upper lobe, left lower lobe or other), and treatment types, including surgery (yes or no), chemotherapy (yes or no), radiotherapy (yes or no), and scope of regional lymph node removed (SRLNR) (none, <4, ≥4 or others). The classification of T stage was performed according to the 7th edition of the TNM stage. Tumor grade was classified as I-IV according to the World Health Organization (WHO) standard grading system. Primary location identified the site in which the primary tumor originated. Other primary location included main bronchus, overlapping lesion of lung and unknown. Surgery described a surgical procedure that removed or destroyed tissue of the primary site. SRLNR described the procedure of removal, biopsy, or aspiration of regional lymph nodes. The primary endpoint was OS. OS was defined as the time from diagnosis to death. OS = (date of last contact – date of diagnosis)/days in a month. Days in a month =365.24/12.

Statistical analysis

All patients were assigned to either the training or validation sets at a 7:3 ratio using the R software. To investigate the baseline features of these patients, the Chi-square test was used for categorical data. Univariate Cox regression (UCR) analysis was conducted to determine independent prognostic factors in the training set, and the significant variables were further subjected to multivariate Cox regression (MCR) analysis. A nomogram for predicting OS in 12-, 36- and 60-month was then developed according to these independent prognostic factors. The nomogram's predictive discriminative capability was assessed by using receiver operating characteristics (ROC) curves, and the AUC. The greater the AUC, the better the accuracy. AUC values range from 0.5 to 1.0, with 0.5 representing random chance and 1.0 representing complete compliance. And an AUC value better than 0.7 indicates a good prediction (13). Calibration curves were employed to assess the nomogram's

Table 1 Clinicopathological characteristics of patients with stage III-N2 lung adenocarcinoma in the training and validation sets

Characteristic	Training set (N=1,290)	Validation set (N=554)	P value
Age (years)			0.78
<60	325 (25.2)	132 (23.8)	
60–69	397 (30.8)	175 (31.6)	
70–79	360 (27.9)	164 (29.6)	
≥80	208 (16.1)	83 (15.0)	
Race			0.504
Black	157 (12.2)	72 (13.0)	
White	971 (75.3)	408 (73.6)	
Other	161 (12.5)	72 (13.0)	
Unknown	1 (0.1)	2 (0.4)	
Gender			0.104
Female	653 (50.6)	304 (54.9)	
Male	637 (49.4)	250 (45.1)	
Location			0.729
RUL	481 (37.3)	208 (37.5)	
RML	53 (4.1)	27 (4.9)	
RLL	219 (17.0)	98 (17.7)	
LUL	299 (23.2)	135 (24.4)	
LLL	124 (9.6)	46 (8.3)	
Others	114 (8.8)	40 (7.2)	
Grade			0.202
I	52 (4.0)	18 (3.2)	
II	241 (18.7)	89 (16.1)	
III	451 (35.0)	184 (33.2)	
IV	4 (0.3)	4 (0.7)	
Unknown	542 (42.0)	259 (46.8)	
T			0.631
T1	280 (21.7)	127 (22.9)	
T2	488 (37.8)	214 (38.6)	
T3	253 (19.6)	112 (20.2)	
T4	269 (20.9)	101 (18.2)	
Surgery			0.304
No	954 (74.0)	423 (76.4)	
Yes	336 (26.0)	131 (23.6)	
SRLNR			0.128
None	688 (53.3)	268 (48.4)	
<4	60 (4.7)	27 (4.9)	
≥4	299 (23.2)	130 (23.5)	
Others	243 (18.8)	129 (23.3)	
Radiation			0.58
No	452 (35.0)	186 (33.6)	
Yes	838 (65.0)	368 (66.4)	
Chemotherapy			0.818
No	353 (27.4)	148 (26.7)	
Yes	937 (72.6)	406 (73.3)	

Data are presented as n (%). RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; SRLNR, scope of regional lymph node removed.

accuracy in predicting 12-, 36-, and 60-month OS.

In addition, using the nomogram, the risk score was measured for all patients. A risk stratification model was built according to the risk score, which assigned the entire cohort into two risk groups (low-risk or high-risk) according to the median risk score of the training set. Kaplan Meier survival analysis was performed to compare the survival rates of high-risk and low-risk groups. R software (version 4.0.1) was employed for all statistical tests. Two-sided P values of <0.05 were deemed statistically significant.

Results

Patient characteristics

This research recruited a total of 1,844 participants with stage III-N2 LUAD. There were 1,290 and 554 patients in the training and validation sets, respectively. *Table 1* indicates the demographics and clinical features of the patients. In all variables, the differences between the training and validation sets did not differ greatly (P>0.05).

Screening for prognostic factors of OS

To reveal the association between the variables and OS, UCR and MCR analyses were conducted (*Table 2*). The

Table 2 Univariate and multivariate regression analysis of overall survival in patients with stage III-N2 lung adenocarcinoma

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<60	1		1	
60–69	1.23 (1.04–1.47)	0.016	1.06 (0.89–1.26)	0.5385
70–79	1.51 (1.28–1.8)	<0.001	1.2 (1–1.43)	0.0468
≥80	2.36 (1.95–2.86)	<0.001	1.38 (1.12–1.7)	0.0029
Race				
Black	1			
White	1.03 (0.85–1.24)	0.765		
Other	0.92 (0.72–1.18)	0.502		
Unknown	0 (0–Inf)	0.99		
Gender				
Female	1		1	
Male	1.43 (1.27–1.62)	<0.001	1.38 (1.22–1.56)	<0.001
Location				
RUL	1		1	
RML	1.17 (0.86–1.58)	0.312	1.17 (0.86–1.58)	0.3282
RLL	0.93 (0.78–1.11)	0.435	0.93 (0.77–1.12)	0.4357
LUL	1.03 (0.88–1.21)	0.707	1.01 (0.86–1.19)	0.9081
LLL	1.04 (0.84–1.3)	0.7	1.1 (0.88–1.37)	0.419
Others	1.58 (1.26–1.97)	<0.001	1.29 (1.02–1.62)	0.0305
Grade				
I	1			
II	0.97 (0.69–1.36)	0.87		
III	1.27 (0.92–1.75)	0.149		
IV	0.54 (0.13–2.23)	0.392		
Unknown	1.23 (0.89–1.69)	0.208		
T				
T1	1		1	
T2	1.16 (0.98–1.37)	0.082	1.14 (0.96–1.34)	0.139
T3	1.39 (1.15–1.69)	0.001	1.41 (1.16–1.71)	<0.001
T4	1.55 (1.28–1.86)	<0.001	1.31 (1.08–1.59)	0.0062
Surgery				
No	1		1	
Yes	0.48 (0.41–0.56)	<0.001	0.76 (0.59–0.98)	0.0318
SRLNR				
None	1		1	
<4	0.43 (0.32–0.59)	<0.001	0.59 (0.42–0.84)	0.0028
≥4	0.37 (0.32–0.44)	<0.001	0.53 (0.4–0.69)	<0.001
Others	0.49 (0.42–0.58)	<0.001	0.6 (0.51–0.72)	<0.001
Radiation				
No	1		1	
Yes	0.68 (0.6–0.77)	<0.001	0.75 (0.64–0.86)	<0.001
Chemotherapy				
No	1		1	
Yes	0.38 (0.33–0.43)	<0.001	0.51 (0.44–0.6)	<0.001

HR, hazard ratio; CI, confidence interval; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; SRLNR, scope of regional lymph node removed.

UCR analysis showed eight factors associated with OS: gender, age, T stage, primary location, surgery, SRLNR, radiation, and chemotherapy. Gender, age, T stage, primary location, surgery, SRLNR, radiation, and chemotherapy were further confirmed to be significantly associated with prognosis in stage III-N2 LUAD in MCR analysis.

Nomogram construction and validation

A nomogram was constructed using the independent prognostic factors for 12-, 36-, and 60-month OS, which was verified using the data of validation cohort. Based on the hazard ratio (HR), the variables in the nomogram were assigned a score ranging from 0 to 100. Total score was obtained by adding the scores of the variables and then placing it on the total subscale to get the probability of 12-, 36-, and 60-month OS (*Figure 2*).

The AUC values of 12-, 36-, and 60-month were 0.784, 0.762 and 0.763 in the training set, while 0.707, 0.685 and 0.705 in the validation set, according to ROC curve analysis (*Figure 3*). The 12-, 36- and 60-month OS were 62.5%, 31.6% and 21.4% in the training cohort, whereas 63.1%, 31.6% and 21.5% in the validation cohort, respectively. Using 62.7%, 32.6%, and 20.5% as thresholds for nomogram predicting 12-, 36-, and 60-month OS,

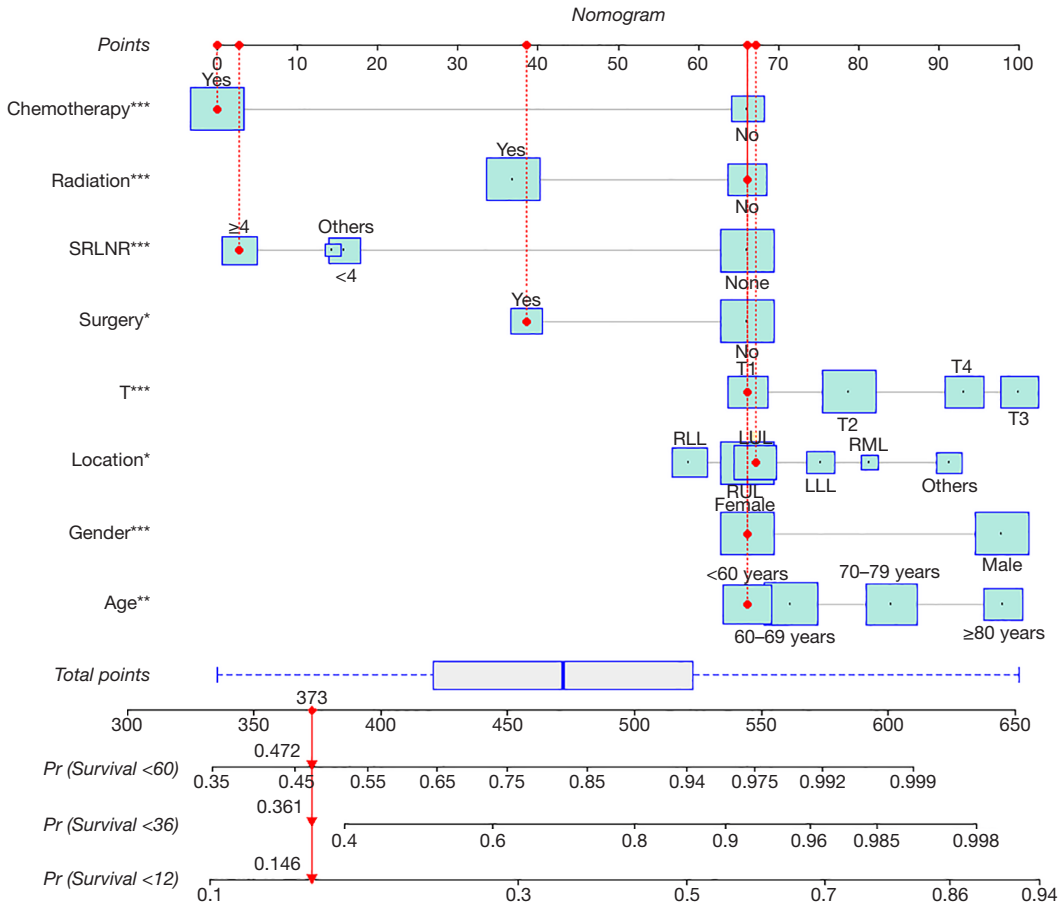

Figure 2 A nomogram to predict 12-, 36- and 60-month overall survival of stage III-N2 lung adenocarcinoma patients. *, P<0.05; **, P<0.01; ***, P<0.001. SRLNR, scope of regional lymph node removed; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.

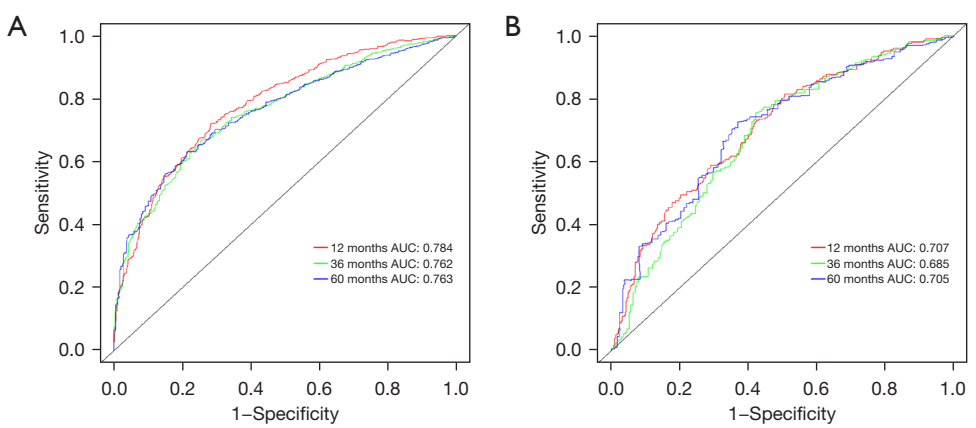

Figure 3 ROC curves for nomograms predicting 12-, 36- and 60-month overall survival in the training (A) and validation cohorts (B). AUC, area under the curve; ROC, receiver operator characteristic.

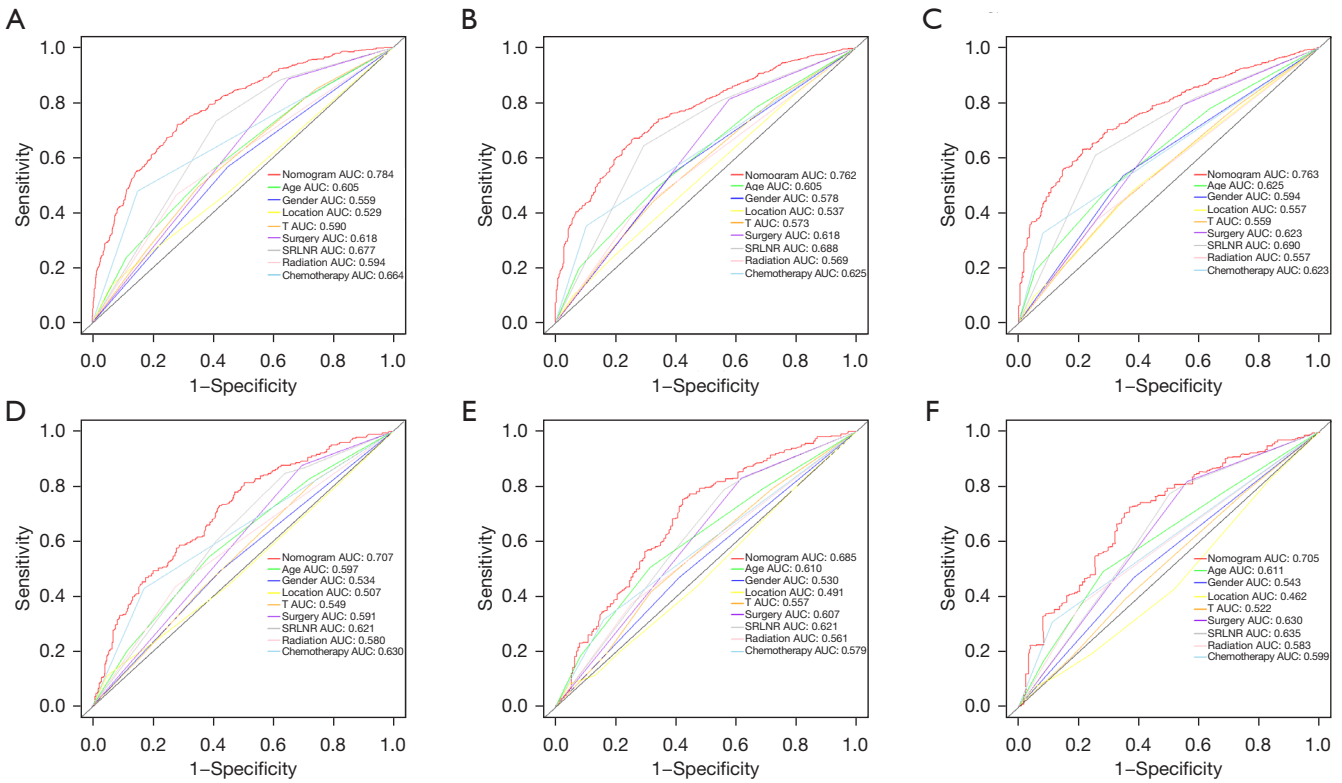

Figure 4 Comparing the AUC values of all independent factors with the AUC values of nomograms predicting 12-, 36-, and 60-month overall survival in the training cohorts (A-C) and validation cohorts (D-F). AUC, area under the curve.

the sensitivity of nomogram in the training cohort was 72.2%, 66.6%, and 63.1%, and the specificity was 71.7%, 74.4%, and 78.9%, whereas the sensitivity in the validation cohort was 59.7%, 59.9%, and 58.6%, and the specificity was 68.5%, 65.2%, and 68.9%. The AUC values of the nomogram at 12-, 36- and 60-month were greater than those that of all independent variables in both training and validation sets (*Figure 4*). The nomogram calibration curves for probability of 12-, 36- and 60-month OS in both training and validation cohorts demonstrated concordance between predicted and observed outcomes (*Figure 5*).

Ability of nomogram to stratify patient risk

Based on their risk assessment, patients were assigned to two groups: high-risk and low-risk. There was significant distinction between the two risk categories according to Kaplan-Meier OS curves. If the patient is classified as being in the low-risk grouping, their prognosis will always be favorable. The prognosis of high-risk patients was obviously lower than that of low-risk patients, demonstrating that the nomogram-based risk classification approach is a significant predictor of patients' survival for stage III-N2 LUAD. *Figure 6* shows an obvious difference (P<0.0001) between the survival curves in the training and validation sets.

Establishment of a web server for evaluating the novel model

We created an online version of this nomogram at https://xwfc.shinyapps.io/dynnomapp/ to help doctors to reduce interventional risk and predict survival for stage III-N2 LUAD patients.

Discussion

LUAD, which accounts for around 40% of all lung cancer cases, is the most frequent subtype. Despite advances in our knowledge of the disease's pathogenesis and the advent of novel therapeutic strategies, LUAD remains one of the most aggressive and quickly lethal tumor species, with an OS of

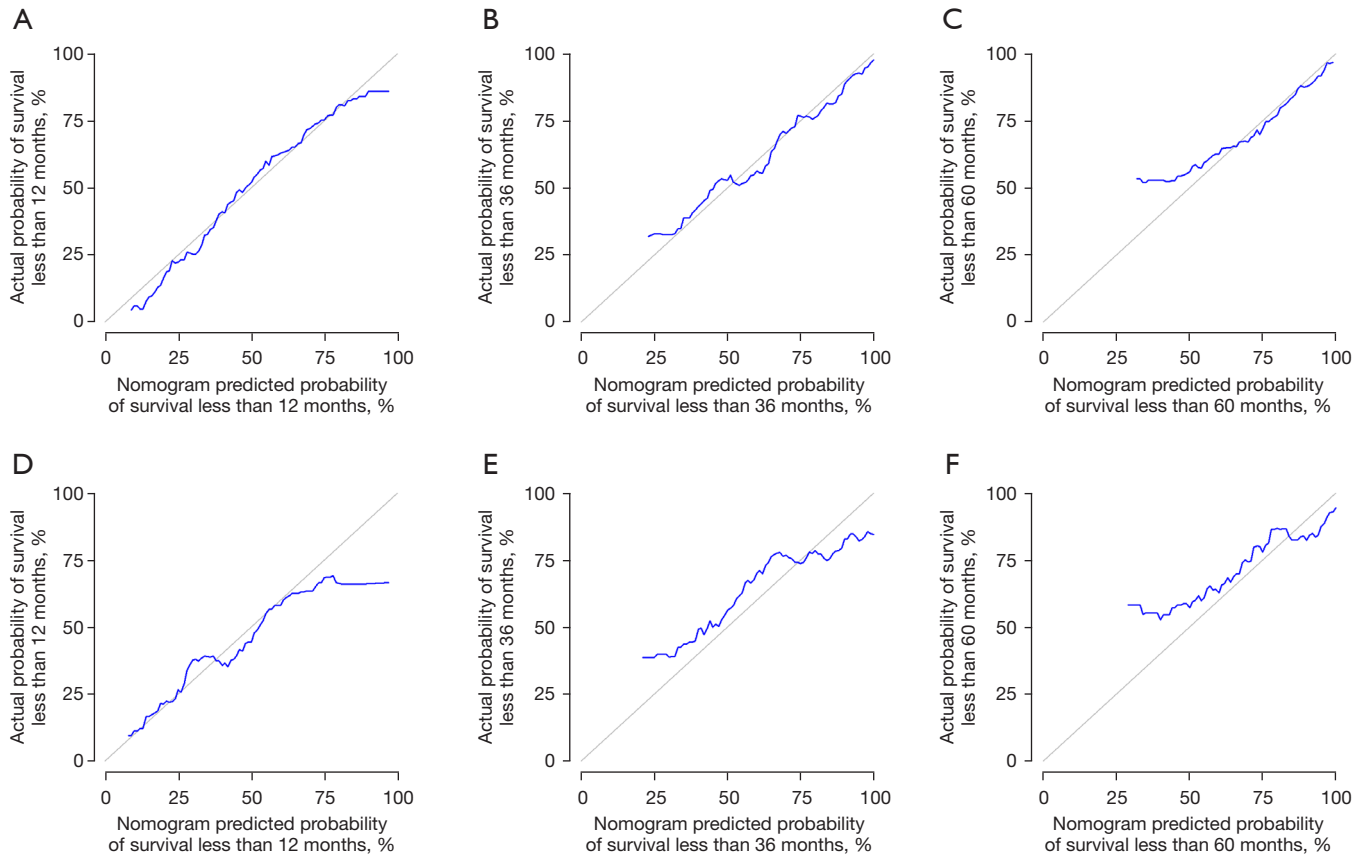

Figure 5 Calibration curves to assess the nomogram's accuracy in predicting 12-, 36-, and 60-month overall survival in the training cohorts (A-C) and validation cohorts (D-F).

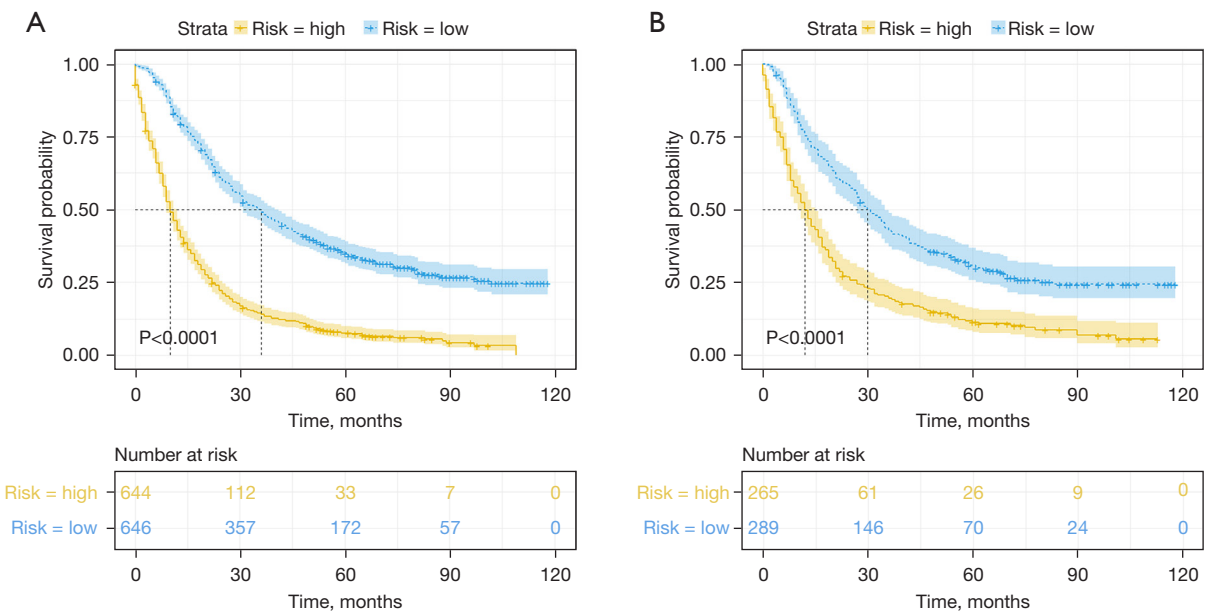

Figure 6 Kaplan-Meier curves for patients with various risks according to risk scores in the training (A) and validation cohorts (B).

lower than five years (14). Surgery is the main course of therapy for resectable and operable LUAD (stages I and II), offering the highest probability for long-term survival (15). However, therapeutic options such as radiation, chemotherapy, and surgical resection are commonly employed in LUAD patients with N2 lymph node metastases. Individualized treatment is obviously becoming a therapeutic strategy for individuals with stage III-N2 LUAD. To choose the most appropriate treatment, the individual data impacting survival results must be analyzed. Treatments will be much improved with this individualized information, and the developed nomogram is a crucial method for providing information on patient survival.

Based on the controlled randomized trial performed by the Lung Cancer Study Group (LCSG) comparing lobectomy and limited resection (anatomical segmentectomy or wedge resection) in T1N0 NSCLC patients, lobectomy and mediastinal node dissection have been regarded as the gold standard for the therapy of all stage 1A NSCLC (16). However, the importance of surgery in treating stage III-N2 LUAD is still debatable. Surgery is not a commonly used treatment option since N2 metastasis is thought to imply systemic disease development (17). An exploratory analysis from the North American Intergroup Trial 0139 appears to support the application of surgery as part of trimodal treatment in some patients. Concurrent chemotherapy and radiation followed by surgical resection were compared to concurrent standard chemotherapy and definitive radiotherapy without resection in this phase 3 trial. Although the median OS in the two groups was fairly similar, surgery was beneficial in the lobectomy group but not in the pneumonectomy group (18). Our results showed that surgery could improve the prognosis of stage III-N2 LUAD patients, but not all the patients would benefit from this treatment. On the one hand, this may be due to the fact that the patients selected for surgery in the retrospective study were tolerant to surgery and had resectable lung cancer. On the other hand, there were many surgical options for the primary site in this study, such as sublobar resection, lobectomy, and pneumonectomy. Therefore, it is necessary to select the right patient and the best surgical method to improve patient survival. In addition, if surgery is performed, mediastinal lymph node dissection is also important. Our findings showed that mediastinal lymph node dissection improved patients' OS and the scope of resection was correlated with OS.

It has been demonstrated that male gender is a distinct, unfavorable prognostic factor for NSCLC survival (19,20). The patient's age is an important prognostic factor that affects lung cancer survival, in which elderly individuals have a worse OS (21,22). Similar results were obtained about the impact of the two independent prognostic factors (i.e., gender and age) on OS in stage III-N2 LUAD patients. Men and patients older than 70 years old had a worse prognosis. In previous studies, tumor grade was demonstrated to be an independent predictor of OS for NSCLC. The lower the tumor grade, the more malignant the tumor and the worse the prognostic outcomes (23,24). The factor of grade was not markedly associated with OS in this study, most probably because there were too many patients with unknown tumor grade. The primary tumor location was also included as a significant prognostic factor in our analysis. It was found that patients with other primary sites (e.g., main bronchus, overlapping lesion of lung and unknown) had poor outcomes. This suggests that central lung cancer or lung cancer with invasion of more than one lung lobe has a worse prognosis. Conventional staging of T has historically included elevated T as having a poor prognosis, and this was also reflected in our prognostic model. In our model, T1 had a better prognosis than T2, T3, and T4, and an obvious difference was found between T1 and T3/T4, but not between T1 and T2. Given these findings, for stage III-N2 LUAD, surgery should be performed with caution, especially in elderly patients, central lung cancer patients, and T4 patients.

Stage III-N2 NSCLC patients are commonly treated with chemotherapy. Adjuvant or neoadjuvant chemotherapy improves NSCLC survival compared to surgery alone, according to the randomized clinical trials and meta-analyses (25-28). Concomitant chemoradiotherapy with curative purpose is advised for unresectable patients (29-31). A retrospective analysis found that patients who were able to undergo resection had a better prognosis following induction concomitant chemoradiation (32). A phase 3 randomized trial, however, found that radiation added little benefit to induction chemotherapy followed by surgery (33). A meta-analysis revealed that postoperative radiation may not be associated with a better OS for resectable stage III-N2 NSCLC patients, advising a cautious selection (34). Another huge database analysis found that adding radiation to adjuvant chemotherapy after surgery of stage N2 NSCLC did not prolong survival (35). This study found that both chemotherapy and radiotherapy can improve the prognosis of stage III-N2 LUAD. Therefore, we believe that chemotherapy is the optimal and necessary choice for stage III-N2 LUAD. Radiotherapy is an option for

inoperable patients.

This study does, however, have certain flaws. The outcomes of this study are undoubtedly impacted by selection bias because it is a retrospective study according to the SEER database. Second, there are some restrictions on the SEER database. For instance, the SEER database is deficient on key elements that are equally crucial for predicting prognosis in stage III-N2 LUAD patients, such as novel treatments. The prognosis of lung cancer has considerably improved over the last decade thanks to advancements in NSCLC treatment, including targeted therapy and immunotherapy (36). Nevertheless, these two novel treatment approaches need further research.

Conclusions

OS is substantially correlated with age, gender, tumor location, T stage, and treatment modalities (chemotherapy, radiation, surgery, and scope of lymph node dissection) in stage III-N2 LUAD patients. The OS rate can be predicted by the Nomogram developed using these factors, which may aid in decision-making and risk stratification. A high-risk patient predicted by the Nomogram may require more frequent surveillance or intensive care.

Acknowledgments

We appreciate the National Cancer Institute making SEER data available to the public.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2757/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2757/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).

References

1. Yang Y, Shen C, Shao J, et al. Based on the Development and Verification of a Risk Stratification Nomogram: Predicting the Risk of Lung Cancer-Specific Mortality in Stage IIIA-N2 Unresectable Large Cell Lung Neuroendocrine Cancer Compared With Lung Squamous Cell Cancer and Lung Adenocarcinoma. Front Oncol 2022;12:825598.
2. Hao X, Li W, Li W, et al. Re-evaluating the need for mediastinal lymph node dissection and exploring lncRNAs as biomarkers of N2 metastasis in T1 lung adenocarcinoma. Transl Lung Cancer Res 2022;11:1079-88.
3. Barletta JA, Yeap BY, Chirieac LR. Prognostic significance of grading in lung adenocarcinoma. Cancer 2010;116:659-69.
4. Sui Q, Liang J, Hu Z, et al. The clinical prognostic factors of patients with stage IB lung adenocarcinoma. Transl Cancer Res 2021;10:4727-38.
5. Pang Z, Yang Y, Ding N, et al. Optimal managements of stage IIIA (N2) non-small cell lung cancer patients: a population-based survival analysis. J Thorac Dis 2017;9:4046-56.
6. Woodard GA, Jones KD, Jablons DM. Lung Cancer Staging and Prognosis. Cancer Treat Res 2016;170:47-75.
7. Jin G, Wang X, Xu C, et al. Disparities in survival following surgery among patients with different histological types of N2-III non-small cell lung cancer: a Surveillance, Epidemiology and End Results (SEER) database analysis. Ann Transl Med 2020;8:1288.
8. Xie B, Chen X, Deng Q, et al. Development and Validation of a Prognostic Nomogram for Lung Adenocarcinoma: A Population-Based Study. J Healthc Eng 2022;2022:5698582.
9. Wen H, Lin X, Sun D. Gender-specific nomogram models to predict the prognosis of male and female lung

adenocarcinoma patients: a population-based analysis. Ann Transl Med 2021;9:1654.
10. You H, Teng M, Gao CX, et al. Construction of a Nomogram for Predicting Survival in Elderly Patients With Lung Adenocarcinoma: A Retrospective Cohort Study. Front Med (Lausanne) 2021;8:680679.
11. Zheng R, Guo D, Dong Y, et al. Prognostic Factors and Prediction of Survival for Patients with Brain Metastases of Lung Adenocarcinoma. J Nippon Med Sch 2021;88:319-25.
12. Wu LL, Chen WT, Liu X, et al. A Nomogram to Predict Long-Term Survival Outcomes of Patients Who Undergo Pneumonectomy for Non-small Cell Lung Cancer With Stage I-IIIB. Front Surg 2021;8:604880.
13. Shen H, Deng G, Chen Q, et al. The incidence, risk factors and predictive nomograms for early death of lung cancer with synchronous brain metastasis: a retrospective study in the SEER database. BMC Cancer 2021;21:825.
14. Denisenko TV, Budkevich IN, Zhivotovsky B. Cell death-based treatment of lung adenocarcinoma. Cell Death Dis 2018;9:117.
15. Lemjabbar-Alaoui H, Hassan OU, Yang YW, et al. Lung cancer: Biology and treatment options. Biochim Biophys Acta 2015;1856:189-210.
16. Hutchinson BD, Shroff GS, Truong MT, et al. Spectrum of Lung Adenocarcinoma. Semin Ultrasound CT MR 2019;40:255-64.
17. Suda K, Sato K, Mizuuchi H, et al. Recent evidence, advances, and current practices in surgical treatment of lung cancer. Respir Investig 2014;52:322-9.
18. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
19. Visbal AL, Williams BA, Nichols FC 3rd, et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. Ann Thorac Surg 2004;78:209-15; discussion 215.
20. Wang ZH, Deng L. Establishment and Validation of a Predictive Nomogram for Postoperative Survival of Stage I Non-Small Cell Lung Cancer. Int J Gen Med 2022;15:7287-98.
21. Tas F, Ciftci R, Kilic L, et al. Age is a prognostic factor affecting survival in lung cancer patients. Oncol Lett 2013;6:1507-13.
22. Atci MM, Sakin A, Uysal E, et al. Survival and Prognostic Factors in Limited-stage Small-cell Lung Cancer. J Coll Physicians Surg Pak 2021;31:1433-7.
23. Wang W, Teng F, Bu S, et al. A Population-Based Study on the Prognostic factors and Efficacy of Adjuvant Chemotherapy in the Postoperative Stage for Patients with Stage IIA Non-Small Cell Lung Cancer. Risk Manag Healthc Policy 2022;15:1581-92.
24. Gu T, Ren J, Hu Z, et al. A predictive model based on liquid biopsy for non-small cell lung cancer to assess patient's prognosis: Development and application. Tissue Cell 2022;77:101854.
25. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 2012;30:172-8.
26. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.
27. McElnay P, Lim E. Adjuvant or neoadjuvant chemotherapy for NSCLC. J Thorac Dis 2014;6 Suppl 2:S224-7.
28. NSCLC Meta-analyses Collaborative Group; Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
29. Casal-Mouriño A, Ruano-Ravina A, Lorenzo-González M, et al. Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. Transl Lung Cancer Res 2021;10:506-18.
30. Glatzer M, Leskow P, Caparrotti F, et al. Stage III N2 non-small cell lung cancer treatment: decision-making among surgeons and radiation oncologists. Transl Lung Cancer Res 2021;10:1960-8.
31. Putora PM, Leskow P, McDonald F, Batchelor T, Evison M. International guidelines on stage III N2 nonsmall cell lung cancer: surgery or radiotherapy?. ERJ Open Res 2020;6:00159-2019.
32. Caglar HB, Baldini EH, Othus M, et al. Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. Cancer 2009;115:4156-66.
33. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. Lancet 2015;386:1049-56. Correction appears in Lancet. 2015;386:1040.
34. Lei T, Li J, Zhong H, et al. Postoperative Radiotherapy for Patients With Resectable Stage III-N2 Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Front Oncol 2021;11:680615.

35. Drake JA, Portnoy DC, Tauer K, et al. Adding Radiotherapy to Adjuvant Chemotherapy Does Not Improve Survival of Patients With N2 Lung Cancer. Ann Thorac Surg 2018;106:959-65.

36. Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med 2020;383:640-9.

Cite this article as: Zhang S, Xiao X, Qin X, Xia H. Development and validation of a nomogram for predicting overall survival in patients with stage III-N2 lung adenocarcinoma based on the SEER database. Transl Cancer Res 2023;12(10):2742-2753. doi: 10.21037/tcr-22-2757

