A prognostic nomogram based on least absolute shrinkage and selection operator Cox regression in patients with pulmonary large-cell neuroendocrine carcinoma

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Background: Pulmonary large-cell neuroendocrine carcinoma (LCNEC) is a rare subtype of breast cancer with a poor prognosis. Despite its rarity, it is important to gain a better understanding of the epidemiological, clinical, and prognostic features of pulmonary LCNEC. The purpose of this study was to design, construct, and validate a new nomogram for predicting overall survival (OS) in patients with pulmonary LCNEC.

Methods: In total, the data of 1,864 LCNEC patients were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, which is maintained by the National Cancer Institute in the United States and serves as a comprehensive source of cancer-related information. Of these patients, 556 served as the validation group and 1,308 served as the training cohort. We constructed a new nomogram with the training cohort that included the independent factors for OS as identified by least absolute shrinkage and selection operator Cox regression. Five independent factors were ultimately selected by the stepwise regression. Every factor of the Cox regression was included in the nomogram. Analyses of the calibration curve, decision curve, area under the curve, and concordance index (C-index) values were performed to assess the effectiveness and discriminative ability of the nomogram.

Results: Five optimal predictive factors for OS were selected and merged to construct a 3- and 5-year OS nomogram. The nomogram had C-index values of 0.716 and 0.708 in the training cohort and validation cohort, respectively. The actual OS rates and the calibration curves showing the predictions of the nomogram were in good agreement.

Conclusions: The prognostic nomogram may be very helpful in estimating the OS of patients with pulmonary LCNEC.

Keywords: Pulmonary large-cell neuroendocrine carcinoma (pulmonary LCNEC); nomogram; least absolute shrinkage and selection operator (LASSO); Cox regression; Surveillance, Epidemiology, and End Results database (SEER database)

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Introduction

Large-cell neuroendocrine carcinoma (LCNEC) is an uncommon and extremely aggressive neuroendocrine tumor subtype with a poor prognosis (1). In 2010, it had an incidence of 1.8 per 100,000 people (2). It can affect any part of the body; however, the pulmonary and gastrointestinal tracts account for the majority of cases (3-6). Pulmonary LCNEC comprises approximately 3% of lung cancers (7). In 2015, the World Health Organization defined LCNEC as morphological non-small cell lung cancer (NSCLC) with the histopathological features of neuroendocrine cancer and the immunohistochemical expression of neuroendocrine markers. In addition, a subgroup of pulmonary LCNEC is described as "LCNEC with components of adenocarcinoma, squamous cell carcinoma, spindle cell carcinoma, and/or giant-cell carcinoma" (8,9).

The International Association for the Study of Lung Cancer introduced the 7th edition of the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging method of malignant tumors in 2010 and it is thought to provide the best staging approach for patients with LCNEC (10,11). However, this system was not specifically designed to predict outcomes for patients with pulmonary LCNEC; thus, new methods need to be developed to identify independent risk variables for the construction of prognostic prediction models.

In 1997, Tibshirani *et al.* presented the least absolute shrinkage and selection operator (LASSO) Cox regression method for variable factor selection, whereby a LASSO regression analysis and a multivariate Cox regression analysis were used to identify prognostic factors, and with which a more accurate model was constructed (12-14). A great deal of research that has employed the LASSO Cox regression method to identify risk genes has shown that it is essential in the study of cancer (15,16). However, few studies have used the LASSO Cox regression method to screen clinical indicators to establish prognostic prediction models (17). He *et al.* generated a nomogram model to predict overall survival (OS) in pulmonary LCNEC, in which univariate and multivariate Cox regression models were used to determine the demographic and clinicopathological features associated with OS (18). Similarly, Ma *et al.* generated a nomogram model for predicting cancer-specific survival in pulmonary LCNEC patients (19). Nomograms have demonstrated an ability to identify influencing factors and provide more accurate, individualized predictions. Additionally, a nomogram is a tool that combines numerous prognostic signs and provides a more convenient and straightforward way to predict the likelihood of an occurrence than traditional approaches (20,21).

Thus, we created a distinctive nomogram using a sizable patient cohort from the Surveillance, Epidemiology, and End Results (SEER) database, which collects and compiles data on cancer incidence, prevalence, treatment, and survival from diverse locations around the United States. This nomogram aims to offer more accurate predictions of OS for patients diagnosed with pulmonary LCNEC. In addition, the newly created nomogram was compared to the 7th edition of the AJCC TNM staging system to ascertain whether it was able to more accurately predict patient prognosis. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1061/rc).

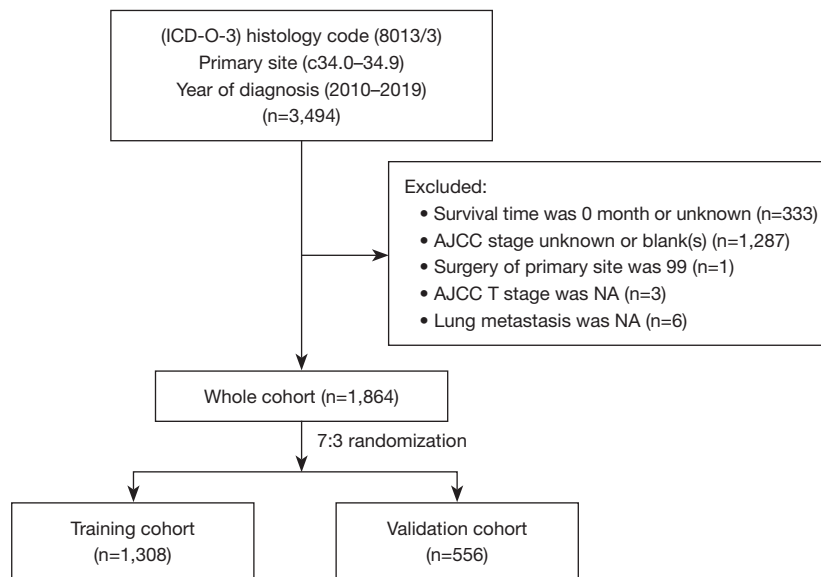**Highlight box**

Key findings
- Age, bone metastasis, liver metastasis, surgery, and chemotherapy were identified as independent risk factors for pulmonary large-cell neuroendocrine carcinoma (LCNEC).

What is known and what is new?
- Pulmonary LCNEC is a rare subtype of breast cancer.
- Our study is one of the largest population-based studies to estimate the prognosis of pulmonary LCNEC patients. Our prognostic nomogram may be very helpful in estimating the overall survival of patients with pulmonary LCNEC.

What is the implication, and what should change now?
- Surgery contributed to a better prognosis for pulmonary LCNEC patients. Importantly, prospective studies need to be conducted to explore tailored treatments and establish surveillance guidelines for pulmonary LCNEC patients at different stages.

Methods

Study population and data processing

In this comprehensive retrospective analysis based on a large population, data were extracted from the SEER database using SEER*Stat 8.4.01. The SEER database includes information about patients diagnosed with LCNEC. The National Cancer Institute's 17 cancer registries provide information to the SEER database (22). The SEER database's most recent follow-up and prognosis

Figure 1 Flow diagram presenting the screening process in the SEER database. ICD-O-3, International Classification of Diseases for Oncology, Third Edition; AJCC, American Joint Committee on Cancer; NA, not applicable; SEER, Surveillance, Epidemiology, and End Results.

data were published in November 2021. We carried out this study in accordance with the guidelines of the Declaration of Helsinki (as revised in 2013).

Patients who were diagnosed with LCNEC between 2010 and 2019 were first identified in the SEER database. Patients were included in the study if they met the following inclusion criteria: (I) had at least one the following SEER primary site codes: C34.0, C34.1, C34.2, C34.3, C34.8, or C34.9; and (II) had the International Classification of Diseases for Oncology, 3rd Edition, histology code of 8013/3, which was used to diagnose LCNEC and to describe the condition. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a survival time of 0 months or less; (II) were death certificate-only cases; and/or (III) lacked or had insufficient information about their race, marital status, primary site, laterality, T stage, N stage, grade, surgery, or radiation treatment. Ultimately, 1,864 patients with pulmonary LCNEC were included in the primary cohort. The detailed screening process is displayed in *Figure 1*.

The following data were obtained from the SEER database: demographics (gender, race, age, and marital status at time of diagnosis); tumor characteristics (primary site, laterality, histologic grade, tumor size, AJCC stage, AJCC-T stage, AJCC-N stage, AJCC-M stage, brain metastasis, bone metastasis, liver metastasis, and lung

metastasis); and treatment information (surgery to primary site, radiation, and chemotherapy); and follow-up information (survival time and survival status).

Retrospective reviews of the patients' medical records were conducted to identify the demographic data and relevant clinicopathological features, such as age (0–59 years old or ≥60 years old), gender (male or female), race (white, black, or other; that is, American Indian/Alaska Native, Asian/Pacific Islander), marital status (married, single, widowed/divorced, or other/unknown), primary site (main bronchus, upper lobe, middle lobe, or lower lobe), tumor stage as per the 7th edition of the AJCC TNM staging system (occult, I, II, III, or IV), T stage as per the 7th edition of the AJCC TNM staging system (TX, T0, T1, T2, T3, or T4), N stage as per the 7th edition of the AJCC TNM staging system (NX, N0, N1, N2, or N3), M stage as per the 7th edition of the AJCC TNM staging system (M0 or M1). The following data were also collected in relation to metastasis status: brain (no/unknown or yes), bone (no/unknown or yes), liver (no/unknown, yes), and lung (no/unknown, yes). Additionally, the following treatment data were collected: surgery (no/unknown or yes), radiotherapy (no/unknown or yes), chemotherapy (no/unknown or yes). Data were also collected on patients' OS. In this study, comprehensive data analyses were completed.

Follow-up

The primary outcome of the study was OS, which was defined as the interval between the diagnosis of pulmonary LCNEC until the final follow-up or death. Patients who participated in this study had a known survival status and a known survival period. The median follow-up time was 12 months (interquartile range: 5–33 months; range: 1–119 months) in the entire cohort.

Statistical analysis

In this study, 1864 eligible patients with pulmonary LCNEC were randomly divided into a training cohort and a validation cohort at a ratio of 7:3 using R (version 3.5.1) and the "caret" package. All the categorical variables were summarized as the count and percentage. The frequency distributions of the demographic, clinical, and pathologic characteristics of the eligible patients were compared between the training and validation sets using the chi-square test.

We converted the continuous variables into classification variables to increase the objectivity and simplicity of the model. In the training cohort, the covariates (e.g., age, gender, race, marital status, primary site, laterality, tumor size, stage, T stage, N stage, and M stage as per AJCC 7th edition, as well as bone metastasis, brain metastasis, liver metastasis, and lung metastasis, and surgery and chemotherapy) were entered into a LASSO regression using the R package "glmnet", and "lambda.1se" was used to select the variables, and a 10-fold cross-validation was used to determine the optimal LASSO penalty. After testing for collinearity, a forward stepwise multivariate Cox proportional hazard regression model was developed to estimate the potential prognostic factors based on the LASSO regression results. Based on the results of the multivariable analysis, five significant variables (P<0.01) were selected and incorporated into the nomogram to provide visualized risk prediction; the nomogram adopted 3- and 5-year OS as the endpoints.

The accuracy of the nomogram for predicting visualized risk and survival outcomes was assessed using the Harrell's concordance index (C-index) as an evaluation index (23). To establish the concordance between the predicted and observed 3- and 5-year OS outcomes and to evaluate the nomogram's predictive accuracy in a well-calibrated model, we developed calibration curves for both the training and validation cohorts using 1,000 bootstrap re-samples.

A decision curve analysis (DCA), which has specific advantages in evaluating the clinical value and utility of nomograms, was used to test the model's reliability (24). We also calculated the area under the curve (AUC) of the time-dependent receiver operating characteristic (ROC) curve to evaluate the discrimination ability and calibration ability of the new nomogram and the 7th edition of the AJCC TNM staging system in the two cohorts. Finally, the net classification improvement (NRI) and integrated discrimination improvement (IDI) indexes were used to compare the clinical utility and net clinical benefits between the two new models and the 7th edition of the AJCC TNM staging system.

The survival curves for several categories of individual predictors were compared using the Kaplan-Meier (K-M) method, and the significance of these differences was assessed using the log-rank test. With the help of the "survivalROC" R package, a K-M curve for OS was also established. This package generated time-dependent ROC curves for the nomogram and all the independent prognostic variables at 3 and 5 years, and it then applied the corresponding time-dependent AUCs to demonstrate the discrimination ability of the model. All the LCNEC patients were split into high- and low-risk groups based on an appropriate cut-off value that was calculated based on the ROC analysis. Using the K-M analysis, survival curves for the low- and high-risk groups were plotted, and the log-rank test was used to demonstrate the difference in OS status between the two groups. A P value <0.05 was considered statistically significant.

The statistical analysis was conducted with SPSS 24.0 (IBM, Chicago, IL, USA), R software (version 3.6.3; http://www.Rproject.org), and MedCalc19.2.0. The categorical variables were classified based on the clinical findings. SPSS 24.0 was used to compare the clinicopathological characteristics between the two cohorts. "Glmnet" package was used to perform the LASSO Cox regression. The "foreign" package, "survival" package, and "rms" package were used to plot the nomograms and calibration plots and calculate the C-index. The "nricens" package for used to calculate the NRI index. "Stdca.R" was downloaded from Memorial Sloan Kettering Cancer Center (www.mskcc.org) and was used to conduct the DCA. The "IDI.INF" package was used to calculate the IDI index. The "time ROC" package was used to calculate the time-dependent ROC curves. The "survivalROC" package was used to generate the K-M curves for OS.

Results

Clinical characteristics of the participants

Based on the screening criteria, the data of 3,494 patients were initially collected from the SEER database. The data of 1,630 patients were then excluded. Ultimately, the final sample comprised 1,864 patients. The cohort was then divided into the following two groups at a 7:3 ratio: the training group (comprising 1,308 patients) and the validation group (comprising 556 cases). The clinicopathological and demographic characteristics of the patients are presented in *Table 1*. Among the patients, 868 were female and 996 were male, and 83.9% of the population was White, 11.9% was Black, and 4.2% were other. The upper lobe was the most common primary site, accounting for 55.0% of cases. The most common distant metastasis organ was the brain, accounting for 17.1% of cases, followed by bone (15.7%), liver (15.2%), and lung (10.0%). Additionally, 35.6%, 35.6%, and 56.6% of the patients received surgery, radiation, and chemotherapy, respectively. Finally, the results of the Chi-square test showed that except for radiation, there were no statistical differences between the two cohorts in terms of the clinicopathological characteristics (P<0.05).

Nomogram construction

We used LASSO regression and multivariate Cox regression analyses to select the optimal variables for the predictive model construction. The LASSO regression was applied to analyze the correlation between the 18 variables and OS; "lambda.1se" was used to select the variables; the value of log (λ) was –2.506296. All the eight variables with non-zero coefficients (i.e., age, tumor stage, N stage, M stage, bone metastasis, liver metastasis, surgery, and chemotherapy) were selected for the multivariate analysis (*Figure 2*). After the multivariate Cox analysis of the eight variable factors, five clinical variable factors were found to be associated with OS (P≤0.05). The results of the multivariate Cox analysis are summarized in *Table 2*. Finally, based on the results, age [≥60 years, hazard ratio (HR) =1.21, 95% confidence interval (CI): 1.06–1.38], bone metastasis (yes, HR =1.20, 95% CI: 1.01–1.43), liver metastasis (yes, HR =1.70, 95% CI: 1.43–2.03), surgery (yes, HR =0.56, 95% CI: 0.46–0.69), and chemotherapy (yes, HR =0.49, 95% CI: 0.42–0.56) were identified as independent risk factors for OS. We used these five independent prognostic factors for OS to construct 3- and 5-year OS nomograms (*Figure 3*), and

each subgroup within these variables was allocated a score (*Table 3*).

Validation of nomogram

The C-indexes of the nomogram were 0.716 (95% CI: 0.687–0.745) and 0.708 (95% CI: 0.661–0.755) in the training cohort and validation cohort, respectively. While the C-indexes of the 7th edition of the AJCC TNM staging system were 0.685 (95% CI: 0.668–0.722) and 0.705 (95% CI: 0.660–0.750) in the training and validation cohorts, respectively. These results indicated that the new model had a great ability to predict for LCNEC.

We also generated calibration curves to assess the calibration ability of the nomogram in the two cohorts. Calibration plots of the nomogram's prediction accuracy are shown in *Figure 4*. There was good agreement between actual and predicted 3- and 5-year OS. Thus, we performed a DCA to compare the clinical usability and benefits between the nomogram and the 7th edition of the AJCC TNM staging system. We found that the nomogram could better predict 3-year OS and had more clinical net benefits than the 7th edition of the AJCC TNM staging system for a specific range of threshold probabilities in both the training and validation cohorts (*Figure 5A,5B*). Similar result was also observed for the 5-year OS prediction (*Figure 5C,5D*). Finally, the NRI and IDI indexes were also calculated to evaluate the accuracy of the nomogram for predicting OS compared with the 7th edition of the AJCC TNM staging system. In the training cohort, the NRI values were 0.296 (95% CI: –0.142–0.349) and 0.161 (95% CI: 0.032–0.252), and the IDI values were 0.054 (95% CI: 0.030–0.082, P<0.01) and 0.055 (95% CI: 0.031–0.089, P<0.01) for 3- and 5-year OS, respectively. In the validation cohort, the NRI values were 0.289 (95% CI: –0.177–0.409) and –0.009 (95% CI: –0.144–0.209), and the IDI values were 0.053 (95% CI: 0.006–0.119, P=0.030) and 0.041 (95% CI: –0.004–0.094, P=0.090) for 3- and 5-year OS, respectively.

We applied the time-dependent ROC curves to compare the sensitivity and specificity of our new nomogram and the 7th edition of the AJCC TNM staging system at 3 and 5 years. We calculated the AUCs for the new nomogram and the 7th edition of the AJCC TNM staging system. In the training cohort, the AUCs for predicting 3-year OS were 0.811 and 0.820, and the AUCs for predicting 5-year OS were 0.821 and 0.828 for the nomogram and the 7th edition of the AJCC TNM staging system, respectively. While in the validation cohort, the AUCs for predicting

**Table 1** Baseline clinical characteristics of LCNEC patients

Characteristics	All patients (n=1,864)	Training set (n=1,308)	Validation set (n=556)	P value
Age, years				0.389
0–59	544 (29.2)	374 (28.6)	170 (30.6)	
≥60	1,320 (70.8)	934 (71.4)	386 (69.4)	
Gender				0.168
Male	996 (53.4)	713 (54.5)	283 (50.9)	
Female	868 (46.6)	595 (45.5)	273 (49.1)	
Race				0.471
White	1,563 (83.9)	1,090 (83.3)	473 (85.1)	
Black	222 (11.9)	158 (12.1)	64 (11.5)	
Other	79 (4.2)	60 (4.6)	19 (3.4)	
Marital status				0.106
Married	964 (51.7)	694 (53.1)	270 (48.6)	
Single	281 (15.1)	199 (15.2)	82 (14.7)	
Widowed/divorced	497 (26.7)	339 (25.9)	158 (28.4)	
Other/unknown	122 (6.5)	76 (5.8)	46 (8.3)	
Primary site				0.623
Main bronchus	75 (4.0)	48 (3.7)	27 (4.9)	
Upper lobe	1,025 (55.0)	732 (56.0)	293 (52.7)	
Middle lobe	75 (4.0)	54 (4.1)	21 (3.8)	
Lower lobe	450 (24.1)	310 (23.7)	140 (25.2)	
Overlapping lesion of lung	21 (1.1)	16 (1.2)	5 (0.9)	
Lung, NOS	218 (11.7)	148 (11.3)	70 (12.6)	
Laterality				0.345
Right	1,046 (56.1)	736 (56.3)	310 (55.8)	
Left	734 (39.4)	519 (39.7)	215 (38.7)	
Other	84 (4.5)	53 (4.1)	31 (5.6)	
Tumor size (mm)				0.057
0–19	344 (18.5)	223 (17.0)	121 (21.8)	
20–39	562 (30.2)	411 (31.4)	151 (27.2)	
40–79	520 (27.9)	361 (27.6)	159 (28.6)	
≥80	438 (23.5)	313 (23.9)	125 (22.5)	
AJCC 7th edition				0.204
Occult	6 (0.3)	4 (0.3)	2 (0.4)	
I	407 (21.8)	281 (21.5)	126 (22.7)	
II	190 (10.2)	135 (10.3)	55 (9.9)	
III	364 (19.5)	239 (18.3)	125 (22.5)	
IV	897 (48.1)	649 (49.6)	248 (44.6)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	All patients (n=1,864)	Training set (n=1,308)	Validation set (n=556)	P value
T stage				0.347
TX	155 (8.3)	105 (8.0)	50 (9.0)	
T0	16 (0.9)	11 (0.8)	5 (0.9)	
T1	454 (24.4)	305 (23.3)	149 (26.8)	
T2	521 (28.0)	375 (28.7)	146 (26.3)	
T3	364 (19.5)	251 (19.2)	113 (20.3)	
T4	354 (19.0)	261 (20.0)	93 (16.7)	
N stage				0.643
NX	49 (2.6)	30 (2.3)	19 (3.4)	
N0	768 (41.2)	536 (41.0)	232 (41.7)	
N1	175 (9.4)	121 (9.3)	54 (9.7)	
N2	621 (33.3)	441 (33.7)	180 (32.4)	
N3	251 (13.5)	180 (13.8)	71 (12.8)	
M stage				0.053
M0	967 (51.9)	659 (50.4)	308 (55.4)	
M1	897 (48.1)	649 (49.6)	248 (44.6)	
Bone metastasis				0.478
No/unknown	1,572 (84.3)	1,098 (83.9)	474 (85.3)	
Yes	292 (15.7)	210 (16.1)	82 (14.7)	
Brain metastasis				0.185
No/unknown	1,546 (82.9)	1,075 (82.2)	471 (84.7)	
Yes	318 (17.1)	233 (17.8)	85 (15.3)	
Liver metastasis				0.080
No/unknown	1,581 (84.8)	1,097 (83.9)	484 (87.1)	
Yes	283 (15.2)	211 (16.1)	72 (12.9)	
Lung metastasis				0.524
No/unknown	1,677 (90.0)	1,173 (89.7)	504 (90.6)	
Yes	187 (10.0)	135 (10.3)	52 (9.4)	
Surgery of primary site				0.602
No/unknown	1,200 (64.4)	847 (64.8)	353 (63.5)	
Yes	664 (35.6)	461 (35.2)	203 (36.5)	
Radiation				0.001
No/unknown	1,200 (64.4)	719 (55.0)	353 (63.5)	
Yes	664 (35.6)	589 (45.0)	203 (36.5)	
Chemotherapy				0.561
No/unknown	809 (43.4)	562 (43.0)	247 (44.4)	
Yes	1,055 (56.6)	746 (57.0)	309 (55.6)	

Data are presented as n (%). LCLEC, large-cell neuroendocrine carcinoma; NOS, not otherwise specified; AJCC, American Joint Committee on Cancer.
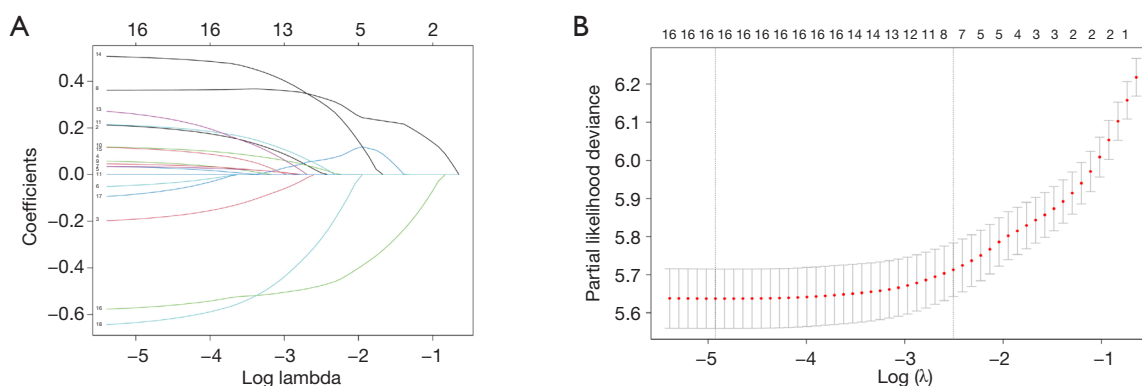
Figure 2 Prognostic indicator selection using the LASSO model analysis. Feature selection using the "1se" shrinkage and selection operator LASSO Cox regression. (A) Profiles of LASSO coefficients for clinical and pathological features. (B) Selection of tuning parameters (lambda) in the LASSO regression using 10-fold cross-validation. LASSO, least absolute shrinkage and selection operator.

3-year OS were 0.791 and 0.822, and the AUCs for 5-year OS were 0.806 and 0.792 for the nomogram and the 7th edition of the AJCC TNM staging system, respectively (*Figure 6*).

K-M curves of significant features

In our study, all five potential predictors of survival were found to be useful in predicting OS in the training cohort (*Figure 7A-7E*). Patients aged over 60 years had a shorter OS than those aged 0–59 years. Patients without bone and liver metastases had better OS than those with bone and liver metastases. Patients who received surgery had a better OS than those who did not receive surgery.Patients who received chemotherapy had a shorter OS than those who did not receive chemotherapy, but there is no statistically significant difference (P=0.12). In addition, the K-M curves showed that pulmonary LCNEC patients with an advanced tumor stage as per the 7th edition of the AJCC TNM staging system had worse OS than those with an earlier stage. According to the K-M curves used in our study for the 7th edition of the AJCC TNM staging system, patients with stage III and IV tumors had a noticeably worse prognosis than those with stage I and II tumors (*Figure 7F*).

We used time-dependent ROC curves to assess the discrimination ability of the nomogram in the two cohorts. We calculated the AUCs of the new nomogram in predicting 3-year OS (0.811 *vs.* 0.791) and 5-year OS (0.821 *vs.* 0.806) for the training cohort (*Figure 8A*) and the validation cohort (*Figure 8B*). Further, the patients were divided into low- and high-risk groups based on the cut-off values of the time-dependent ROC curve at a survival

time of 5 years in the training cohort (AUC =0.811, cut-off =0.668) and validation cohort (AUC =0.821, cut-off =0.626). Survival curves for the low- and high-risk groups were plotted using a K-M analysis. Patients in the high-risk groups had significantly lower chances of surviving than those in the low-risk groups (*Figure 8C,8D*), which suggests that the developed nomogram can successfully identify high-risk patients.

Discussion

This was the first time that we used the LASSO Cox regression method for variable selection and shrinkage in Cox proportional hazards models. The simulations showed that the LASSO selection was more accurate than the stepwise selection, as it compressed coefficients and produced some coefficients that were precisely zero. By experimentally expanding the LASSO penalty, it generated an understandable final model and decreased the false discovery rate in the univariate and multivariate Cox regression (13,25). After using the LASSO regression to examine the relationship between OS and the 18 other variables, eight variables with non-zero coefficients were chosen for the multivariate analysis. The nomogram included five parameters linked with OS that were found to be independent predictive factors of pulmonary LCNEC in the multivariate Cox analysis. Finally, we created 3- and 5-year OS nomograms using these five independent prognostic markers for OS.

In the training cohort, the nomogram model demonstrated strong discriminative accuracy (C-index =0.716), which was verified in the validation cohort (C-index

Table 2 Multivariate analyses of variables for OS in the training cohort

Characteristic	HR	95% CI	P value
Age, years			
0–59	Reference		
≥60	1.21	1.06–1.38	0.01
AJCC 7th edition			
Occult	Reference		
I	0.69	0.22–2.18	0.53
II	1.33	0.42–4.27	0.63
III	1.61	0.51–5.10	0.42
IV	2.64	0.47–1.03	0.10
N stage			
NX	Reference		
N0	0.69	0.7–1.03	0.07
N1	0.84	0.55–1.29	0.43
N2	0.92	0.63–1.35	0.67
N3	1.19	0.80–1.75	0.39
M stage			
M0	Reference		
M1	NA	NA	NA
Bone metastasis			
No/unknown	Reference		
Yes	1.20	1.01–1.43	0.04
Liver metastasis			
No/unknown	Reference		
Yes	1.70	1.43–2.03	<0.01
Surgery			
No/unknown	Reference		
Yes	0.56	0.46–0.69	<0.01
Chemotherapy			
No/unknown	Reference		
Yes	0.49	0.42–0.56	<0.01

OS, overall survival; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; NA, not applicable.

=0.708). However, the C-indexes for the 7th edition AJCC TNM staging system in the training set and validation set were 0.685 and 0.705, respectively. These results demonstrated the excellent ability of the proposed model to predict pulmonary LCNEC. Further, the calibration plots showed that this nomogram performed exceptionally well in calculating the prognosis of pulmonary LCNEC patients, with good agreement for the prediction of OS at 3 and 5 years in both cohorts. The DCA results showed that the nomogram also performed well compared to the 7th edition
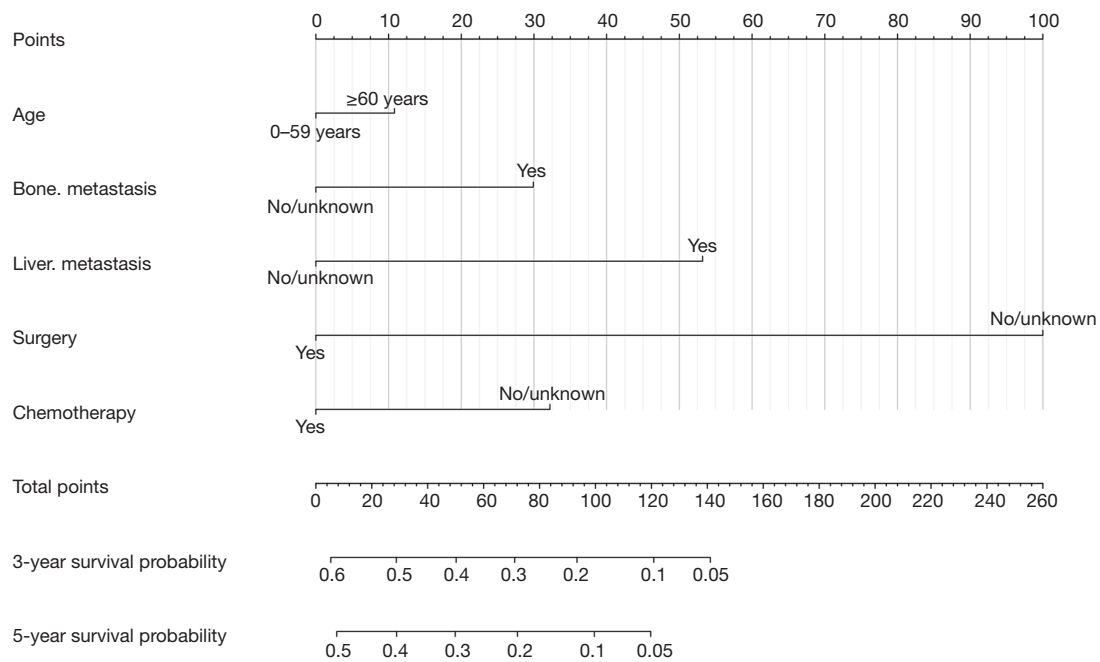
Figure 3 Nomogram for predicting 3- and 5-year overall survival in pulmonary LCNEC patients. LCNEC, large-cell neuroendocrine carcinoma.

**Table 3** Score of every subgroup for each variable

Characteristics	Points
Age, years	
0–59	0
≥60	11
Bone metastasis	
No/unknown	0
Yes	30
Liver metastasis	
No/unknown	0
Yes	53
Surgery	
No/unknown	100
Yes	0
Chemotherapy	
No/unknown	32
Yes	0

of the AJCC TNM staging system, and thus the nomogram might improve the precision of customized clinical decisions. Our findings clarified the features of pulmonary LCNEC and were consistent with another SEER database-based LCNEC study (19).

Our study demonstrated that an absence of bone and liver metastases was associated with longer OS in patients with pulmonary LCNEC. Zhao *et al.* conducted a study to examine the survival outcomes, prevalence of brain metastasis, and recurrence patterns of LCNEC patients, and found that disease relapse occurred in 73% of patients who had received curative treatment, most frequently in the local lymph nodes, brain, bones, and liver. The incidence of brain metastasis in LCNEC was higher than that observed in other types of NSCLCs (26,27). Fisch *et al.* retrospectively examined 191 patients with metastatic pulmonary LCNEC in the data from German, and the type of systemic treatment was the single factor most significantly associated with patients' outcomes. Fisch *et al.* reported that patients who received immune checkpoint inhibitors (ICIs) (n=13) had a median OS of 26.4 months, while those who received first-line platinum doublets

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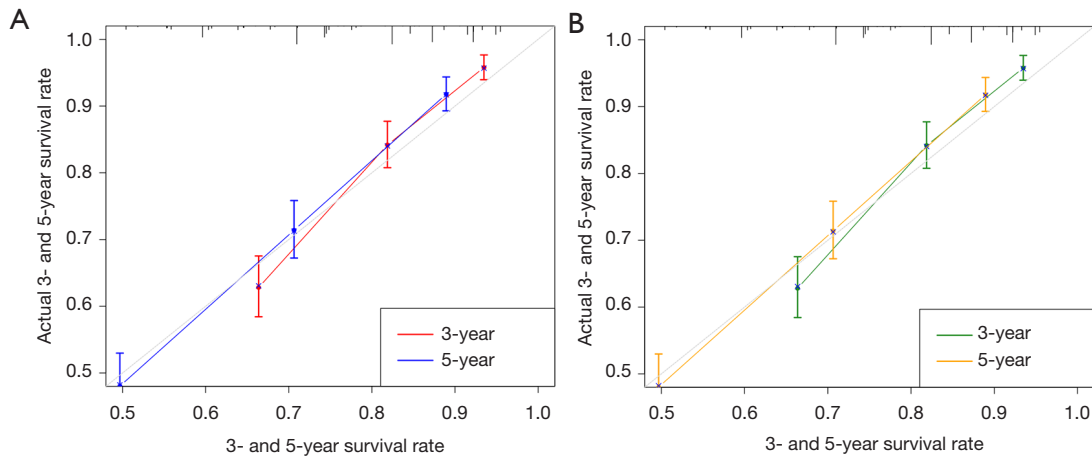
Figure 4 Calibration plots of 3- and 5-year overall survival for the training cohort (A) and validation cohort (B). Observed and estimated survival outcomes are plotted on the y-axis and x-axis, respectively.
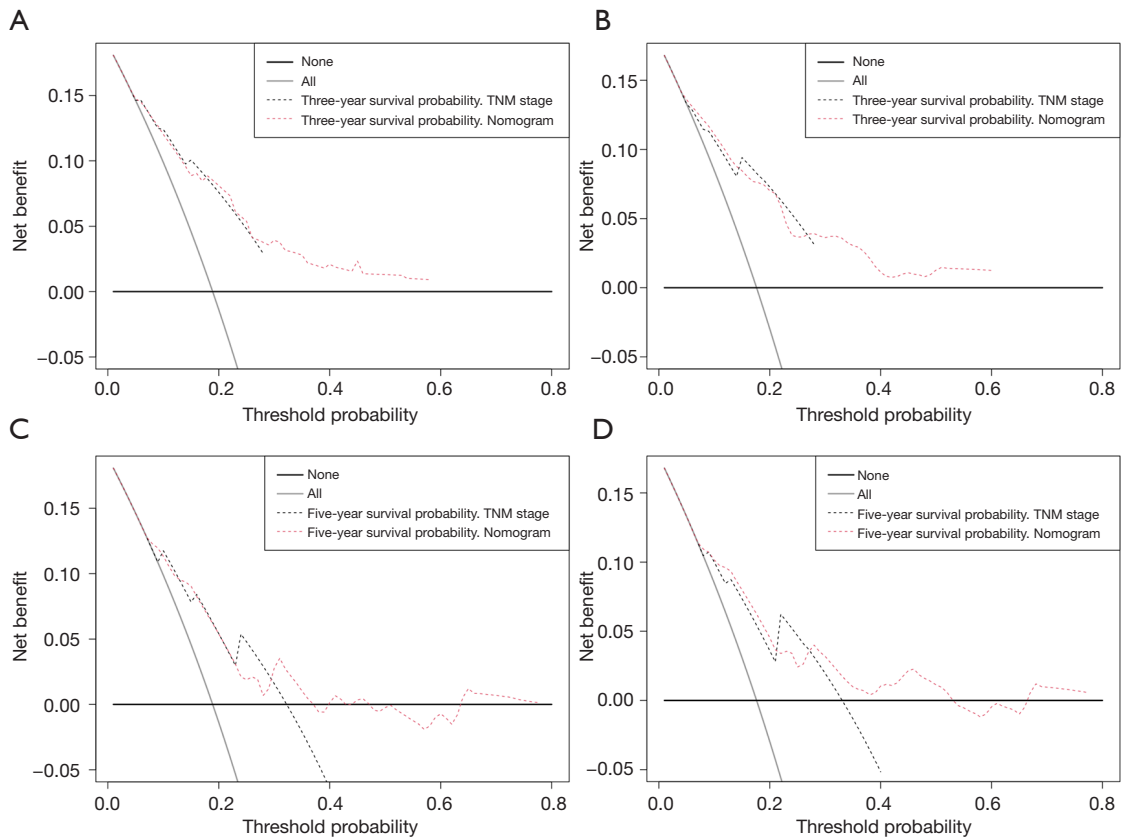
Figure 5 Comparison of the decision curve analysis results for the nomogram and the 7th edition of the AJCC TNM staging system for the 3- and 5-year OS in the training cohort (A,C) and the validation cohort (B,D). Black line: all patients dead. Gray line: no patients dead. Black-dashed line: model of nomogram 1. Red-dashed line: model of the 7th edition of the AJCC TNM staging system. OS, overall survival; AJCC TNM, American Joint Committee on Cancer tumor, node, and metastasis.
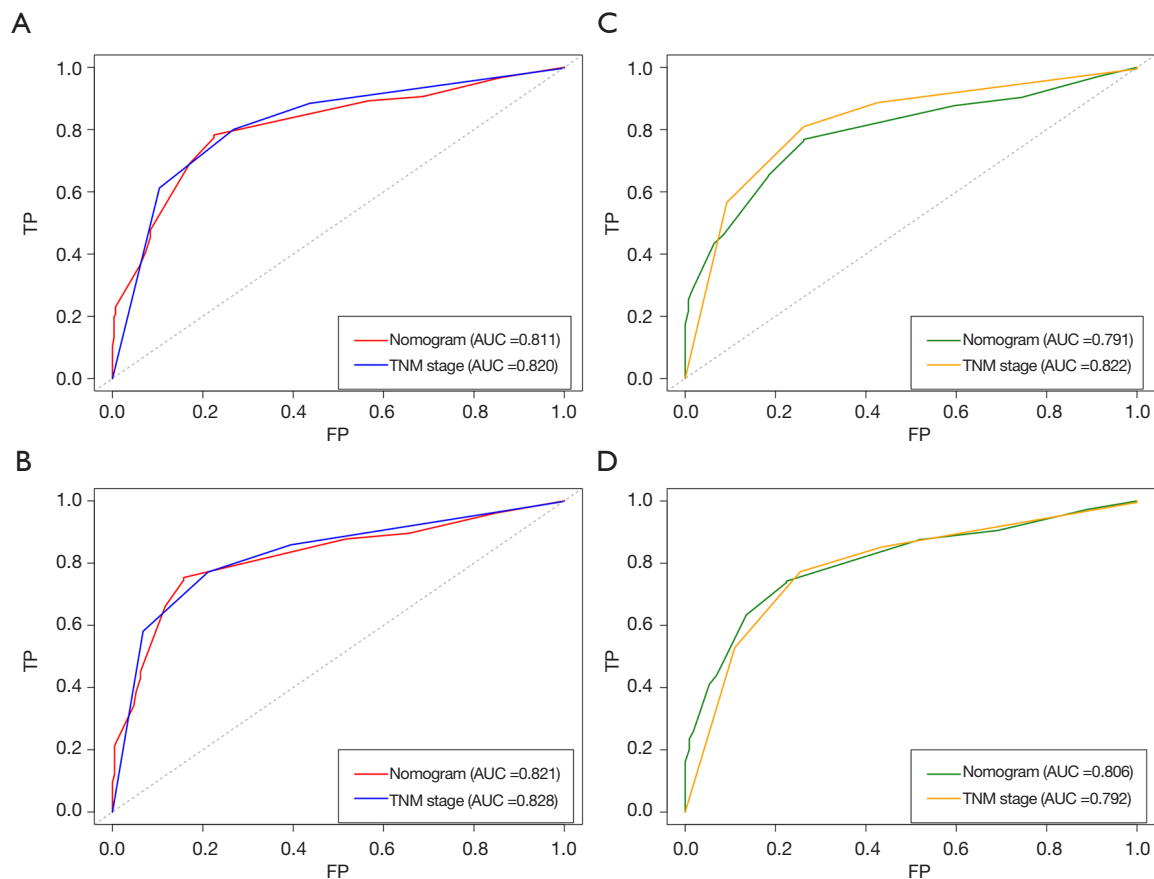
Figure 6 Comparison of the area under the receiver operating characteristic curves between the nomogram and the 7th edition of the AJCC TNM staging system for the 3-year (A,C), and 5-year (B,D) survival in the training cohort and validation cohort. FP, false positive; TP, true positive; AUC, area under the curve; AJCC TNM, American Joint Committee on Cancer tumor, node, and metastasis.

(n=129) had a median OS of 9.0 months, and those who received non-platinum chemotherapies had a median OS of 4.0 months (n=17, P=0.01) (28). We observed that the brain was the most common distant metastasis organ (17.1% of the patients had distant brain metastasis). Stereotactic radiosurgery may be an option for LCNEC patients who are receiving upfront treatment for localized brain metastasis, according to several studies. A multivariate Cox regression analysis revealed that bone metastasis and liver metastasis were independent prognostic factors in a training group, and the 3-year survival rates in the bone metastasis and liver metastasis groups were 2.86% (95% CI: 1.30–6.29%) and 0.474% (95% CI: 0.067–3.35%), respectively (29,30). Thus, there is an urgent need for additional safe and effective therapy choices.

Radiotherapy had no discernible effect on patient prognosis; however, our investigation verified the prognostic

usefulness of surgery and chemotherapy for OS in patients with pulmonary LCNEC. Surgery has been linked to an increase in OS. A previous study found that patients with pulmonary LCNEC had a median OS of 66.0 months and a 5-year OS rate of 52.5% (31). In our analysis, the 3- and 5-year OS rates for surgical patients were 50.35% (95% CI: 45.97–55.14%) and 39.57% (95% CI: 35.29–44.36%), respectively. All patients with early stage (I–III) pulmonary LCNEC should be treated with surgery as a first option (32). Further, retrospective studies indicate that surgical resection of pulmonary LCNEC at pathologic stages I and II, most frequently lobectomy and pneumonectomy, was linked to a 5-year OS of 49.2% (33,34). However, a different study reported that sublobar lung resection was linked to a lower survival rate for individuals with early (stage I) pulmonary LCNEC (35).

In addition, certain studies have found evidence of

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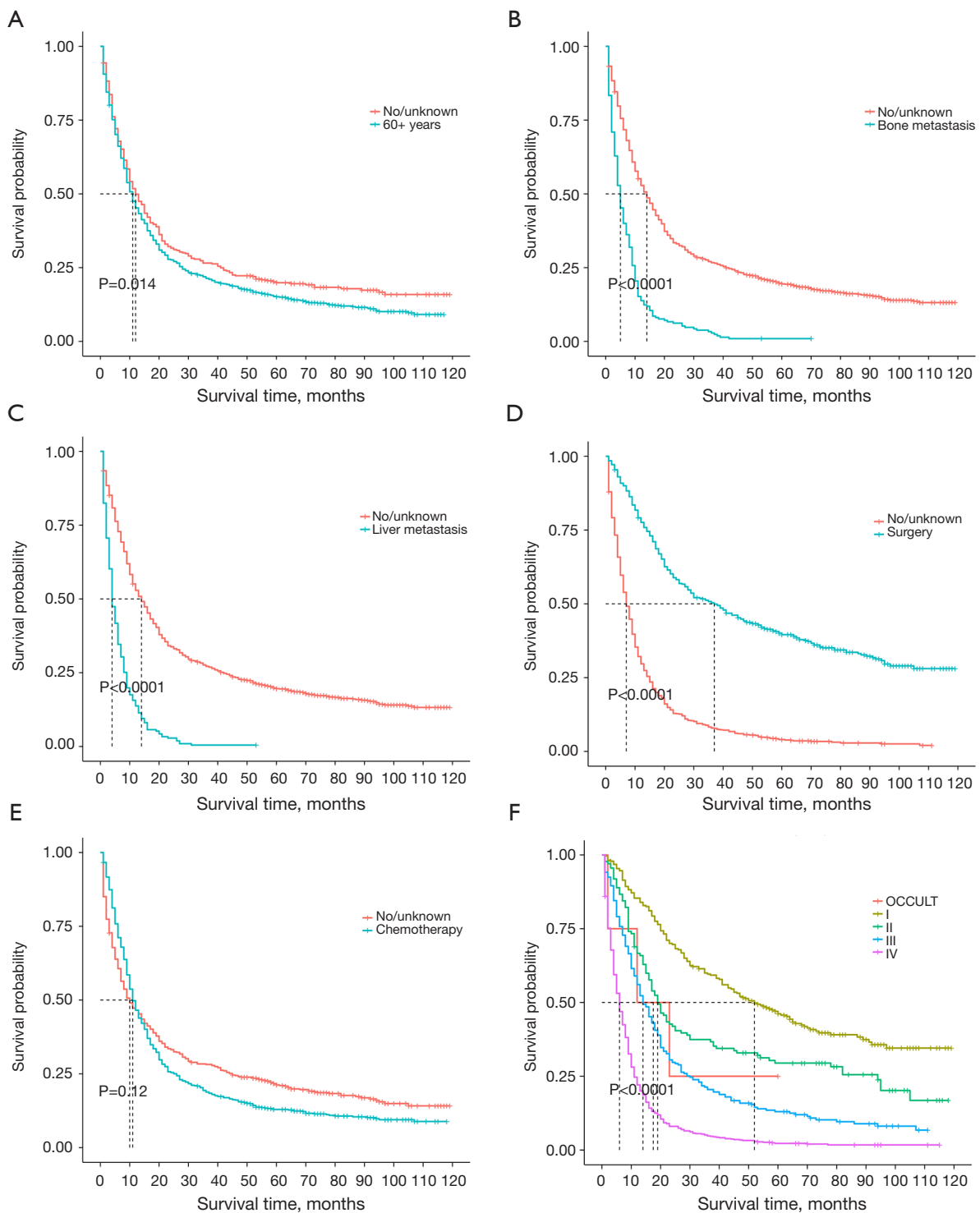
Figure 7 Overall survival of pulmonary LCNEC patients stratified by (A) age; (B) bone metastasis; (C) liver metastasis; (D) surgery; (E) chemotherapy; (F) AJCC tumor stage. LCNEC, large-cell neuroendocrine carcinoma; AJCC, American Joint Committee on Cancer.
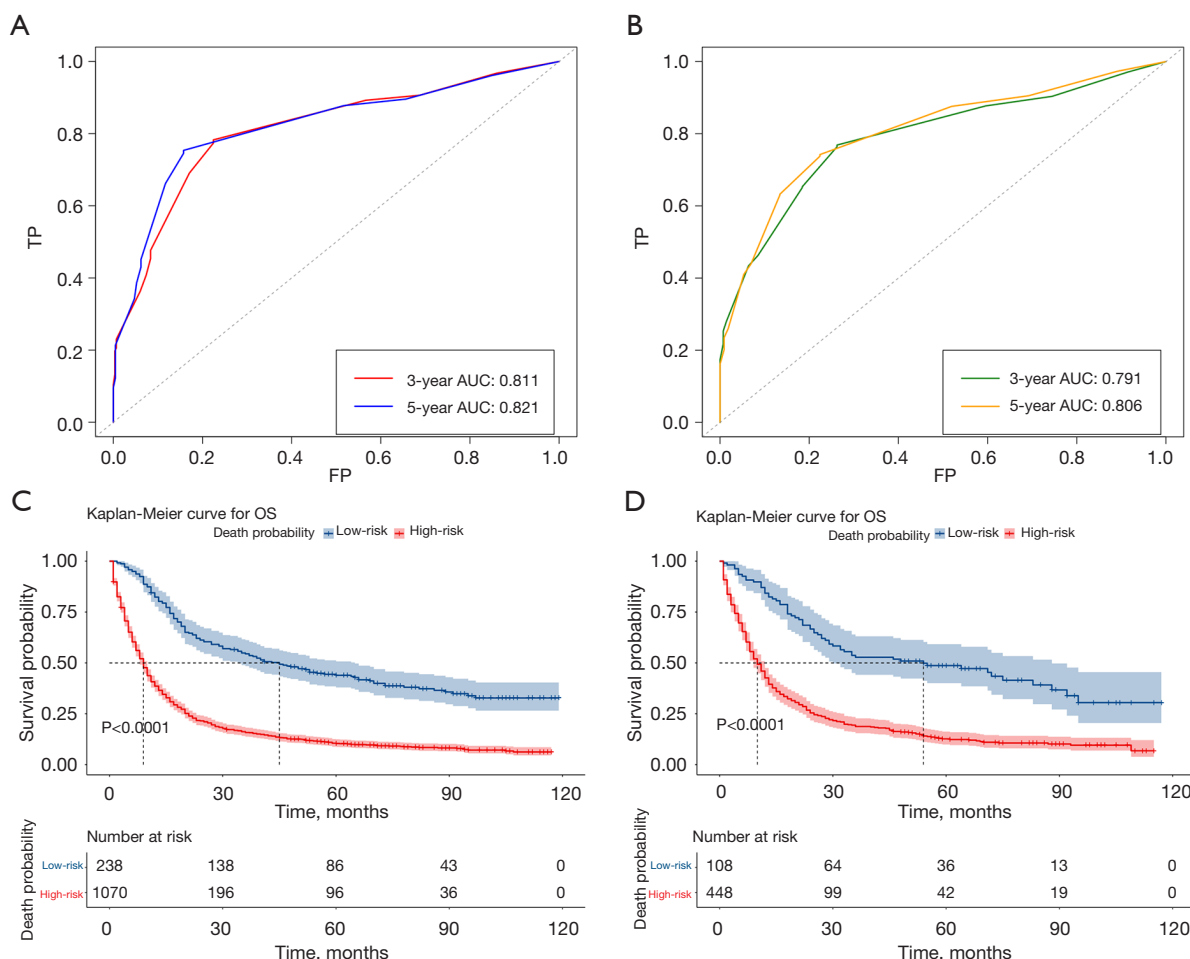
Figure 8 The ROC curve analysis and Kaplan-Meier plots for the two cohorts. Time-dependent ROC curve analysis of the nomogram for 3- and 5-year OS in the training cohort (A) and the validation cohort (B). Kaplan-Meier plots comparing OS between patients in the low- and high-risk groups in the training cohort (C) and validation cohort (D). The 3- and 5-year OS rates for the high-risk group (red curve) were significantly lower than those for the low-risk group (blue curve). FP, false positive; TP, true positive; AUC, area under the curve; OS, overall survival; ROC, receiver operating characteristic.

the value of adjuvant treatment for pulmonary LCNEC, particularly at pathologic stage II or higher (36,37). Upfront surgery is suggested in the early stages (I to IIB), and adjuvant chemotherapy should also be administered in accordance with the small-cell lung cancer (SCLC) protocol, according to current treatment recommendations. Results of pertinent prospective clinical studies evaluating adjuvant therapy for pulmonary LCNEC have also been published (38,39). However, adjuvant therapy following surgery has been shown to be essential to prevent tumor recurrence, and in locally advanced stages (III–IV), a multimodality approach was suggested (40-42). According to research by Jiang *et al.*, lobectomy might considerably

increase OS and lung cancer-specific survival for patients with stage I to II pulmonary LCNEC, while radiation could dramatically increase the survival time of patients with stage III LCNEC.

Conversely, radiation might shorten the period that patients with LCNEC survive surgery (43). Zhang *et al.* performed a multicenter retrospective study and showed that the median disease-free survival time of the SCLC-regimen group was not significantly longer than that of the NSCLC-regimen group in the adjuvant cohort. The median progression-free survival (PFS) time of the SCLC-regimen group in the first-line cohort was 11.5 months, which was longer than the PFS time of the NSCLC-regimen

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group. Thus, the SCLC treatment was found to be a more effective choice as either a first-line treatment or adjuvant chemotherapy for LCNEC patients (44). According to Cao *et al.*, radiotherapy may increase the lifespan of patients with pulmonary LCNEC, particularly those who did not have surgery or chemotherapy (45). Conversely, another study found that postoperative chemotherapy, radiation, or combination therapy had no effect on the survival of patients with pulmonary LCNEC who had had surgery (46). Interestingly, our results showed that radiotherapy and chemotherapy had a significant detrimental effect on OS, as the patients receiving radiotherapy and chemotherapy had shorter OS than those receiving neither treatment. Possible explanations for this contentious outcome include the fact that these two trials did not provide many details on the treatment regimens.

Numerous studies have demonstrated that platinum-based and SCLC-based chemotherapy results in longer OS for patients with pulmonary LCNEC (47,48). Recent research suggests that pulmonary LCNEC patients were significantly less chemo-responsive to this regimen; however, prospective studies using platinum-based etoposide in patients with extensive-stage SCLC have reported response rates of around 50% and up to 80% (49,50). However, the clinical course and treatment of patients with advanced LCNEC are limited (51). These studies revealed that for advanced-stage LCNEC patients who received a combination of cisplatin-etoposide or cisplatin-irinotecan, the median OS was 7.7 (95% CI: 6–9.6) *vs.* 15.1 (95% CI: 11.2–19) months (52,53). Additionally, four to six cycles of chemotherapy that included etoposide in addition to cisplatin or carboplatin were typically shown to improve the prognosis of the advanced-stage patients (48,54). Certain studies also noted that patients with unresectable pulmonary LCNEC (including stage I and II) who received treatment with a variety of modalities had higher OS results than those who received chemotherapy alone (10,55). Thus, we must create novel treatments for patients with pulmonary LCNEC.

With the development of new techniques, tyrosine kinase inhibitors (TKIs) and other targeted medications may improve the quality of life and survival of patients with advanced or relapsed high-grade neuroendocrine carcinoma. However, only a few studies have described cases of LCNEC with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations (56-59). Currently, the clinical value of TKI in pulmonary LCNEC is relatively restricted; thus, it is crucial to identify other treatment targets (60,61). An

inescapable question in the current treatment is whether LCNEC could be vulnerable to treatment with ICIs. According to certain published case reports and research, individuals with pulmonary LCNEC appear to live longer after receiving ICIs (62-65). Naganuma *et al.* performed a retrospective study and showed that the overall response rate, median PFS, and median OS of previously treated advanced LCNEC patients who then received anti-programed death-blockade monotherapy were 9.1%, 2.7 months, and 4.6 months, respectively, and observed adverse events in 9 patients (82%) (66). Levra *et al.* showed that pulmonary LCNEC patients with stages IIIB to IV could gain a survival benefit from nivolumab or pembrolizumab after platinum-based first-line therapy (63). However, there were no data on immunotherapy in the SEER database, and as there is no prospective evidence, we cannot yet determine if immunotherapy is effective in treating pulmonary LCNEC. Future clinical trials should include numerous sizable multicenter studies to confirm the findings. It may be that this divergence in findings was caused by the limited sample sizes and the potential for follow-up bias.

Conclusions

In conclusion, our results demonstrated that this newly designed nomogram has remarkable power in predicting the likelihood of survival of patients with LCNEC compared to the 7th edition of the AJCC TNM staging system. The key feature of the study is that we were able to decrease the selection and surveillance biases related to specific institutions by employing one of the largest population-based cohorts of patients with pulmonary LCNEC across 17 United States registries. However, some of the significant limitations of this study must be acknowledged. First, due to the small sample size and potential for follow-up bias, every retrospective study inevitably contains bias. Second, specific details about chemotherapy, surgery, radiotherapy, or other therapies were not provided, nor were the reasons as to why patients preferred some therapy methods over others. Finally, the SEER database lacked data on tumor recurrence trends and post-recurrence treatment histories. Thus, real-world data needs to be gathered to externally verify our results in the future.

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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-23-1061/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1061/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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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