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Construction and validation of a nomogram based on the log odds of positive lymph nodes to predict cancer-specific survival in patients with small cell lung cancer after surgery

Ce Chao [1], Kun Mei [1], Min Wang, Renzhe Tang, Yongxiang Qian, Bin Wang [*], Dongmei Di [**]

Department of Cardiothoracic Surgery, The Third Affiliated Hospital of Soochow University, Changzhou, 213003, China

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ABSTRACT

Background: The lymph node ratio (LNR) is useful for predicting survival in patients with small cell lung cancer (SCLC). The present study compared the effectiveness of the N stage, number of positive LNs (NPLNs), LNR, and log odds of positive LNs (LODDS) to predict cancer-specific survival (CSS) in patients with SCLC.

Materials and methods: 674 patients were screened using the Surveillance Epidemiology and End Results database. The Kaplan-Meier survival and receiver operating characteristic (ROC) curves were performed to address optimal estimation of the N stage, NPLNs, LNR, and LODDS to predict CSS. The optimal LN status group was incorporated into a nomogram to estimate CSS in SCLC patients. The ROC curve, decision curve analysis, and calibration plots were utilized to test the discriminatory ability and accuracy of this nomogram.

Results: The LODDS model showed the highest accuracy compared to the N stage, NPLNs, and LNR in predicting CSS for SCLC patients. LODDS, age, sex, tumor size, and radiotherapy status were included in the nomogram. The results of calibration plots provided evidences of nice consistency. The ROC and DCA plots suggested a better discriminatory ability and clinical applicability of this nomogram than the 8th TNM and SEER staging systems.

Conclusions: LODDS demonstrated a better predictive power than other LN schemes in SCLC patients after surgery. A novel LODDS-incorporating nomogram was built to predict CSS in SCLC patients after surgery, proving to be more precise than the 8th TNM and SEER staging.

1. Introduction

Lung cancer is a common malignant cancer and accounts for a large proportion of cancer-related mortality worldwide [1]. Small cell lung cancer (SCLC) accounts for 14% of lung cancer cases [2]. In the classification of lung cancer, SCLC is a neuroendocrine lung

* Corresponding author. Department of Cardiothoracic Surgery, The Third Affiliated Hospital of Soochow University, No.185, Juqian Street, Tianning District, Changzhou, 213003, Jiangsu Province, China.

** Corresponding author. Department of Cardiothoracic Surgery, The Third Affiliated Hospital of Soochow University, No.185, Juqian Street, Tianning District, Changzhou, 213003, Jiangsu Province, China.

E-mail addresses: colin_iverson@163.com (B. Wang), ddm5122@163.com (D. Di).

[1] These authors have contributed equally to this work.

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tumor with a poor prognosis [3]. Comprehensive treatment of SCLC includes surgery, radiotherapy, and chemotherapy. The patients with SCLC are sensitive to chemoradiotherapy in the early treatment of SCLC [4]. Systemic platinum-based chemotherapy either combined with concurrent radiotherapy or alone may be a potentially curative treatment for SCLC [4]. However, treatment resistance and relapse are the ultimate causes of death. Surgery is the main method of cancer treatment, although a previous trial has demonstrated that radiotherapy resulted in a better prognosis than surgery for SCLC patients before the 1970s [5]. In-depth research has allowed patients with stage I–II and even stage III N2 SCLC to be regarded as a surgical evaluation population [6–9]. Multiple studies have shown that the management of surgery can prolong the survival time of early-stage SCLC patients compared to those treated with concurrent chemoradiation [10,11].

At present, the Veterans Administration Lung Study Group (VALSG) two-stage classification scheme is widely used to define the degree of the disease in SCLC patients [12]. However, the tumor–node–metastasis (TNM) system has been recommended to replace the VALSG staging system [13]. The lymph node (LN) status plays a vital role in surgery and prognosis assessment [14]. Recently, more and more evidences have demonstrated that the log odds of positive LNs (LODDS), defined as the logarithmic odds of the number of positive and negative LNs, can predict the prognosis better than other LN schemes for multiple malignancies, including medullary thyroid carcinoma [15], lung squamous cell carcinoma [16], oral squamous cell carcinoma [17], esophageal squamous cell carcinoma [18], and pancreatic cancer [19]. However, LODDS was not the same result in prognosis of gallbladder carcinoma [20]. Published research studies have shown that the LN ratio (LNR) has a potential ability to predict prognosis in SCLC patients [21,22]. To date, there have been no data screening the most appropriate alternative LN scheme in cases with resectable SCLC. The present study compared the effectiveness of the N stage, number of positive LNs (NPLNs), LNR, and LODDS to predict cancer-specific survival (CSS) in SCLC patients and generated a novel nomogram to predict the prognosis based on an optimal LN scheme in cases with resectable SCLC.

2. Materials and methods

2.1. Study population

Patients with the first primary SCLC were selected from the Surveillance Epidemiology and End Results (SEER) Research Plus Data 18 population-based registries. They provided some clinicopathological data, including age at diagnosis, race, year of diagnosis, sex, primary site, TNM stage, histological tumor type, nuclear grade, surgical methods used, chemotherapy status, radiation therapy status, tumor size, CSS time, and survival month. According to the SEER database, the endpoint of cases is death from lung cancer or time of last contact. And, the start of follow-up is date of cancer diagnosis. Therefore, CSS time was defined as the time from lung cancer diagnosis to death from lung cancer. OS time was defined as the time from lung cancer diagnosis to death. 73,683 patients were the first primary SCLC in the SEER database between 2004 and 2018. Eligible patients were included according to the following inclusion criteria: (1) patients diagnosed with SCLC (code: 8041/3–8045/3) by positive histology without previous history of tumors in 2004–2018; (2) surgery (code: 21, 22, 25, 30–70) and LNs were removed; and (3) age over 18 years. The exclusion criteria were as follows: (1) without enough clinical data (unknown age, race, primary site, radiotherapy status, tumor size, nuclear grade, number of lymph node, and survival time); (2) died within one month after surgery (survival time was 0); (3) patients with advanced small-cell lung cancer who are not candidates for surgery (disease was at stage N3 or M1). The flowchart of screening is shown in Fig. 1. Since the study utilized the database's anonymous data, it was not necessary to obtain the institutional review board's approval or individual patient consent. The TNM information was re-grouped based on the AJCC 8th TNM staging.

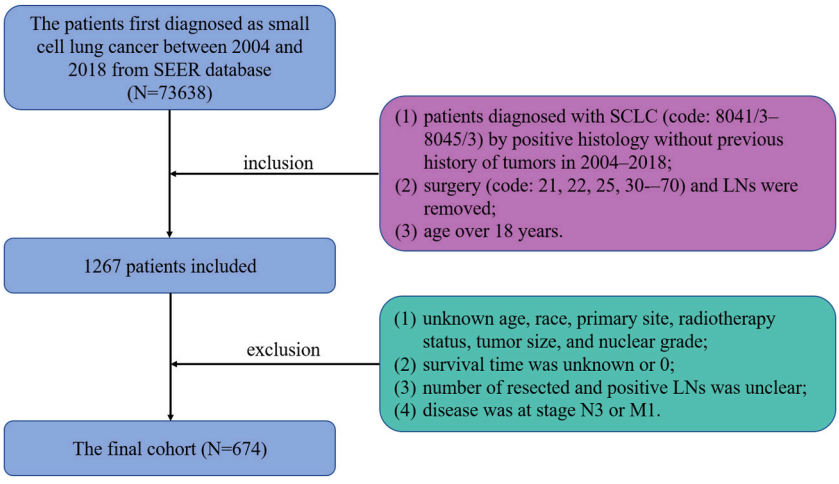

Fig. 1. The flowchart of screening the applicable patients with SCLC from SEER database. SEER, the Surveillance, Epidemiology and End Results.

Table 1
The clinical and pathological characteristics of the final cohort, the training set, and the testing set.

Characteristics	Total (N = 674)	Training set (N = 471)	Testing set (N = 203)	*P*-value
Race				0.091
Black	49 (7.3)	41 (8.7)	8 (3.9)	
White	608 (90.2)	418 (88.7)	190 (93.6)	
Other	17 (2.5)	12 (2.5)	5 (2.5)	
Sex				0.198
Female	369 (54.7)	266 (56.5)	103 (50.7)	
Male	305 (45.3)	205 (43.5)	100 (49.3)	
Age group				0.932
<65 years	259 (38.4)	180 (38.2)	79 (38.9)	
≥65 years	415 (61.6)	291 (61.8)	124 (61.1)	
Location site				0.414
Lower lobe, left	115 (17.1)	81 (17.2)	34 (16.7)	
Lower lobe, right	111 (16.5)	79 (16.8)	32 (15.8)	
Main bronchus	10 (1.5)	4 (0.8)	6 (3.0)	
Middle lobe, right	36 (5.3)	27 (5.7)	9 (4.4)	
Upper lobe, left	204 (30.3)	140 (29.7)	64 (31.5)	
Upper lobe, right	198 (29.4)	140 (29.7)	58 (28.6)	
Tumor size				0.891
<3 cm	434 (64.4)	302 (64.1)	132 (65.0)	
≥3 cm	240 (35.6)	169 (35.9)	71 (35.0)	
Grade				0.670
I/II	48 (7.1)	34 (7.2)	14 (6.9)	
III	341 (50.6)	233 (49.5)	108 (53.2)	
IV	285 (42.3)	204 (43.3)	81 (39.9)	
TNM				0.544
IA	230 (34.1)	153 (32.5)	77 (37.9)	
IB	113 (16.8)	79 (16.8)	34 (16.7)	
IIA	50 (7.4)	33 (7.0)	17 (8.4)	
IIB	115 (17.1)	81 (17.2)	34 (16.7)	
IIIA	143 (21.2)	107 (22.7)	36 (17.7)	
IIIB	23 (3.4)	18 (3.8)	5 (2.5)	
T stage				0.743
T1	334 (49.6)	228 (48.4)	106 (52.2)	
T2	241 (35.8)	171 (36.3)	70 (34.5)	
T3	54 (8.0)	38 (8.1)	16 (7.9)	
T4	45 (6.7)	34 (7.2)	11 (5.4)	
SEER Stage				0.203
Regional	354 (52.5)	258 (54.8)	96 (47.3)	
Localized	314 (46.6)	209 (44.4)	105 (51.7)	
Distant	6 (0.9)	4 (0.8)	2 (1.0)	
Surgery				0.789
Sublobectomy	135 (20.0)	96 (20.4)	39 (19.2)	
Lobectomy	515 (76.4)	357 (75.8)	158 (77.8)	
Pneumonectomy	24 (3.6)	18 (3.8)	6 (3.0)	
Radiation				0.451
No	439 (65.1)	302 (64.1)	137 (67.5)	
Yes	235 (34.9)	169 (35.9)	66 (32.5)	
Chemotherapy				0.571
No	218 (32.3)	156 (33.1)	62 (30.5)	
Yes	456 (67.7)	315 (66.9)	141 (69.5)	
N stage				0.190
N0	420 (62.3)	283 (60.1)	137 (67.5)	
N1	137 (20.3)	101 (21.4)	36 (17.7)	
N2	117 (17.4)	87 (18.5)	30 (14.8)	
NPLN				0.188
NPLN1	428 (63.5)	289 (61.4)	139 (68.5)	
NPLN2	151 (22.4)	110 (23.4)	41 (20.2)	
NPLN3	95 (14.1)	72 (15.3)	23 (11.3)	
LNR				0.264
LNR1	431 (63.9)	292 (62.0)	139 (68.5)	
LNR2	133 (19.7)	99 (21.0)	34 (16.7)	
LNR3	110 (16.3)	80 (17.0)	30 (14.8)	
LODDS				0.661
LODDS1	328 (48.7)	225 (47.8)	103 (50.7)	
LODDS2	168 (24.9)	117 (24.8)	51 (25.1)	
LODDS3	178 (26.4)	129 (27.4)	49 (24.1)	

TNM, tumor-node-metastasis; SEER, stage Surveillance, Epidemiology, and End Results stage; NPLN, the number of positive lymph nodes; LNR, the lymph node ratio; LODDS, the log odds of positive lymph nodes.

2.2. Variable calculation, grouping, and screening

The SEER database provides the number of dissected LNs (NDLN), number of positive LNs (NPLN), and N stage directly. The LNR is defined as NPLN divided by NDLN. LODDS is calculated according to the following formula: log ((NPLN+0.05)/(NDLN-NPLN+0.05)). The NPLN, LNR, and LODDS data were divided into three groups according to CSS using X-tile software (version 3.6.1; Yale University, New Haven, CT, USA). Finally, NPLN data were categorized into NPLN1 (range 0–0), NPLN2 (range 1–2), and NPLN3 (range 3–13) datasets. LNR data were categorized into LNR1 (range 0–0.02), LNR2 (range 0.03–0.30), and LNR3 (range 0.31–1.00) datasets. LODDS data were categorized into LODDS1 (−2.96–1.80), LODDS2 (−1.79–0.77), and LODDS3 (−0.76–2.15) datasets. The independent prognostic factors were screened by univariate and multivariate Cox proportional hazards regression models. The Kaplan-Meier survival and receiver operating characteristic (ROC) curves were conducted to access the effectiveness of the N stage, NPLNs, LNR, and LODDS in predicting the CSS.

2.3. Construction and validation of nomograms

The analyses showed that LODDS was the optimal LN scheme and performed better distinguishing and predicting ability than LNR, NPLN, and N stage. The study cohort was randomly divided into a training set and a testing set at a ratio of 7:3.

Univariate and multivariate Cox proportional hazards regression models were used to identify the independent prognostic factors, where CSS was the primary outcome. LODDS, age at diagnosis, race, sex, primary site, tumor size, nuclear grade, SEER stage, surgical methods, chemotherapy status, and radiation therapy status were all included in the multivariate analysis using the stepwise Akaike information criterion (AIC) method to identify the optimal final predictors. These factors, including LODDS, age at diagnosis, sex, tumor size, and radiation status, were included in the final models. Based on the multivariate Cox proportional hazards regression

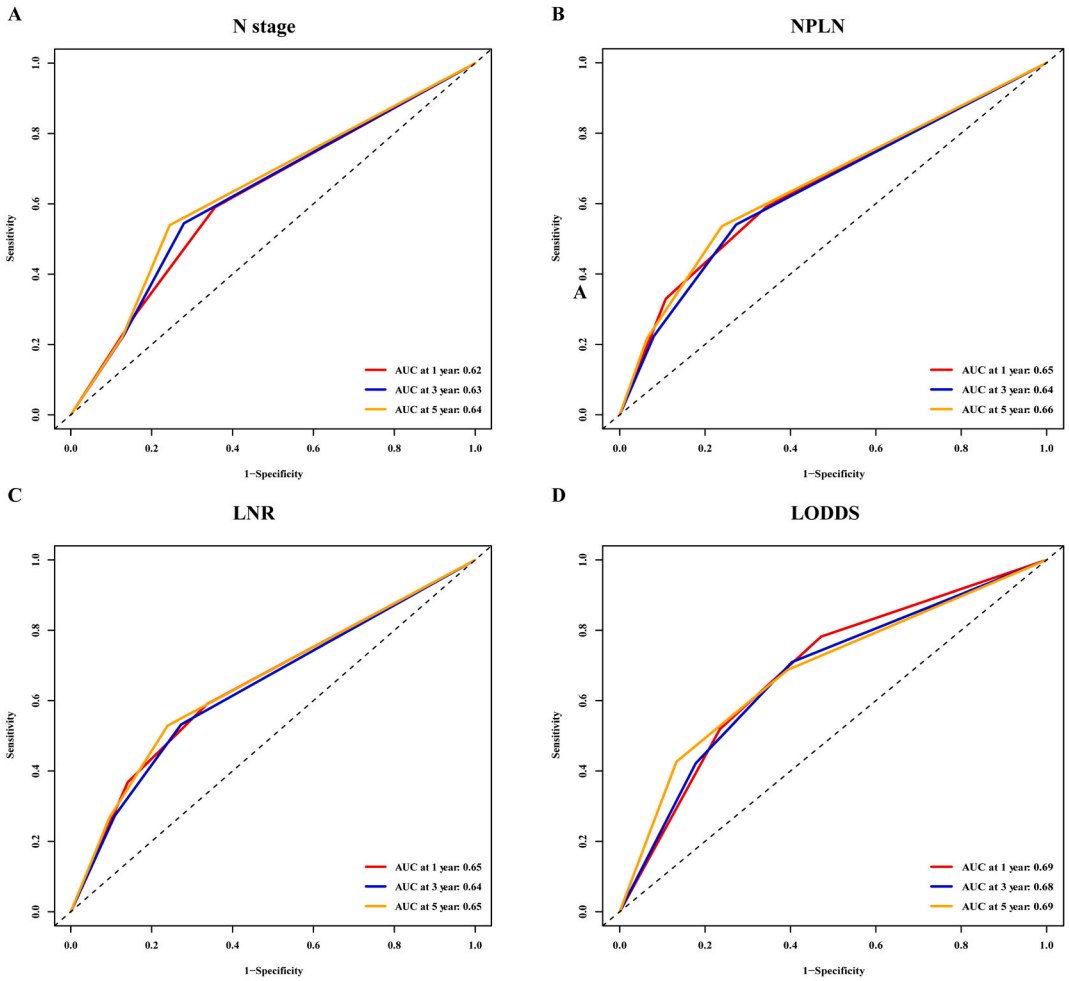

Fig. 2. The ROC curves for predicting 1-, 3- and 5-year lung cancer-specific survival based on N stage (A), NPLN (B), LNR (C), and LODDS (D) in patients with SCLC. ROC, receiver operating characteristic curve; AUC, areas under the ROC curve; NPLN, the number of positive lymph nodes; LNR, the lymph node ratio; LODDS, the log odds of positive lymph nodes.

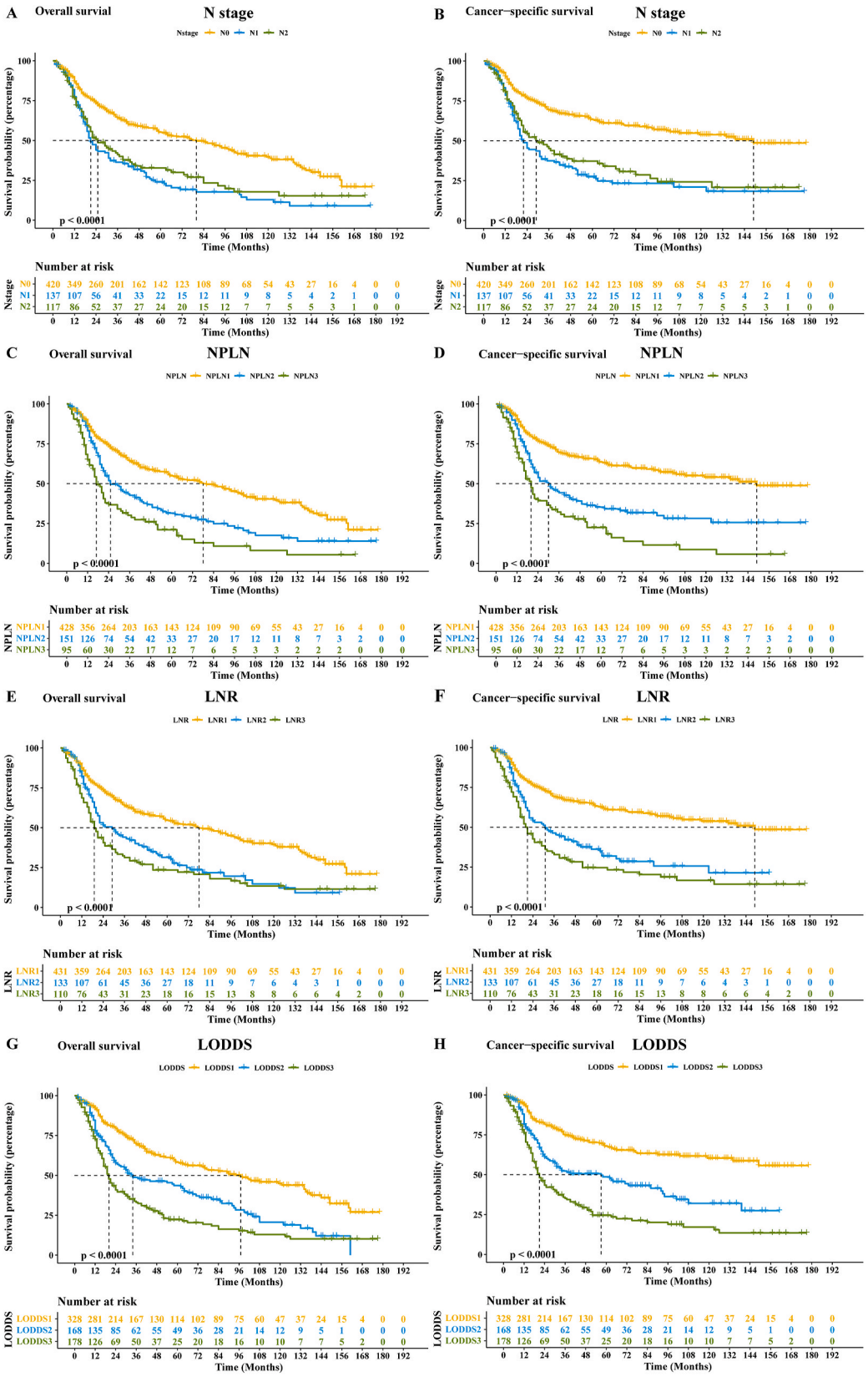

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Fig. 3. The prognostic effect of N stage (A and B), NPLN (C and D), LNR (E and F), and LODDS (G and H) on the overall survival (A, C, E, and G) and lung cancer-specific survival (B, D, F, and H) of patients with SCLC. NPLN, the number of positive lymph nodes; LNR, the lymph node ratio; LODDS, the log odds of positive lymph nodes.

model, a novel nomogram was generated to predict the CSS in patients with SCLC using the "rms" package [23,24].

To test the discrimination ability and accuracy of the novel model, the ROC curves (area under the curve, AUC), decision curve analysis (DCA), and calibration plots were utilized in the training and testing sets. The AUC value was used to access the predictive ability of the nomogram. DCA plots were utilized to evaluate the clinical benefit of the nomogram. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to compare the improvements of the novel model with the 8th TNM and SEER staging systems. The risk of patients in the training and testing cohorts was stratified based on the risk score of the nomogram. Kaplan-Maier curves were adopted to evaluate the discriminative power of the nomogram, TNM staging, and SEER staging.

2.4. Statistical analyses

All statistical analyses were performed using R software (version 4.1.2; USA) with two-sided tests, where $P < 0.05$ was considered statistically significant. In this study, "data.table", "survival", "timeROC", "survminer", "caret", "MASS", "rms", "rsconnect", "riskRegression", "ggDCA", "ggprism", "nricens", and "survIDINRI" R packages were used.

3. Results

3.1. Patient characteristics

A total of 674 SCLC patients were included in the final cohort of the study (Table 1). In this cohort, the majority of cases were in the early disease stages. In addition, there were more elderly patients and more patients with poorly differentiated tumors. Interestingly, 21.2% of cases were patients diagnosed with stage IIIA cancer. Lobectomy (76.4%) was the primary method of surgery for SCLC treatment, followed by sublobectomy (20%). Overall, 456 (67.7%) patients received chemotherapy, while only 235 (34.9%) patients received radiotherapy. Patients with lesions smaller than 3 cm or lesions located on the upper lobe were more likely to undergo surgery.

3.2. Screening of optimal LN schemes

Fig. 2(A-D) shows the predictive abilities of NPLN, LNR, LODDS, and N stage. The time-dependent one-, three-, and five-year AUC values for LODDS status were 0.69, 0.68, and 0.69, respectively. The time-dependent one-year AUC values for NPLN, LNR, and N stage were 0.65, 0.65, and 0.62, respectively. They were 0.64, 0.64, and 0.63 for the three-year AUC and 0.66, 0.65, and 0.64 for the five-year AUC, respectively. The Cox proportional hazards regression analysis and Kaplan-Meier curves were used to validate the discrimination ability of NPLN, LNR, LODDS, and N stage. The results showed that LODDS, NPLN, LNR, and N stage can be used as independent prognostic factors, but the LODDS status was able to better distinguish the three groups [Fig. 3(A-H), Table 2].

Table 2
The univariate and multivariate Cox proportional hazards regression models and survival analysis of the different LNs schemes.

LNs status	No. Of cases	Univariate analysis		Multivariate analysis[a]		1-year survival rate	3-year survival rate	5-year survival rate
		HR (95% CIs)	*P*-value	HR (95% CIs)	*P*-value			
N stage								
N0	420 (62.3)	Reference		Reference		90.11%	69.33%	63.31%
N1	137 (20.3)	2.66 [2.04, 3.46]	<0.001	2.70 [1.84, 3.98]	<0.001	78.60%	37.45%	27.40%
N2	117 (17.4)	2.26 [1.70, 3.02]	<0.001	2.11 [1.41, 3.16]	<0.001	80.52%	45.09%	37.19%
NPLN								
NPLN1	428 (63.5)	Reference		Reference		90.29%	69.53%	63.54%
NPLN2	151 (22.4)	2.15 [1.66, 2.79]	<0.001	2.18 [1.47, 3.22]	<0.001	84.39%	44.30%	35.26%
NPLN3	95 (14.1)	3.50 [2.62, 4.68]	<0.001	4.07 [2.67, 6.19]	<0.001	69.41%	32.22%	22.55%
LNR								
LNR1	431 (63.9)	Reference		Reference		90.36%	69.19%	63.23%
LNR2	133 (19.7)	2.17 [1.64, 2.86]	<0.001	2.20 [1.48, 3.28]	<0.001	83.99%	46.37%	36.25%
LNR3	110 (16.3)	3.02 [2.30, 3.96]	<0.001	3.31 [2.21, 4.95]	<0.001	72.10%	32.87%	24.66%
LODDS								
LODDS1	328 (48.7)	Reference		Reference		93.87%	74.78%	67.86%
LODDS2	168 (24.9)	2.13 [1.59, 2.86]	<0.001	2.10 [1.53, 2.88]	<0.001	81.51%	52.32%	48.63%
LODDS3	178 (26.4)	3.67 [2.81, 4.80]	<0.001	4.08 [2.80, 5.93]	<0.001	76.05%	35.13%	24.46%

LNs, lymph nodes; NPLN, the number of positive lymph nodes; LNR, the lymph node ratio; LODDS, the log odds of positive lymph nodes.

[a] The multivariate Cox proportional hazards regression models were adjusted by age, sex, race, location site, grade, tumor size, stage, surgery, radiation, and chemotherapy.

Nomogram construction and validation.

The whole cohort was randomly divided into the training (N = 471) and testing (N = 203) sets. First, the independent prognostic factors were identified using univariate and multivariate Cox proportional hazards regression models in the training set. LODDS status and age at diagnosis were the independent prognostic factors. After stepwise regression, five variables, including LODDS, age at diagnosis, sex, tumor size, and radiation therapy status, were utilized together to build a novel model with a minimal AIC value. Second, the "rms" package was used to plot a nomogram to predict the CSS for SCLC patients based on the five-variable multivariate Cox regression model (Fig. 4). Meanwhile, we developed a web-based version of the prognostic score calculator based on the nomogram. The web version of the nomogram (https://chaoce.shinyapps.io/DynNomapp_LCSS/) was published online in order to facilitate its use. Meanwhile, we also developed a nomogram based on the log odds of positive lymph nodes to predict overall survival in patients with small cell lung cancer after surgery (Fig. S1) and this web version of nomogram was developed (https://chaoce.shinyapps.io/DynNomapp_OS/).

Third, internal and external validation was performed to test the discrimination and stability of the nomogram. The AUC values of the nomogram in the training set were 0.76 (95% confidence interval (CI): 0.70–0.83), 0.72 (95%CI: 0.67–0.77), and 0.74 (95%CI: 0.68–0.79) for the one-, three- and five-year CSS, respectively. In the testing set, they were 0.76 (95%CI: 0.65–0.87), 0.73 (95%CI: 0.65–0.81), and 0.74 (95%CI: 0.65–0.82) for the one-, three- and five-year CSS, respectively [Fig. 6(A-F)]. The calibration curves proved a good agreement between actual and predicted survival conditions for the one-, three-, and five-year CSS. The calibration curves for the testing set had similar results [Fig. 5(A-F)].

3.3. Comparison among nomogram, TNM staging, and SEER staging

Compared to the SEER and TNM staging, DCA analysis suggested that the novel nomogram significantly increased the net benefits for almost all threshold probabilities in the training and testing sets [Fig. 7(A-F)]. Moreover, the NRI and IDI for the nomogram were

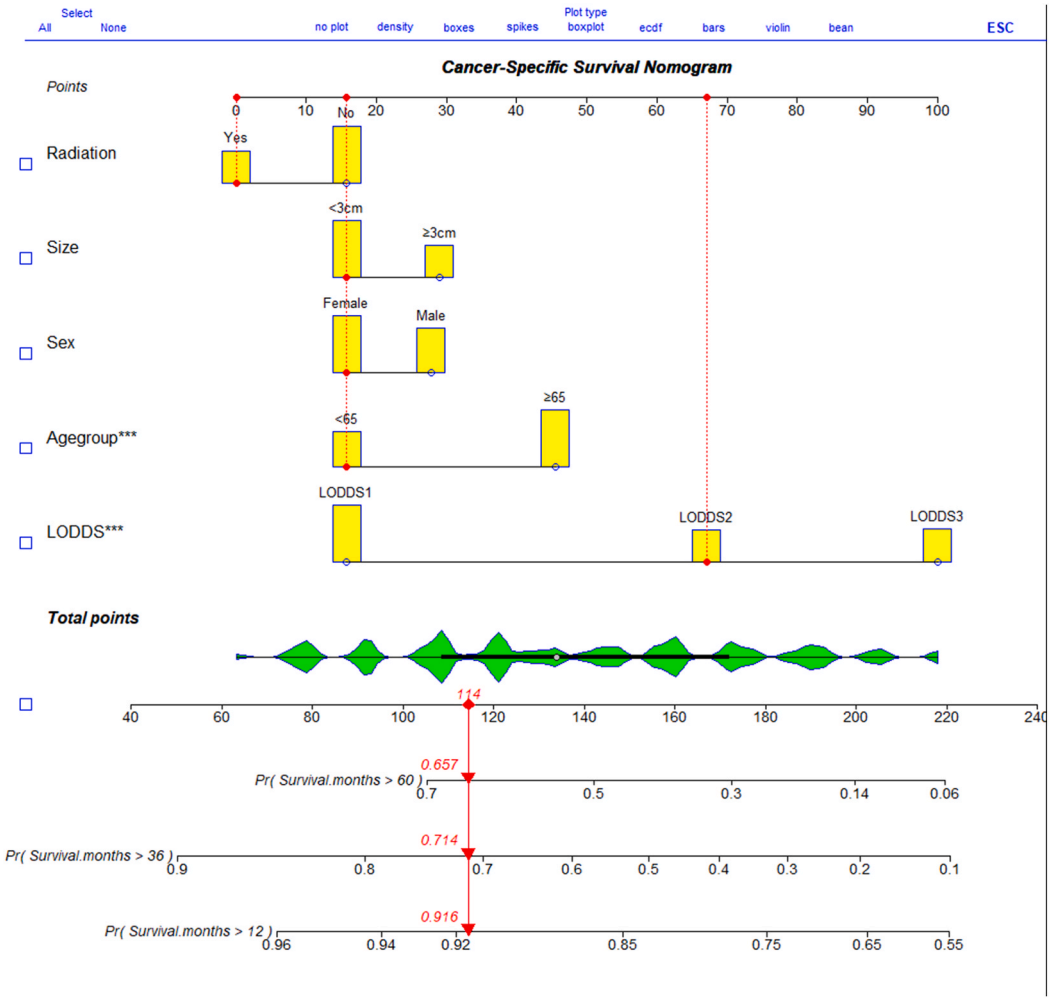

Fig. 4. A novel nomogram predicted 1-, 3- and 5-year lung cancer-specific survival for SCLC patients. LODDS, the log odds of positive lymph nodes.

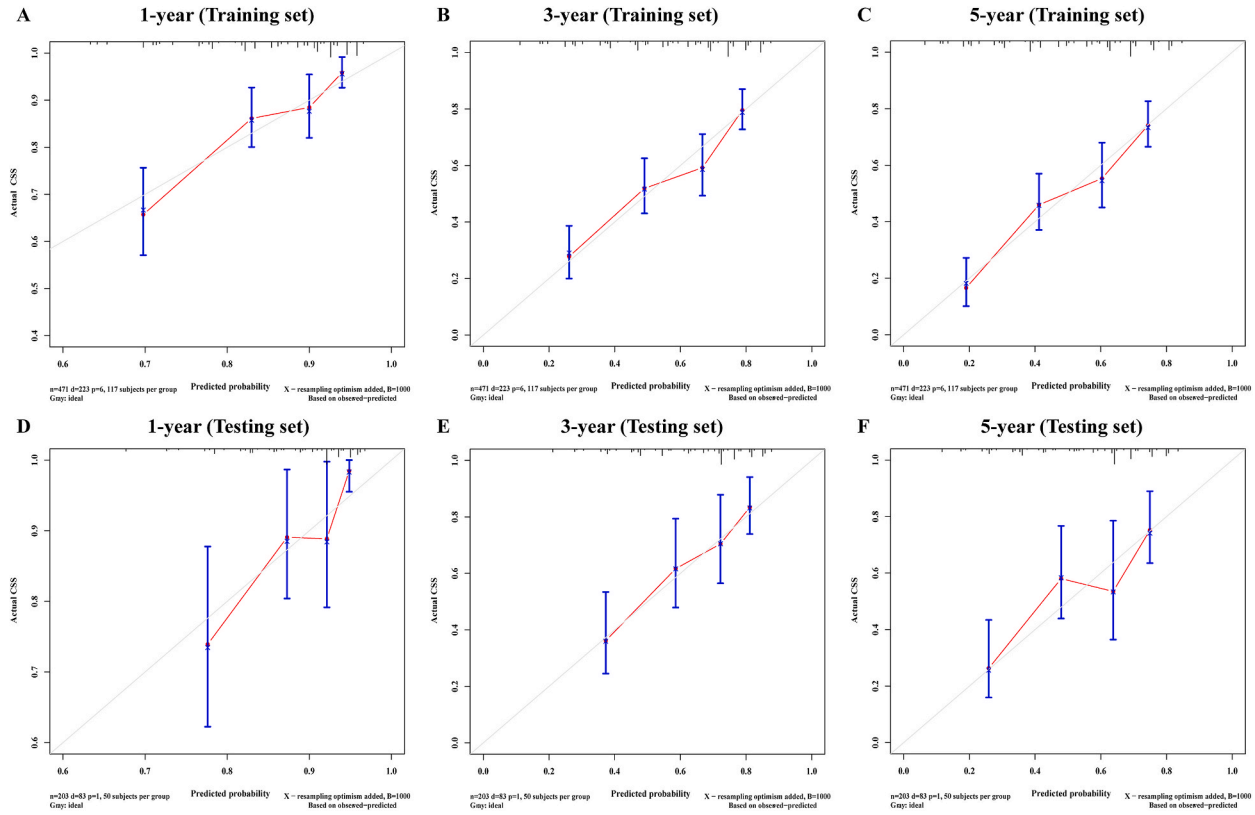

Fig. 5. The calibration plots for predicting 1-, 3- and 5-year lung cancer-specific survival for SCLC patients in training set (A, B, and C) and testing set (D, E, and F).

calculated using TNM and SEER staging (Table 3). Compared to the TNM stage, the NRI values for the nomogram were 0.393 (95%CI: 0.192–0.500), 0.293 (95%CI: 0.207–0.427), and 0.307 (95%CI: 0.208–0.460) for the one-, three-, and five-year CSS in the training cohort, respectively. They were 0.478 (95%CI: 0.139–0.597), 0.243 (95%CI: 0.052–0.407), and 0.300 (95%CI: 0.116–0.462) for the one-, three-, and five-year CSS in the testing cohort, respectively. Compared to the SEER stage, the NRI values for the nomogram were 0.395 (95%CI: 0.230–0.526), 0.255 (95%CI: 0.122–0.391), and 0.275 (95%CI: 0.156–0.427) for the one-, three-, and five-year CSS in the training cohort, respectively. They were 0.374 (95%CI: 0.132–0.555), 0.289 (95%CI: 0.049–0.444), and 0.323 (95%CI: 0.100–0.450) for the one-, three-, and five-year CSS in the testing cohort, respectively. Similarly, the IDI values for the one-, three-, and five-year CSS were 0.075 (95%CI: 0.037–0.127), 0.110 (95%CI: 0.055–0.174), and 0.120 (95%CI: 0.066–0.186), respectively, compared to the SEER stage, and 0.069 (95%CI: 0.036–0.121), 0.116 (95%CI: 0.076–0.171), and 0.127 (95%CI: 0.081–0.185), respectively, compared to the TNM stage in the training cohort. In the testing cohort, the IDI values for the one-, three-, and five-year CSS were 0.062 (95%CI: 0.021–0.122), 0.101 (95%CI: 0.015–0.190), and 0.118 (95%CI: 0.031–0.213), respectively, compared to the SEER stage, and 0.057 (95%CI: 0.019–0.116), 0.091 (95%CI: 0.014–0.167), and 0.107 (95%CI: 0.023–0.189), respectively, compared to the TNM stage.

3.4. A novel risk stratification based on the nomogram

According to the total score calculated by the nomogram, the SCLC patients were divided into three groups as follows: nomo1 (−1.36–0.08), nomo2 (−0.07–0.66), and nomo3 (0.67–1.46). Compared to the SEER and TNM staging, the three nomo groups were able to better distinguish the SCLC patients using Kaplan-Meier curves [Fig. 8(A-L)].

4. Discussion

The LN status plays a vital role in the treatment and prognosis of the majority of solid tumors. In SCLC patients, surgery has been demonstrated to improve the local control rate [25]. With the gradual increase in the number of surgical patients, clinicians lack effective tools to evaluate patients with LN metastasis. Moreover, the VALSG and TNM staging systems have been shown to be inefficient in predicting the prognosis of SCLC patients [21]. The N stage can be used to determine the long-term survival of SCLC patients [26]. However, there is no prognostic significance between the N1 and N2 status. The accuracy of the N stage may be limited by the number of resected LNs, which is sometimes difficult to accomplish [26]. For NSCLC, multiple guidelines have provided

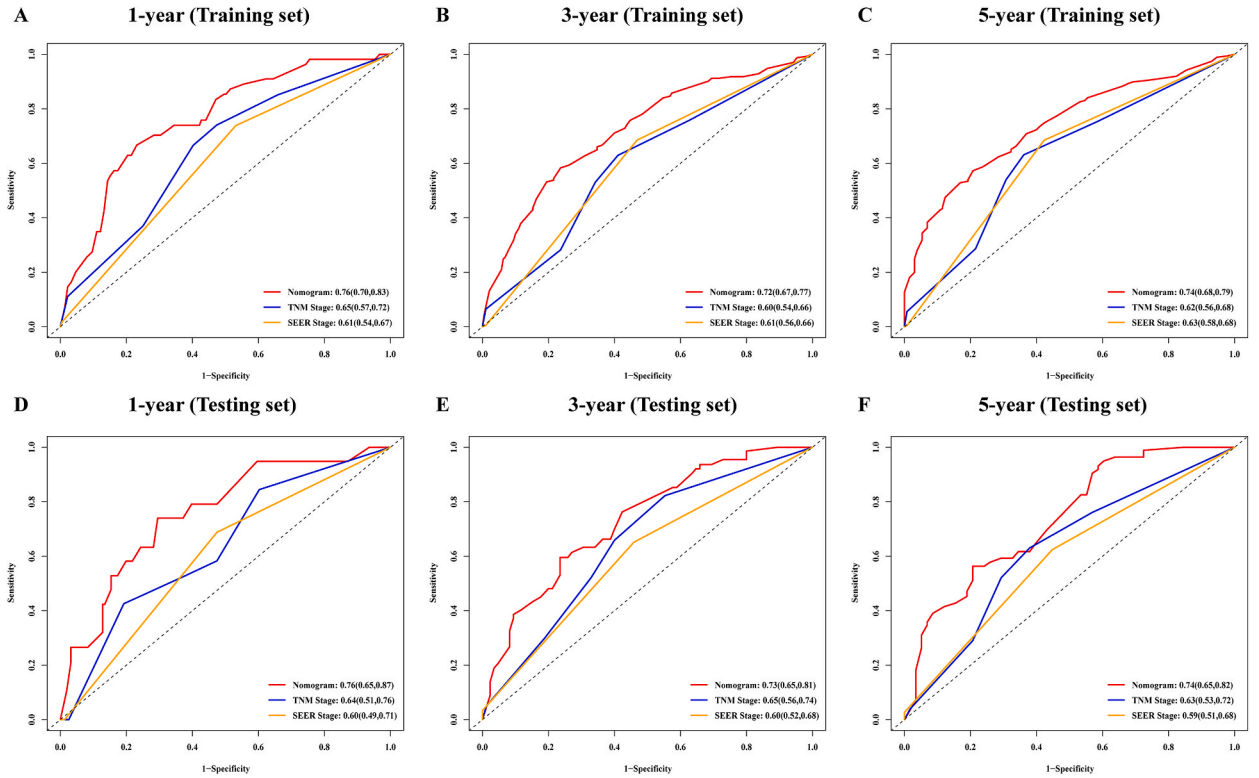

Fig. 6. The ROC curves for predicting 1-, 3- and 5-year lung cancer-specific survival based on the nomogram, TNM stage, and SEER stage in training set (A, B, and C) and testing set (D, E, and F). TNM, tumor-node-metastasis; SEER, the Surveillance, Epidemiology and End Results.

direction for an adequate nodal examination [27]: at least 10 LNs should be resected in early-stage NSCLC according to the American College of Surgeons Commission on Cancer, three mediastinal nodal stations are the minimum standard to remove according to the National Comprehensive Cancer Network, and three N1 and three mediastinal LNs should be removed based on the Union for International Cancer Control recommendations. However, only <40% of cases have met the current guidelines for the resected number of LNs [28]. Although LNR has shown a good effectiveness in predicting prognosis of resected SCLC patients [22], it cannot further stratify cases that have 0 or 1 NPLNs. Therefore, LODDS was introduced in order to assess LN metastasis in SCLC patients and to compare the predictive and discriminative ability of LNR, NPLN, and N stage. The LODDS stage can distinguish some N0 stage patients with poor prognosis. The present study demonstrated that LODDS was the optimal LN scheme to predict prognosis of SCLC patients and constructed a novel nomogram that was better distinguishing and predicting ability than the VALSG and TNM staging systems.

In the final model, LODDS, age at diagnosis, sex, tumor size, and radiotherapy status were utilized to assess the CSS in SCLC patients. The LODDS status was the most important factor in predicting CSS for SCLC patients, followed by age at diagnosis. In the existing studies, the TNM staging system contributed the most to predicting prognosis in SCLC patients [21,22,29,30]. However, the LN status did not contribute as much as the T stage, which may be due to inaccurate LN staging. This showed that the accurate LN status played an important role in increasing the discriminatory ability of the model. Elderly patients had a worse prognosis than young patients, likely due to worse tumor burden and degenerative changes [31]. Female patients had a better prognosis than male patients, which was consistent with previous studies [32]. In addition, smaller tumor size meant better survival, which has been confirmed by Wang et al. [33]. Early radiotherapy has been shown to be beneficial to the long-term prognosis of SCLC patients, while postoperative radiotherapy might be able to improve the survival benefit for high-risk patients [34,35].

A novel prognostic nomogram was generated based on the LODDS status for SCLC patients. Many researchers have focused on the construction of a prognostic evaluation for SCLC and have built nomograms related to it [21,22,29,30,36,37]. The majority of them have been used to predict the entire pan-stage of SCLC patients. For example, Wang et al. have created a nomogram with high prognostic accuracy based on eight factors, including the AJCC 8th TNM staging [29]. In addition, some researchers have built nomograms to predict long-term survival of particular patient groups, including SCLC patients with metastasis and combined SCLC patients [38,39]. To evaluate the efficacy of different treatments, nomograms can also be established to evaluate the survival of SCLC patients after radiotherapy, chemotherapy, or surgery [37,40,41]. So far, there have been three nomograms built to predict the overall survival of SCLC patients after surgery, where LODDS was not calculated and incorporated into the models. Wang et al. have built the first nomogram to predict the one-, three-, and five-year overall survival for SCLC patients that was better than TNM staging [21]. However, two types of N status, N stage, and LNR were included in the model, which was inconvenient for use in clinical work. Similarly, LN dissected and LN metastasis were both used to build a novel nomogram for SCLC [36]. In addition, Wu et al. have added

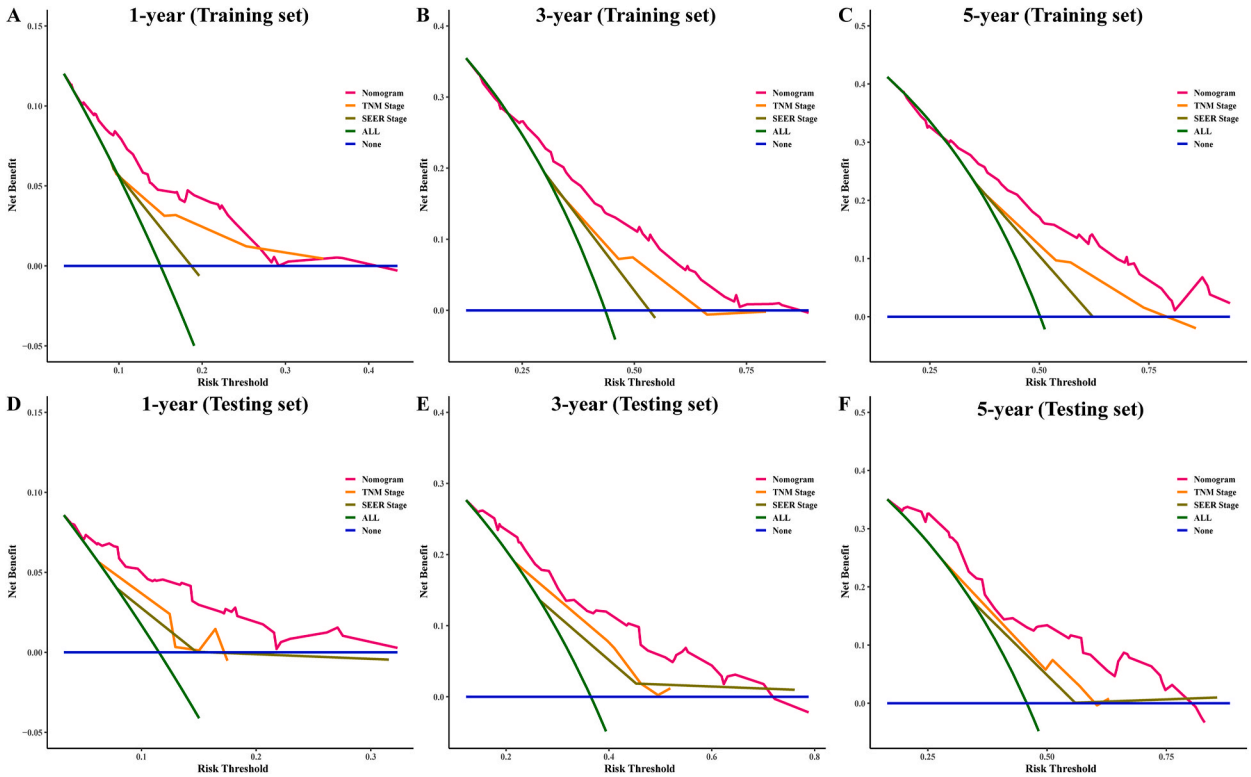

Fig. 7. The clinical decision curve analysis of nomogram, TNM stage, and SEER stage in prediction of 1-, 3- and 5-year lung cancer-specific survival from training set (A, B, and C) and testing set (D, E, and F). TNM, tumor-node-metastasis; SEER, the Surveillance, Epidemiology and End Results.

Table 3
The NRI and IDI of the nomogram, TNM stage, and SEER stage system in cancer-specific survival prediction for SCLC patients.

Index	Training set		Testing set	
	Estimate and 95% CI	*P*-value	Estimate and 95% CI	*P*-value
NRI (vs. SEER Stage)				
1-year CSS	0.395 (0.230, 0.526)	<0.001	0.374 (0.132, 0.555)	0.014
3-year CSS	0.255 (0.122, 0.391)	<0.001	0.289 (0.049, 0.444)	0.024
5-year CSS	0.275 (0.156, 0.427)	<0.001	0.323 (0.100, 0.450)	0.004
NRI (vs. TNM stage)				
1-year CSS	0.393 (0.192, 0.500)	<0.001	0.478 (0.139, 0.597)	<0.001
3-year CSS	0.293 (0.207, 0.427)	<0.001	0.243 (0.052, 0.407)	0.016
5-year CSS	0.307 (0.208, 0.460)	<0.001	0.300 (0.116, 0.462)	0.010
IDI (vs. SEER Stage)				
1-year CSS	0.075 (0.037, 0.127)	<0.001	0.062 (0.021, 0.122)	0.004
3-year CSS	0.110 (0.055, 0.174)	<0.001	0.101 (0.015, 0.190)	0.026
5-year CSS	0.120 (0.066, 0.186)	<0.001	0.118 (0.031, 0.213)	0.002
IDI (vs. TNM Stage)				
1-year CSS	0.069 (0.036, 0.121)	<0.001	0.057 (0.019, 0.116)	<0.001
3-year CSS	0.116 (0.076, 0.171)	<0.001	0.091 (0.014, 0.167)	0.024
5-year CSS	0.127 (0.081, 0.185)	<0.001	0.107 (0.023, 0.189)	0.008

NRI, net reclassification improvement; IDI, integrated discrimination improvement; SCLC, small cell lung cancer; CI, confidence interval; SEER, stage Surveillance, Epidemiology, and End Results stage; TNM, tumor-node-metastasis; CSS, cancer-specific survival.

age, sex, and LNR to the new model based on the AJCC 8th TNM staging, although their AUC value was not high enough [37]. The present model did not utilize TNM staging data in the nomogram, but its accuracy was better than that of TNM staging. It was speculated that the TNM staging is only suitable for evaluating patients before surgery, while a nomogram is more appropriate for predicting long-term survival after surgery. Last but not least, for convenience of clinicians, we developed a web-based tool via 'DynNom' package, which could easily show the predicting survival rate across time by inputting corresponding clinical features. For example, a 60-year-old woman with small cell lung cancer, no radiotherapy, a lesion less than 3 cm, and lymph node stage LODDS1 had a 5-year survival rate of 0.8 (0.74, 0.87).

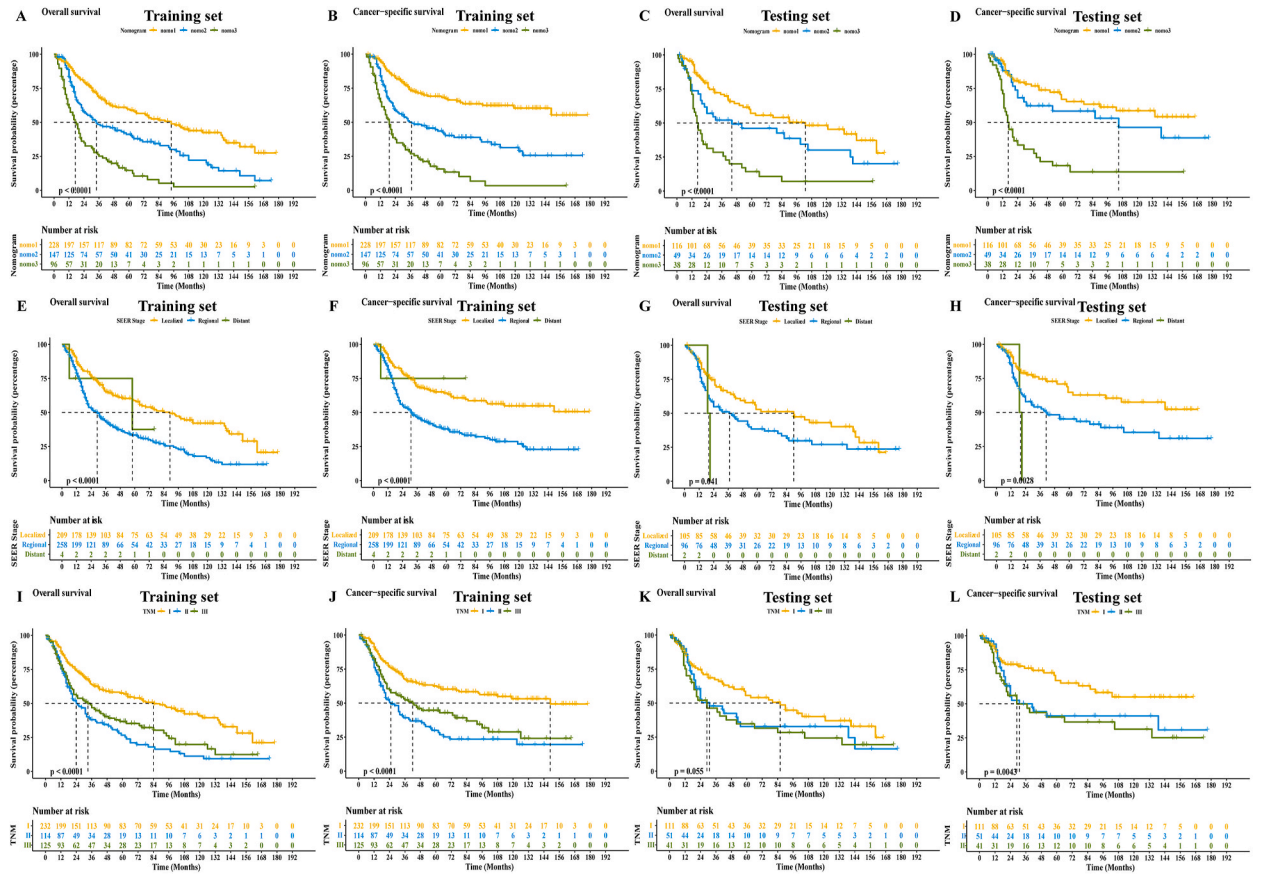

Fig. 8. The Kaplan-Maier survival curves of overall survival and the lung cancer-specific survival based on the nomogram (A, B, C, and D), TNM stage (E, F, G, and H), and SEER stage (I, J, K, and L) in training set and testing set. TNM, tumor-node-metastasis; SEER, the Surveillance, Epidemiology and End Results.

Nevertheless, there were some limitations in the present study. First, smoking index has been shown to be an independent prognostic factor and has been incorporated into some nomograms to predict survival [42]. However, the present study database lacked data related to smoking. Second, tumor markers were also important indicators. For example, neuron-specific enolase is a specific marker for SCLC. Xie et al. and Pan et al. have built a nomogram with high prognostic accuracy using these variables [30,43]. In addition, Naples Prognostic Score is calculated based on nutritional and inflammatory status and is an independent prognostic factor [44]. However, the SEER database do not include there associated data. Third, chemotherapy is the basic treatment for SCLC, but the present model did not consider it due to the lack of detailed chemotherapy protocols. Last but not least, this model has not been validated by local clinical data. In our hospital, small cell lung cancer patients are rarely operated on and it is difficult to collect sufficient clinical data. It is expected that more SCLC patients will benefit from surgery and more accurate clinical prediction models will be developed.

5. Conclusions

In conclusion, LODDS was the optimal LN scheme for predicting CSS in SCLC patients after surgery and had a greater ability to recognize the high-risk population after surgery, especially for stage N0 patients. A novel nomogram based on LODDS, age, sex, tumor size, and radiotherapy status was built to predict CSS for SCLC patients after surgery. Internal and external validation both confirmed its predictive accuracy, reliability, and clinical applicability, which were better than those for TNM and SEER staging.

Ethics statement

The data was derived from the SEER database, it was unnecessary to obtain patient consent again.

Consent for publication

Not applicable.

Author contribution statement

Ce Chao: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Bin Wang; Dongmei Di: Conceived and designed the experiments.

Kun Mei: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Min Wang; Renzhe Tang; Yongxiang Qian: Contributed reagents, materials, analysis tools or data; Analyzed and interpreted the data.

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Data availability statement

Data were from a public database.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18502.

Abbreviations

LN	lymph node
LNR	lymph node ratio
SCLC	small cell lung cancer
NPLNs	number of positive LNs
LODDS	log odds of positive LNs
CSS	cancer-specific survival
ROC	receiver operating characteristic curves
SEER	the Surveillance Epidemiology and End Results database
DCA	decision curve analysis
VALSG	the Veterans Administration Lung Study Group
TNM	tumor–node–metastasis
AIC	Akaike information criterion
NRI	net reclassification improvement
IDI	integrated discrimination improvement

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