Original Article

Development and validation of a nomogram for predicting the overall survival of patients with lung large cell neuroendocrine carcinoma

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Background: Lung large cell neuroendocrine carcinoma (L-LCNEC) is a rare and rapidly progressing lung cancer. We aimed to formulate a nomogram model to predict the survival of L-LCNEC patients.

Methods: Clinical data of patients with L-LCNEC, lung large cell cancer (L-LCC) and small cell lung cancer (SCLC) were derived from the Surveillance, Epidemiology, and End Results (SEER) database. The characteristics and prognosis of L-LCNEC were investigated by comparing with that of L-LCC and SCLC, respectively. All L-LCNEC patients were randomly assigned into training group and validation group. A prognostic nomogram model was established for the overall survival (OS) in L-LCNEC patients. Furthermore, we enrolled 112 L-LCNEC patients from our department to validate the nomogram model.

Result: 3,076 L-LCNEC, 11,163 L-LCC, and 78,097 SCLC patients were collected and enrolled in our analyses. Compared with L-LCC and SCLC, differences were observed in L-LCNEC in age, sex, race, marital status, SEER registry, TNM stage, and treatment. Furthermore, higher proportions of L-LCNEC were located at the upper lobe and unilateral lung compared with SCLC. L-LCNEC has similar survival to L-LCC, but better than SCLC. We identified that the age, gender, T, N, and M classification, and treatment were the independent prognostic predictors. A nomogram model was formulated to predict the OS. Calibration curves were performed to show optimal coherence between predicted probability of survival and actual survival, with a concordance index of 0.775. The external cohort included 112 patients and all of them underwent surgical treatment. The external validation demonstrated the reliability of this model.

Conclusions: The nomogram demonstrated its discrimination capability to predict the OS for L-LCNEC patients.

Keywords: Lung large cell neuroendocrine carcinoma (L-LCNEC); SEER database; nomogram; validation

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Introduction

Lung large cell neuroendocrine carcinoma (L-LCNEC) is an uncommon histological type of lung cancer and presents an aggressive biological behavior, taking up approximately 3% of lung cancers (1).

According to the classification of 2004 World Health Organization (WHO), L-LCNEC was grouped into

lung large cell carcinomas (L-LCC) (2). While in the recent WHO criteria, this subtype is categorized as a neuroendocrine tumor (3). L-LCNEC has been demonstrated as an aggressive tumor. Several reports suggested that the prognoses of L-LCNEC were poorer than that of L-LCC but similar to that of small cell lung cancer (SCLC) (4-6). Some researches revealed that L-LCNEC has a 5-year survival rate of 15% to 57% (7,8). But some reports considered that SCLC and L-LCNEC were different tumors according to their morphology and phenotype (9,10), and which therapeutic strategy to use for SCLC and for the treatment of L-LCNEC remains controversial. Based on the previous studies, whether L-LCNEC should be classified as SCLC or as L-LCC needs to be further evaluated. Therefore, we determined the characteristics and survival outcomes of L-LCNEC.

In addition, the prognostic characteristics of patients with LCNEC have been less extensively investigated. Nomogram models are widely used for prediction of survival in cancer patients, but there is still no report on a model for L-LCNEC. As a result, this study intended to develop a nomogram model based on the significant independent risk factors to predict the overall survival (OS) of patients with L-LCNEC. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-780).

Methods

The data of L-LCNEC, L-LCC and SCLC cases were derived from the Surveillance, Epidemiology, and End Results (SEER) database. This database is publicly accessible. Thus, the research containing the data from SEER database was not required ethical approval. For the external validation cohort, the written informed consent was exempted by the Ethics Committee of Zhongshan Hospital, Fudan University for this retrospective study.

Patients with L-LCNEC (ICD-O-3 8013/3) from 2004 to 2015 and other L-LCC (8012/3, 8014/3) and SCLC (8041/3, 8043/3, 8044/3, 8045/3) from 2000 to 2015 were obtained and enrolled in this study. For the tumors, the labeled primary sites were limited to C34.1, C34.2, C34.3, C34.8, C34.9. The old version of tumor TNM stage was converted to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM stage, manually.

The data of patients and tumor characteristics, such as age, gender, race, year of diagnosis, marital status, origin recode NAACCR Hispanic Identification Algorithm (NHIA), SEER registry, tumor primary site, laterality, tumor differentiation, T, N, M classification, stage, surgery recode, chemotherapy recode, radiation recode, survival time and survival outcomes, were obtained and enrolled in this study. Age was categorized subjectively as ≤60, 60–70, and >70 years.

The characteristics of patients with L-LCNEC, L-LCC, and SCLC, respectively, were compared using chi-square and Wilcoxon tests by IBM SPSS Statistics 24. In order to investigate the survival of three types of lung cancer, the propensity score matching (PSM) model was applied to control for variation in characteristics. Some important factors were matched between the L-LCNEC and L-LCC and between the L-LCNEC and SCLC groups: age, sex, race, TNM stage and treatment. For each patient with L-LCNEC, one case with L-LCC and SCLC was randomly chosen for pairing by PSM. The Kaplan-Meier survival curves were performed and compared using log-rank tests in the three lung cancer groups. All L-LCENEC patients (n=3,076) were randomized to training cohort (n=2,461) and validation cohort (n=615) by the ratio of 8:2. Univariate survival analyses and multivariate Cox model were performed to determine the independent predictors of the patients with L-LCNEC in the training group. The nomogram model was formulated based on the outcomes of the multivariate analyses. The concordance index (C-index) and the calibration curves were used to assess the prediction ability and compliance of the nomogram model.

Furthermore, internal validation using the validation cohort and external validation using the cohort (n=112) provided by the database of the Department of Thoracic Surgery of Zhongshan Hospital were performed to examine the generalizability of the nomogram model.

Survival analysis, nomogram model establishment, and calibration curves were analyzed and plotted using R version 3.5.1. In this study, results of all statistical tests were considered significant if P value was at a level of less than 0.05.

Results

Patients characteristics

The cases were selected as *Figure 1*. After selection, there were 3,076 patients with L-LCNEC, 11,163 patients with L-LCC, and 78,097 patients with SCLC involved in the current research (*Table 1*). No significant differences were observed in aspect of origin record NHIA, tumor primary

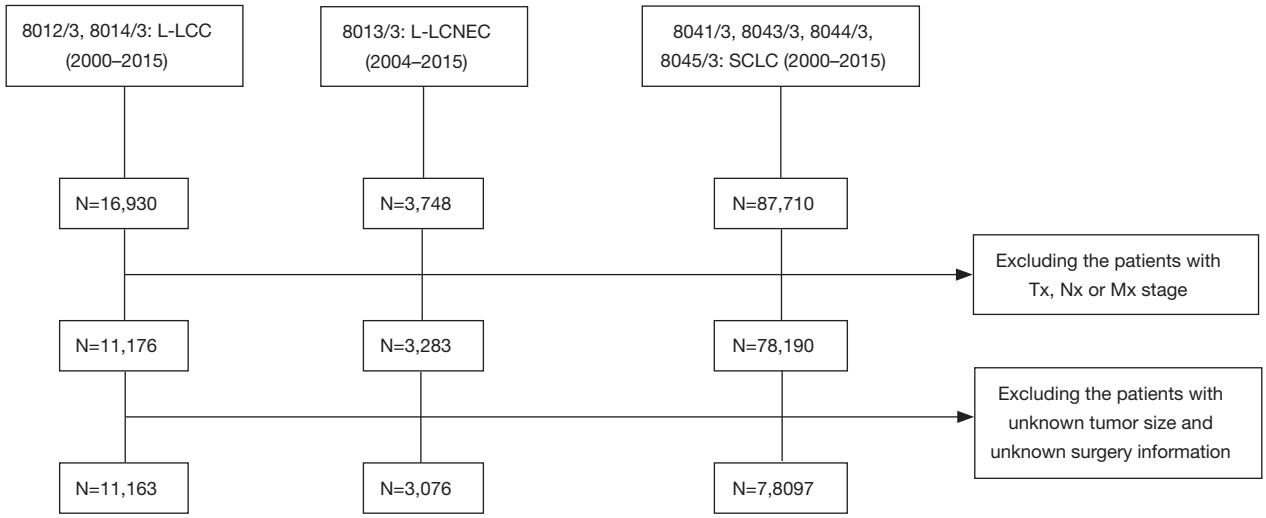

Figure 1 The flow chart of the patients selection.

site and laterality between L-LCNEC and L-LCC and also in origin record NHIA between L-LCNEC and SCLC, respectively. L-LCNEC patients were at younger ages than those with L-LCC or SCLC (all P<0.001). Male patients occupied a larger proportion in L-LCNEC than SCLC (P<0.001), but smaller than L-LCC (P=0.001). White patients with LCNEC had a greater proportion than those with L-LCC (P=0.002), but had a smaller proportion than those with SCLC (P<0.001). More L-LCNEC patients were living without a spouse than L-LCC (P=0.002) and SCLC patients (P=0.048). Compared with SCLC, L-LCNEC and L-LCC were more likely to occur in the upper lobe and unilateral lung (all P<0.001). More L-LCNEC were at relatively early stage than L-LCC (P<0.001), while the vast majority of SCLC were at advanced stage (P<0.001). More L-LCNEC patients received active treatment than L-LCC and SCLC patients (all P<0.001).

Patient survival

The median survival times of L-LCNEC, L-LCC, and SCLC patients were 12, 9, and 7 months, respectively. In general, before PSM, the 5-year OS rate was 20.2% of L-LCNEC, 15.8% of L-LCC, and 5.4% of SCLC patients. L-LCNEC patients had better survival than L-LCC and SCLC patients, and the latter had the poorest prognosis (*Figure 2A*; P<0.001). After matching, survival of L-LCNEC patients was close to that of L-LCC, but better than that of SCLC patients (*Figure 2B*; P<0.001).

The L-LCNEC patients were randomly divided into two groups, and all the characteristics of the patients between the two groups were not significant (*Table 2*). For the patients with L-LCNEC in the training cohort, univariate analyses showed that the age, sex, SEER registry, tumor primary site, laterality, tumor grade, T classification, N classification, M classification, TNM stage, and treatment were the statistically significant predictors of OS (all P<0.05). No significance was found in aspects of race, marital status and origin record NHIA (all P≥0.05). Multivariate analyses identified age, sex, T classification, N classification, M classification, and treatment as the independent prognostic predictors for L-LCNEC (P<0.05; *Table 3*).

Nomogram model

Based on the independent predictors in the training cohort, a nomogram model was formulated for prediction of the prognosis of individual L-LCNEC patient (*Figure 3*). We subjectively set the maximum score of the point scale to 100. According to the hazard level related to the prognosis, each risk factor was set to a specific score. The nomogram illustrated that the factor of treatment was the largest contributor to prognosis of L-LCNEC, followed by the factor of M classification, N classification, age, T classification and sex. After adding up the scores for all risk factor of each patients, we could easily calculate the survival possibility at any time point. The calibration curves presented a preferable coherence between the predicted survival probability and actual survival rate

Table 1 The characteristics of L-LCNEC, L-LCC and SCLC patients before and after matching

Characteristics	L-LCNEC (n=3,076)	Before				After			
		L-LCC (n=11,163)	SCLC (n=78,097)	P1	P2	L-LCC (n=3,076)	SCLC (n=3,076)	P3	P4
Age (mean)	66.56	67.65	67.67	<0.001	<0.001	66.47	66.93	0.178	0.159
≤60	871	2,928	19,349	<0.001	<0.001	876	877	0.987	0.738
61-70	1,043	3,365	26,675			1,038	1,015		
>70	1,162	4,870	32,073			1,162	1,184		
Sex				0.001	<0.001			0.959	0.293
Male	1,691	6,505	39,812			1,693	1,732		
Female	1,385	4,658	38,285			1,383	1,344		
Race				0.002	<0.001			0.196	0.4
White	2,597	9,164	68,400			2556	2,600		
Black	351	1,543	6,719			397	330		
Others	128	456	2,978			123	146		
Origin record NHIA				0.516	0.409			0.143	0.38
NSHL	2,936	10,685	74,782			2,959	2,950		
SHL	140	478	3,315			117	126		
Marital status				0.002	0.048			0.006	0.6
Unmarried	421	1,289	9,529			352	377		
Married	2,536	9,485	65,489			2,628	2,551		
Unknown	119	389	3079			96	148		
SEER registry				<0.001	0.001			<0.001	0.072
Eastern	1,833	6,393	44,177			1,979	1,902		
Western	1,243	4,770	34,920			1,097	1,174		
Primary site				0.255	<0.001			0.273	<0.001
Upper lobe	1,810	6,697	38,879			1880	1643		
Middle lobe	128	521	3,438			146	144		
Lower lobe	823	2,794	17,019			773	806		
Overlapping lesions	37	171	1,392			40	49		
Lung, NOS	268	980	17,369			237	434		
Laterality				0.939	<0.001			1	<0.001
One site	3,010	10,926	72,706			3,010	2,955		
Paired sites	66	237	5,391			66	121		
TNM stage				<0.001	<0.001			0.957	0.999
I	739	1,904	2,873			725	741		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	L-LCNEC (n=3,076)	Before				After			
		L-LCC (n=11,163)	SCLC (n=78,097)	P1	P2	L-LCC (n=3,076)	SCLC (n=3,076)	P3	P4
II	342	1,171	2,160			353	338		
III	687	3,766	21,652			690	689		
IV	1,308	4,322	51,412			1,308	1,308		
Treatment				<0.001	<0.001			0.997	0.517
No treatment	446	2,363	18,891			445	540		
Surgery alone	760	2,261	763			761	697		
RT alone	258	1,643	4,734			258	278		
CT alone	412	1,189	23,186			412	454		
Surgery + RT	49	260	90			49	44		
Surgery + CT	327	470	786			313	327		
RT + CT	658	2,519	28,814			659	658		
Surgery + CT + RT	166	458	833			179	178		

(*Figure 4A*,*B*,*C*). The C-index of the nomogram model was 0.775 (95% CI: 0.786–0.764), indicating a strong predictive value of this model. We performed an internal validation of the nomogram model by using the validation cohort. The calibration curves showed a good coherence (*Figure 4D*,*E*,*F*). The C-index was 0.785 (95% CI: 0.765–0.805).

Furthermore, we also validated the nomogram model by using the cohort in our department (n=112). There were 73 male patients and 39 female patients. All of them received the surgical treatment. Among them, 43 patients received adjuvant chemotherapy. The mean overall survival time was 37.2 months. The factors of age, sex, T stage, N stage and M stage were included to validate the nomogram model (*Table 4*). The calibration curves also showed an acceptable coherence (*Figure 4G*,*H*,*I*). The C-index was also great for the nomogram prediction (0.742, 95% CI: 0.679–0.806).

Based on the total risk scores, we subjectively classified all primary cohort as five subgroups (≤50, 50–100, 100–150, 150–200, and >200), and the survival differences of these groups were evaluated (*Table 5*). Each group represented a distinct prognosis. The higher the score, the worse the prognosis (*Figure 5*). Furthermore, we analyzed the risk subgroup stratification within each TNM stage and the results exhibited significant distinctions of OS (all P<0.001; *Figure 6*).

Discussion

In the present study, we compared the characteristics and survival of L-LCNEC with that of L-LCC and SCLC. There were some differences between L-LCNEC and L-LCC and between L-CNEC and SCLC regarding age, gender, race, tumor differentiation, TNM stage, RNE, surgery, chemotherapy, and radiotherapy rates. We showed that the survival of L-LCNEC was close to that of L-LCC rather than SCLC. Furthermore, we established a nomogram model to predict the prognosis of the patients with L-LCNEC. Lung neuroendocrine tumors are regarded as a unique classification of lung cancer, which can be further classified into four subtypes of SCLC, LCNEC, typical carcinoid, and atypical carcinoid according to the morphology (3). Among them, SCLC and L-LCNEC are considered to be high-grade neuroendocrine tumors. Although L-LCNEC and SCLC share some similar biological characteristics, such as expression of neuroendocrine markers (11) and genetic alterations (12), there are still some differences between the two subtypes of lung cancers in genomic profiles (13)

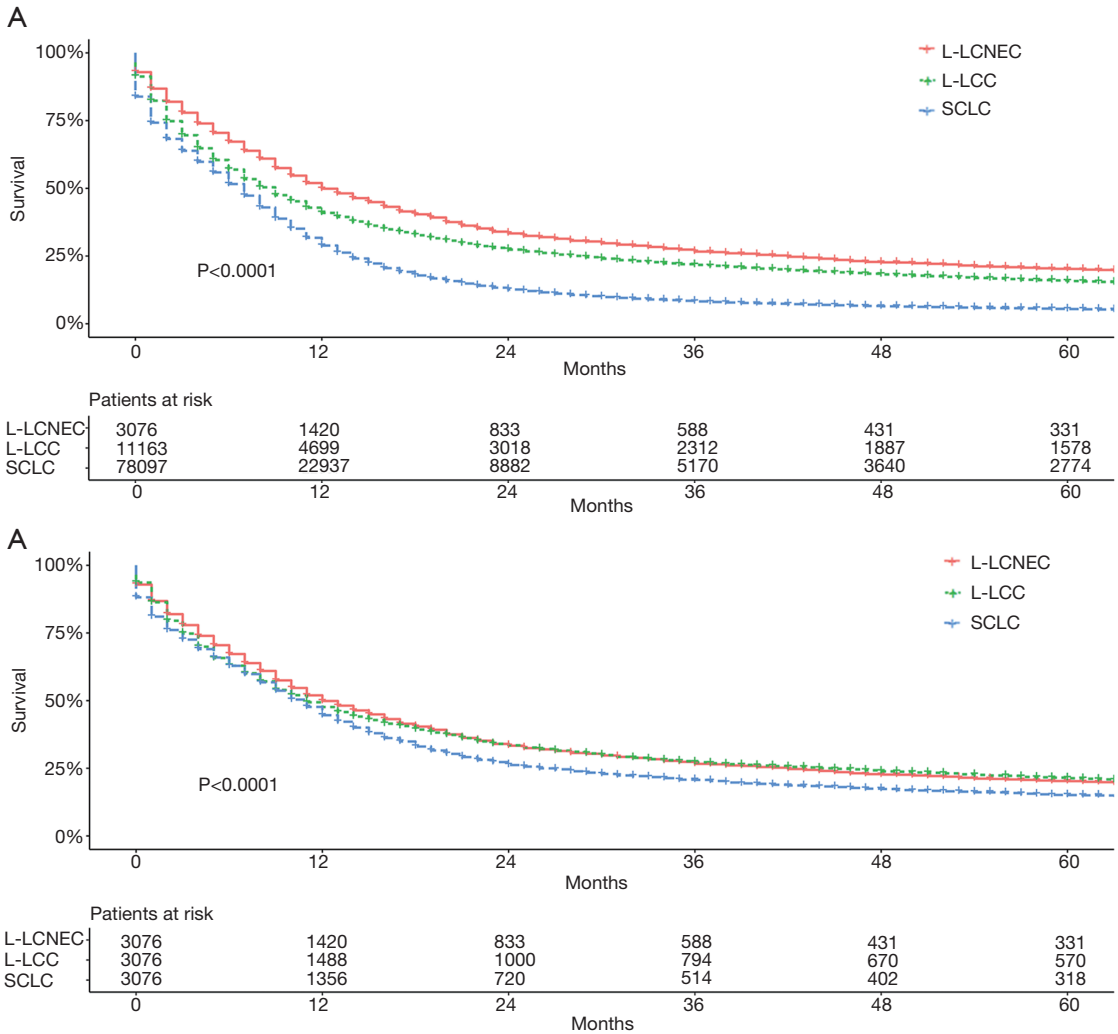

Figure 2 The overall survival of patients with L-LCNEC, L-LCC and SCLC were estimated by Kaplan-Meier analyses and log-rank tests. (A) Before matching; (B) After matching.

and the expression of other makers such as E-cadherin and CK7 (9). Therefore, whether L-LCNEC should be categorized as classic L-LCC or SCLC remains controversial. Varlotto *et al.* (14) compared the OS and cause-specific survival (CSS) of L-LCNEC with L-LCC and SCLC, revealing that the survival of L-LCNEC was close to other L-LCC and superior to SCLC. Moreover, they found L-LCNEC was more similar to L-LCC than to SCLC in aspects of the clinical, histopathological, and biological features. Similarly, Sun and associates (15) showed that L-LCNEC had a poor survival and observed no significant difference compared with classic L-LCC. In a small cohort study, the patients with L-LCNEC were more likely to receive open thoracotomy than those with L-LLC. Postoperative adjuvant treatment was not associated to the histologic subtypes (15). Isaka *et al.* (16) suggested that better prognoses were observed in L-LCNEC patients than SCLC patients with small-size tumors (maximum diameter of 3.0 cm), but they did not investigate the larger size tumors. However, studies reported that L-LCNEC had poorer prognosis than L-LCC but similar to SCLC, even in early stages (4-6,17-20).

This study identified the age, gender, T, N, M classification, and treatment were independent prognostic predictors for L-LCNEC. Male patients had poor prognosis probably because of a preponderance of male smokers. We showed that the treatment strategy was an independent predictor for the prognoses of L-LCNEC patients. Patients

Table 2 The characteristics of the patients in the training group and validation group

Variables	Training set	Validation set	P value
Age (year)			0.608
≤60	701	170	
61-70	824	219	
>70	936	226	
Sex			0.792
Male	1,350	341	
Female	1,111	274	
Race			0.609
White	2,082	515	
Black	281	70	
Others	98	30	
Origin record NHIA			0.194
NSHL	106	34	
SHL	2,355	581	
Marital status			0.223
Married	324	97	
Unmarried	2,043	493	
Unknown	94	25	
SEER registry			0.436
Eastern	1,475	358	
Western	986	257	
Primary Site			0.333
Upper lobe	1,469	341	
Middle lobe	107	31	
Lower lobe	651	172	
Overlapping lesion	29	8	
Lung, NOS	205	63	
Laterality			0.237
One site	2,412	698	
Paired site	49	17	
Grade			0.921
I	8	3	
II	40	8	
III	930	227	
IV	292	76	
Unknown	1,191	301	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Training set	Validation set	P value
T classification			0.996
T1	699	175	
T2	599	147	
T3	406	103	
T4	757	190	
N classification			0.433
N0	1,129	277	
N1	250	59	
N2	797	193	
N3	285	86	
M classification			0.617
M0	1,420	348	
M1	1,041	267	
TNM stage			0.757
I	589	150	
II	281	61	
III	550	137	
IV	1,041	267	
Treatment			0.773
No treatment	348	98	
Surgery alone	609	151	
RT alone	204	54	
CT alone	341	71	
Surgery + RT	39	10	
Surgery + CT	259	68	
RT + CT	524	134	
Surgery + RT + CT	137	29	

Table 3 Univariate and multivariate analyses of overall survival for L-LCNEC patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (year)			<0.001			<0.001
≤60	Reference			Reference	Reference	
61-70	1.156	1.037–1.288	0.009	1.22	1.078–1.381	0.002
>70	1.541	1.390–1.709	<0.001	1.484	1.315–1.675	<0.001
Sex						
Male	Reference			Reference	Reference	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Female	0.805	0.741–0.875	<0.001	0.8	0.727–0.879	<0.001
Race			0.479			
White	Reference					
Black	0.925	0.811–1.055	0.246			
Others	0.954	0.773–1.177	0.661			
Origin record NHIA						
NSHL	Reference					
SHL	1.202	0.978–1.476	0.08			
Marital status			0.018			
Married	Reference					
Unmarried	0.847	0.751–0.955	0.007			
Unknown	0.792	0.619–1.014	0.064			
SEER registry						
Eastern	Reference					
Western	1.15	1.058–1.250	0.001			
Primary Site			<0.001			
Upper lobe	Reference					
Middle lobe	1.113	0.915–1.353	0.285			
Lower lobe	1.063	0.965–1.171	0.219			
Overlapping lesion	1.472	1.019–2.128	0.04			
Lung, NOS	2.172	1.893–2.492	<0.001			
Laterality						
One site	Reference					
Paired site	1.685	1.304–2.178	<0.001			
Grade			<0.001			
I	Reference					
II	0.891	0.389–2.040	0.785			
III	1.199	0.569–2.523	0.633			
IV	1.354	0.639–2.867	0.429			
Unknown	2.057	0.978–4.325	0.057			
T classification			<0.001			<0.001
T1	Reference			Reference	Reference	
T2	1.201	1.065–1.356	0.003	1.028	0.894–1.182	0.697
T3	1.768	1.552–2.015	<0.001	1.325	1.136–1.545	<0.001
T4	2.7	2.420–3.013	<0.001	1.428	1.242–1.641	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
N classification			<0.001			<0.001
N0	Reference			Reference	Reference	
N1	1.504	1.299–1.740	<0.001	1.466	1.234–1.742	<0.001
N2	2.503	2.272–2.757	<0.001	1.527	1.340–1.740	<0.001
N3	3.553	3.119–4.048	<0.001	2.01	1.692–2.387	<0.001
M classification						
M0	Reference			Reference	Reference	
M1	3.68	3.370–4.017	<0.001	2.104	1.867–2.372	<0.001
TNM stage			<0.001			
I	Reference					
II	1.286	1.083–1.528	0.004			
III	2.363	2.069–2.699	<0.001			
IV	5.495	4.868–6.203	<0.001			
Treatment			<0.001			<0.001
No treatment	Reference			Reference	Reference	
Surgery alone	0.119	0.103–0.137	<0.001	0.249	0.206–0.302	<0.001
RT alone	0.562	0.478–0.661	<0.001	0.619	0.514–0.745	<0.001
CT alone	0.441	0.382–0.508	<0.001	0.345	0.292–0.408	<0.001
Surgery + RT	0.197	0.140–0.278	<0.001	0.403	0.275–0.589	<0.001
Surgery + CT	0.086	0.070–0.104	<0.001	0.148	0.117–0.189	<0.001
RT + CT	0.315	0.277–0.360	<0.001	0.289	0.247–0.338	<0.001
Surgery + RT + CT	0.136	0.109–0.169	<0.001	0.189	0.145–0.247	<0.001

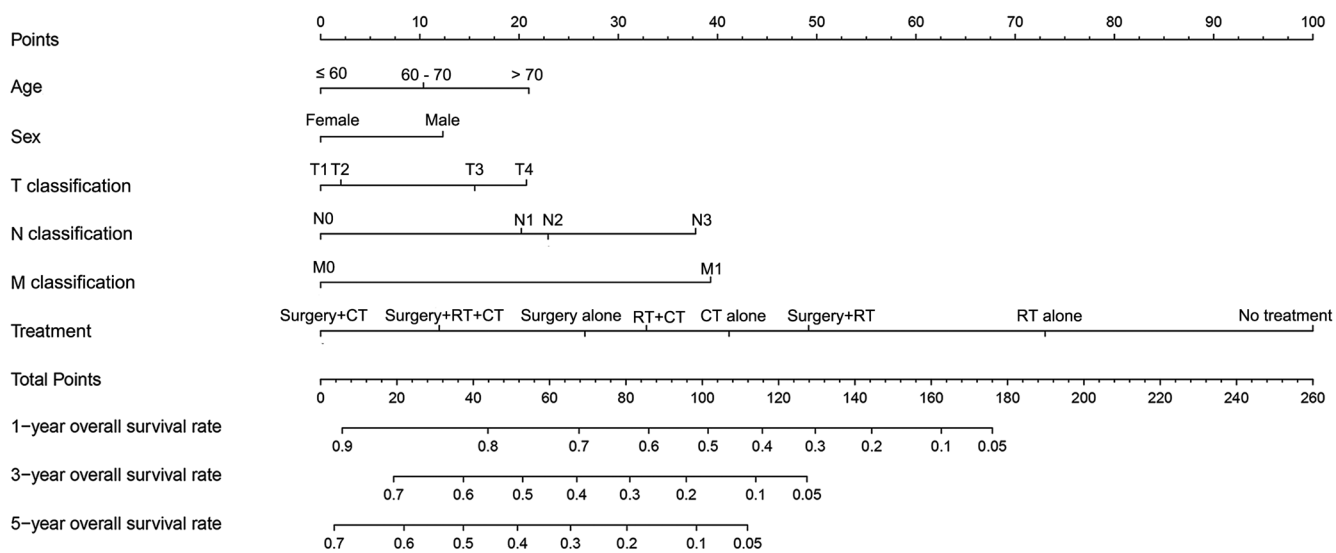

Figure 3 Nomogram to predict 1-, 3-, and 5-year overall survival of patients with L-LCNEC.

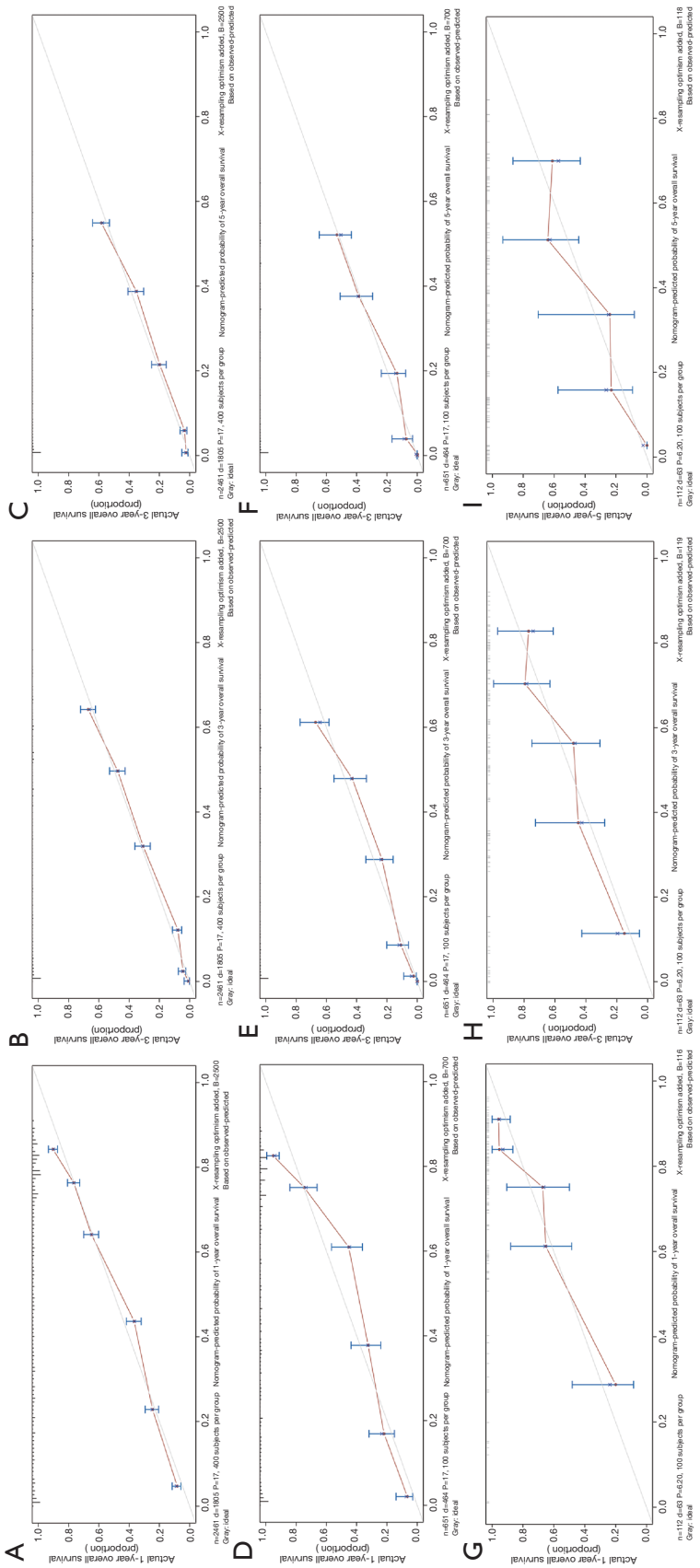

Figure 4 Calibration plots of the nomogram prediction of 1-, 3-, and 5-year overall survival of the primary cohort patients (A, B, C), internal validation cohort (D, E, F) and external validation cohort (G, H, I).

Table 4 The characteristics of the patients with L-LCNEC in external validation cohort

Characteristics	No. (n=112)
Age (year)	
≤60	39
61–70	35
>70	38
Sex	
Male	73
Female	39
T classification	
T1	49
T2	37
T3	17
T4	9
N classification	
N0	80
N1	15
N2	17
N3	0
M classification	
M0	108
M1	4
TNM stage	
I	38
II	44
III	26
IV	4
Treatment	
Surgery alone	69
Surgery + CT	43

who received no treatment had the highest scores in the nomogram model, indicating that these patients had poorest survival. At present, surgical treatment remained the main curative option for L-LCNEC, but surgery alone may be not enough, even in the early stages (21). L-LCNEC patients could benefit from adjuvant chemotherapy. It was reported that surgery plus chemotherapy showed survival benefit over surgery alone for L-LCNEC patients (21-23). However, the role of radiotherapy in L-LCNEC remained unclear because of the lack of prospective studies (24-26). For the L-LCNEC patients treated with nonoperative treatment, survival were dismal (23,27). Derks *et al.* (28) showed that patients with metastatic LCNEC receiving platinum/gemcitabine have a better OS than those receiving a longer overall survival than those receiving SCLC-oriented chemotherapy. The response rate to platinum-based neoadjuvant chemotherapy was high in LCNEC (29). However, the chemotherapy efficacy was poor in clinic. Tyrosine kinase inhibitors have clinically significant effect in NSCLC harboring EGFR mutations. But EGFR mutations were rarely found in LCNEC. Aroldi *et al.* (30) report a L-LCNEC patient with EGFR mutations was response well to gefitinib. In the present study, surgery combined with adjuvant chemotherapy achieved better results than other treatment approaches in terms of survival for patients with L-LCNEC.

This study developed a nomogram model to predict the survival probability of individual L-LCNEC patients. This is the first nomogram model to our knowledge reported for the L-LCNEC patients based on a large clinical database, with long-term follow-up. In our nomogram model, the characteristics of the patients with L-LCNEC, including advanced age, male, higher T, N, M classification and non-treatment, acquired higher points indicating less probability of OS. Calibration curves presented preferable coherence between the predicted survival probability and actual

Table 5 The 1-, 3-, 5-year survival rate of stratified risk groups

Total prognostic scores	No.	MST (month)	1-year overall survival rate (%)	3-year overall survival rate (%)	5-year overall survival rate (%)
≤50	616	61	86.2	60.2	50.6
50–100	689	20	66.6	34.5	23.2
100–150	685	8	30.3	5.7	2.7
150–200	367	2	10.8	1.3	0.0
>200	104	1	3.1	0	0

MST, median survival time.

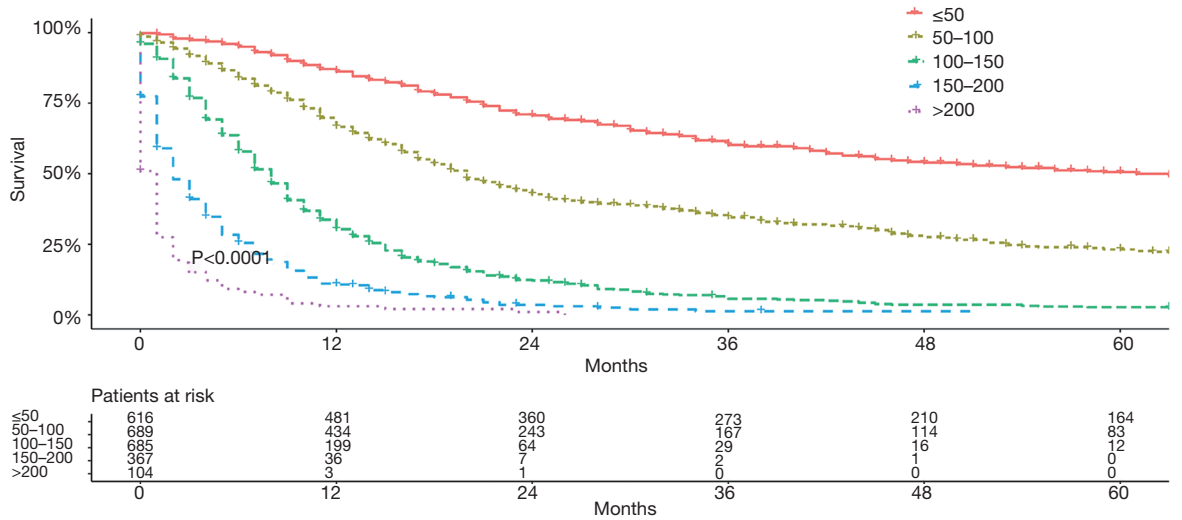

Figure 5 The overall survival of patients with L-LCNEC were analyzed by dividing five subgroups according to the prognostic scores.

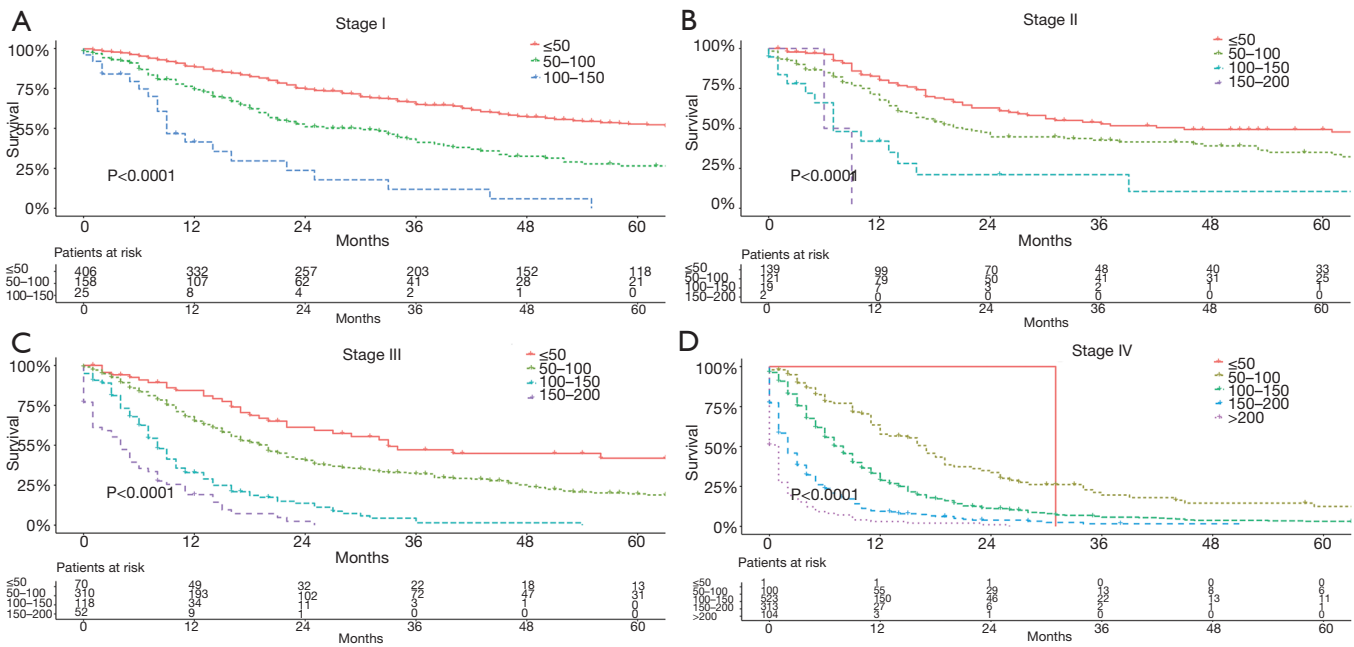

Figure 6 Risk groups stratification within each TNM stage were analyzed by Kaplan-Meier analyses and log-rank tests.

survival rate, indicating the model had satisfied feasibility and reliability. In this nomogram model, the C-index was 0.775, exhibiting a sufficient level of discrimination. Moreover, we performed the internal and external validation of the nomogram model and demonstrated its the reliability. Hence, we believe that both clinicians and patients could predict an individual survival according to this model.

The most important limitation of this study derived from the failure to incorporate more potential prognostic factors. The clinical data were obtained from the SEER database, and many parameters were not recorded or incomplete. Therefore, some important characteristics, such as vascular invasion and peri-neural invasion, and some important molecular factors, such as epidermal growth factor receptor mutations, were not included in the analyses. Further efforts incorporating more factors should be made to improve this

nomogram model.

Conclusions

L-LCNEC had distinct clinical characteristics from L-LCC and SCLC. The L-LCNEC patients have similar survival with L-LCC patients, but significantly better than SCLC patients. The nomogram model we established demonstrated its prediction capability and could help clinicians more precisely estimate the survival rate of individual patient with L-LCNEC.

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Footnote

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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 research containing the data from SEER database was not required ethical approval. For the external validation cohort, the written informed consent was exempted by the Ethics Committee of Zhongshan Hospital, Fudan University for this retrospective study.

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