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ORIGINAL RESEARCH

Nomograms Predict PFS and OS for SCLC Patients After Standardized Treatment: A Real-World Study

Ke Li[1,2,*], Lupeng Qiu[1,2,*], Yang Zhao[3,*], Xiaohui Sun[1,2], Jiakang Shao[1], Chang He[1,2], Boyu Qin[4], Shunchang Jiao[4]

[1]Medical School of Chinese PLA, Beijing, 100853, People's Republic of China; [2]Department of Oncology, The First Medical Center of Chinese PLA General Hospital, Beijing, 100853, People's Republic of China; [3]Department of Vascular Intervention, Special Medical Center for Strategic Support Forces, Beijing, 100101, People's Republic of China; [4]Department of Oncology, The Fifth Medical Center of Chinese PLA General Hospital, Beijing, 100071, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shunchang Jiao; Boyu Qin, Department of Oncology, The Fifth Medical Center of Chinese PLA General Hospital, 8 Dongdajie Street, Fengtai District, Beijing, 100071, People's Republic of China, Email jiaosc@vip.sina.com; qpm2017@126.com

Purpose: This study aims to investigate the process of small cell lung cancer (SCLC) patients from achieving optimal efficacy to experiencing disease progression until death. It examines the predictive value of the treatment response on progression free survival (PFS) and overall survival (OS) of SCLC patients.

Patients and Methods: We conducted a retrospective analysis on 136 SCLC patients diagnosed from 1992 to 2018. Important prognostic factors were identified to construct nomogram models. The predictive performance of the models was evaluated using the receiver operating characteristic curves and calibration curves. Survival differences between groups were compared using Kaplan–Meier survival curves. Subsequently, an independent cohort consisting of 106 SCLC patients diagnosed from 2014 to 2021 was used for validation.

Results: We constructed two nomograms to predict first-line PFS (PFS1) and OS of SCLC. The area under the receiver operating characteristic curves for the PFS1 nomogram predicting PFS at 3-, 6-, and 12-months were 0.919 (95% CI: 0.867–0.970), 0.908 (95% CI: 0.860–0.956) and 0.878 (95% CI: 0.798–0.958), and for the OS nomogram predicting OS at 6-, 12-, and 24-months were 0.814 (95% CI: 0.736–0.892), 0.819 (95% CI: 0.749–0.889) and 0.809 (95% CI: 0.678–0.941), indicating those two models with a high discriminative ability. The calibration curves demonstrated the models had a high degree of consistency between predicted and observed values. According to the risk scores, patients were divided into high-risk and low-risk groups, showing a significant difference in survival rate. And these findings were validated in another independent validation cohort.

Conclusion: Based on the patients' treatment response after standardized treatment, we developed and validated two nomogram models to predict PFS1 and OS of SCLC. The models demonstrated good accuracy, reliability and clinical applicability by validating in an independent cohort.

Keywords: small cell lung cancer, treatment response, patient prognosis, nomogram prognostic model

Introduction

Small cell lung cancer (SCLC) is a highly malignant and rapidly progressing type of cancer with limited treatment options.[1] Currently, the standard treatment regimen[2] still relies on chemotherapy with etoposide and cisplatin (EP) or etoposide and carboplatin (EC), which is applicable as first-line therapy for limited stage small cell lung cancer (LS-SCLC) and extensive stage small cell lung cancer (ES-SCLC). On this basis, the progress has mainly focused on the improvement of radiotherapy methods for LS-SCLC and the combination of immunotherapy and chemotherapy for ES-SCLC.[3] However, the intratumor heterogeneity (ITH)[4,5] leads to significantly different prognosis among different patients. In clinical practice, individualized risk assessment is crucial for patients and can assist clinicians in developing subsequent treatment plans.

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Currently, there is a focus on identifying specific biomarkers and developing prognostic prediction models to predict the outcomes of SCLC. Biomarkers are typically analyzed based on clinical features,[6] pathological subtypes,[7] peripheral blood tests,[8] and imaging findings,[9] but SCLC exhibits complex biological behaviors that is difficult to predict using a single factor. Statistical prediction models, such as nomogram models, are widely used to predict patient outcomes. A nomogram model is a visual statistical prediction model that can predict the probability of specific events, such as tumor recurrence or death.[10] Its main advantage is that it can integrate various patient characteristics and tumor features to estimate the individualized risk of clinical events, thus achieving personalized medical care.[11] Nomogram models have also been widely used in prognostic studies of SCLC. Although the nomogram models based on the database had a large sample size, which ensure the universality of the model in clinical application, the candidate variables in the database are limited, often only including basic information such as gender, age, race, and marital and childbearing status.[12] Treatment status was often simplified as baseline variable without considering specific treatment regimens, treatment application times, and tumor progression. Therefore, researchers often considered treatment as a baseline variable when establishing predictive models based on databases. They could only assume that the specific treatment combination was determined at the time of diagnosis, which did not correspond to the actual clinical practice.[13] Other established nomogram models based on real-world data also did not include specific treatment regimens, treatment efficacy, disease progression, and other factors as candidate variables.[14]

This study aims to investigate the random process of SCLC patients from achieving optimal efficacy to developing disease progression until death after receiving treatment. Understanding the initial response and subsequent development of SCLC after treatment and exploring the underlying patterns are crucial to identify valuable prognostic indicators.[15] In combination with patient clinical characteristics and relevant laboratory tests, SCLC prognostic nomogram models were constructed, evaluated, and validated. These models can provide reference for predicting patient outcomes and selecting treatment plans, and then help to improve patient treatment efficacy, improve their quality of life, and prolong their survival.

Objects and Methods

Study Population

A retrospective analysis was conducted on SCLC patients who were diagnosed, treated, and had complete treatment and death records at the Chinese PLA General Hospital from 1992 to 2018. Inclusion criteria: (1) Pathologically confirmed diagnosis of SCLC;[16] (2) Complete treatment process and death records available in the hospital's case system. Exclusion criteria: (1) Patients with concurrent benign or malignant tumors in other sites; (2) Patients with other pathological subtypes of lung tumors;[17] (3) Patients without a pathological diagnosis or with an unclear pathological diagnosis before the first line chemotherapy. A total of 136 patients were included in the training cohort (Figure 1). In addition, 106 patients diagnosed with SCLC between 2014 and 2021 were included as a separate validation cohort. This study was a retrospective analysis of clinical practice and did not collect patients' informed consent forms. The study was approved by the Ethics Committee of the Chinese PLA General Hospital (S2022-158-01) and conformed to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study Methods

Clinical data of the patients, including gender, age at diagnosis, diagnosis time, Karnofsky Performance Status (KPS), body surface area, symptoms and signs,[18,19] metastatic sites, Veteran's Administration Lung Cancer Study Group (VALG) staging,[20] International Association for the Study of Lung Cancer (IASLC) staging, comorbidities, age-adjusted Charlson comorbidity index (aCCI),[21] smoking status, alcohol consumption, and family history of tumors were collected from the electronic medical record system of the Chinese PLA General Hospital. Peripheral blood test results within 1 week prior to first-line treatment, including lactate dehydrogenase (LDH),[22] serum sodium, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red cell distribution width (RDW), and tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), cytokeratin 19 fragment (CYFRA21-1), neuron specific enolase (NSE), squamous cell carcinoma (SCC) and pro-gastrin-releasing peptide (proGRP)[23] were included. Treatment status, including surgery, radiotherapy, and chemotherapy status (start and end dates, chemotherapy regimens, and number of

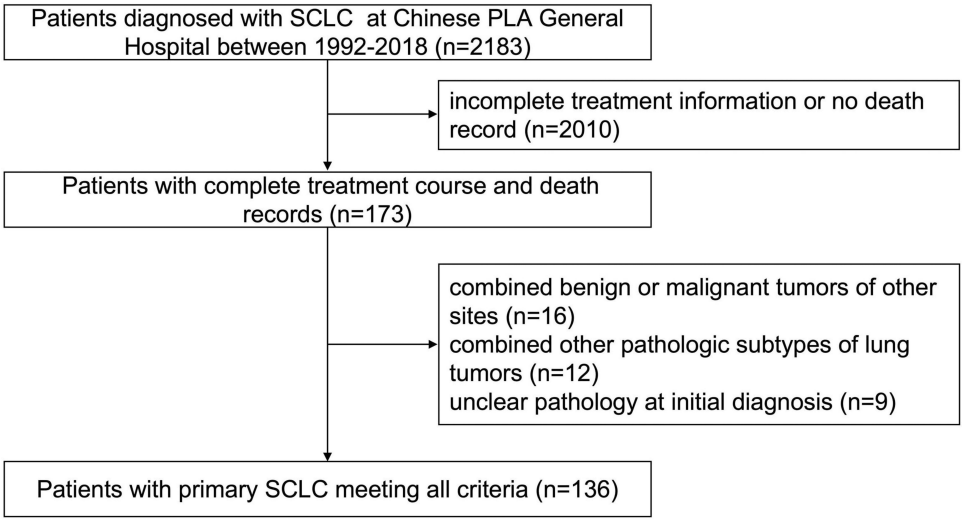

Figure 1 Selection flowchart for SCLC patients in the training cohort.

cycles), as well as treatment response such as first-line optimal efficacy, date of optimal efficacy, date of progression, and date of death were also collected. Four additional variables were derived from the detailed treatment information: time to optimal efficacy, duration of optimal efficacy, duration of first-line treatment, and chemotherapy-free interval (CFI).

Response to treatment was evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).[24] The treatment response was described based on the number and size changes of lesions as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The optimal treatment efficacy achieved throughout the treatment course was recorded as the "optimal efficacy", and the time from the start of treatment until the appearance of the optimal efficacy was recorded as the "time to optimal efficacy". The "duration of optimal efficacy" was recorded as the time from the appearance of the optimal efficacy to tumor progression. The duration from the initiation of first-line chemotherapy to the completion was defined as the "duration of first-line treatment", while the interval between the completion of first-line chemotherapy and the initiation of second-line chemotherapy was defined as "CFI". Overall survival (OS) referred to the time from the patient's pathological diagnosis to death from any cause, while first-line progression-free survival (PFS1) referred to the time from the initiation of first-line treatment to tumor progression or death from any cause.

As the treatment process and disease outcomes of the included patients were fully documented, there was no telephone, outpatient, or inpatient follow-up conducted for the patients.

Statistical Methods

SPSS 26.0 statistical software was used to conduct basic information statistics and describe patients' baseline characteristics. We used univariate and multivariate Cox regression analysis to explore the factors influencing PFS1 and OS in SCLC patients. Based on the results of the multivariable analysis, R software (version 4.1.0) was used to construct nomogram prediction models for PFS1 and OS in SCLC patients who received standard treatment. The accuracy of the nomogram models was evaluated using the area under the curve (AUC)[25] of the receiver operating characteristic (ROC) curve. Calibration curves were plotted to evaluate the consistency between the predicted and actual survival rates.[10] The patients were then grouped according to their risk scores, and the survival differences between groups were compared using Kaplan–Meier survival curves. Finally, external validation of the models was performed by including patients in the validation cohort. Statistical significance was defined as $p<0.05$.

Results

Baseline Characteristics of Patients

In the training cohort, males (118/136, 86.8%) were the majority.[26] The median age at diagnosis was 67.5 years, with a wide range of ages (22–89 years), and 10 patients (7.4%) were aged 80 years or older. Most patients had

a history of smoking (99/136, 72.8%).[27] The KPS scores at initial diagnosis were mainly ≥90 (87/136, 64.0%), while only 13 cases (9.5%) had a score below 70. In terms of treatment, 8 patients (5.9%) underwent surgical treatment, and 6 patients (4.4%) did not receive any treatment. Among the patients who underwent systemic treatment, first-line treatment consisted of chemotherapy alone or combined with radiotherapy, without the use of immune checkpoint inhibitors (ICIs). Four cases (2.9%) of patients used ICIs in the second-line treatment, and 5 cases (3.7%) used ICIs in the backline treatment. The demographic characteristics of the patients in the validation cohort, such as gender and age distribution, were generally consistent with the training cohort. In terms of treatment, 3 patients (2.8%) in the validation cohort underwent surgical treatment, while 43 patients (40.6%) received ICIs in the first-line, as 32 patients (30.2%) received ICIs in the second-line, and 31 patients (29.2%) received ICIs in backlines. Detailed baseline characteristics were presented in Table 1.

Table 1 Baseline Characteristics of Patients in the Training and Validation Cohort

Characteristics		Training Cohort (n, %)	Validation Cohort (n, %)	P
No. of cases		136	106	
Period of diagnosis		1992–2018	2014–2021	
Gender				0.654
	Male	118 (86.8)	94 (88.7)	
	Female	18 (13.2)	12 (11.3)	
Age (years)				0.002
	<65	57 (41.9)	66 (62.3)	
	≥65	79 (58.1)	40 (37.7)	
Body surface area (m^2)				0.003
	≤1.73	59 (43.4)	32 (30.2)	
	>1.73	59 (43.4)	74 (69.8)	
	unknown	18 (13.2)	0 (0.0)	
KPS score				< 0.001
	≥90	87 (64.0)	92 (86.8)	
	70–80	36 (26.5)	14 (13.2)	
	<70	13 (9.5)	0 (0.0)	
Smoking status				0.417
	No	37 (27.2)	24 (22.6)	
	Yes	99 (72.8)	82 (77.4)	
Smoking index				0.185
	≤400	59 (43.4)	39 (36.8)	
	>400	70 (51.5)	66 (62.3)	
	unknown	7 (5.1)	1 (0.9)	
Alcohol consumption				0.058
	No	79 (58.1)	49 (46.2)	
	Yes	56 (41.2)	57 (53.8)	
	unknown	1 (0.7)	0 (0.0)	
Alcohol consumption (years)				0.512
	≤30	97 (71.3)	78 (73.6)	
	>30	30 (22.1)	27 (25.5)	
	unknown	9 (6.6)	1 (0.9)	
VALG stage				0.210
	LS	29 (21.3)	30 (28.3)	
	ES	107 (78.7)	76 (71.7)	

(*Continued*)

Table 1 (Continued).

Characteristics		Training Cohort (n, %)	Validation Cohort (n, %)	P
Lesion location				0.009
	Single lung lobe	107 (78.7)	89 (83.9)	
	Multiple lung lobes	6 (4.4)	11 (10.4)	
	Pulmonary hilar	23 (16.9)	6 (5.7)	
Liver metastasis				< 0.001
	No	103 (75.7)	59 (55.7)	
	Yes	33 (24.3)	47 (44.3)	
Bone metastasis				0.015
	No	102 (75.0)	64 (60.4)	
	Yes	34 (25.0)	42 (39.6)	
Brain metastasis				0.121
	No	119 (87.5)	85 (80.2)	
	Yes	17 (12.5)	21 (19.8)	
Hypertension				0.609
	No	89 (65.4)	66 (62.3)	
	Yes	47 (34.6)	40 (37.7)	
Diabetes				0.218
	No	116 (85.3)	84 (79.2)	
	Yes	20 (14.7)	22 (20.8)	
Coronary artery disease				0.823
	No	118 (86.8)	93 (87.7)	
	Yes	18 (13.2)	13 (12.3)	
Family history of lung cancer				0.296
	No	128 (94.1)	96 (90.6)	
	Yes	8 (5.9)	10 (9.4)	
Family history of other tumors				0.115
	No	117 (86.0)	83 (78.3)	
	Yes	19 (14.0)	23 (21.7)	
Surgery				0.258
	No	128 (94.1)	103 (97.2)	
	Yes	8 (5.9)	3 (2.8)	
First-line radiotherapy				0.026
	No	97 (71.3)	61 (57.5)	
	Yes	39 (28.7)	45 (42.5)	
First-line chemotherapy cycles				< 0.001
	<4	60 (44.1)	21 (19.8)	
	≥4	76 (55.9)	85 (80.2)	
Immunotherapy				< 0.001
	None	127 (93.4)	0 (0.0)	
	First-line	0 (0.0)	43 (40.6)	
	Second-line	4 (2.9)	32 (30.2)	
	Backline[a]	5 (3.7)	31 (29.2)	
First-line optimal efficacy				0.618
	CR	8 (5.9)	3 (2.8)	
	PR	74 (54.4)	68 (64.2)	
	SD	25 (18.4)	23 (21.7)	
	PD	13 (9.5)	11 (10.4)	
	unknown	16 (11.8)	1 (0.9)	

Notes: a: Third-line and subsequent line chemotherapy.

Abbreviations: KPS, Karnofsky Performance Status; VALG, Veteran's Administration Lung Cancer Study Group; LS, limited stage; ES, extensive stage; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Prognostic Factors Analysis for PFS1 and OS in the Training Cohort

Univariate and Multivariate Cox Analysis for PFS1 in the Training Cohort

A total of 129 patients in the training cohort were included in the analysis for PFS1. The results of the multivariate analysis showed that first-line radiotherapy (HR=0.223, 95% CI: 0.102–0.488, P < 0.001), first-line chemotherapy cycles (HR = 0.110, 95% CI: 0.041–0.290, P < 0.001), and NSE (HR = 3.246, 95% CI: 1.344–7.840, P = 0.009) were independent prognostic factors for PFS1 (Table 2).

Table 2 Univariate and Multivariate Cox Analysis for PFS1 in the Training Cohort

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	P	HR (95% CI)	P
KPS score					
	≥90	Reference		Reference	
	70–80	1.564 (1.048–2.335)	0.029	1.098 (0.524–2.300)	0.805
	<70	7.379 (3.434–15.857)	< 0.001	2.589 (0.463–14.488)	0.279
VALG stage					
	LS	Reference		Reference	
	ES	1.597 (1.038–2.456)	0.033	1.075 (0.396–2.919)	0.888
IASLC stage					
	LS	Reference		Reference	
	ES	1.454 (1.005–2.103)	0.047	1.117 (0.400–3.119)	0.832
lymph node metastasis[a]					
	No	Reference		Reference	
	Yes	1.431 (1.000–2.048)	0.050	0.621 (0.293–1.318)	0.215
Liver metastasis					
	No	Reference		Reference	
	Yes	2.148 (1.391– 3.317)	< 0.001	0.773 (0.308– 1.940)	0.584
Bone metastasis					
	No	Reference		Reference	
	Yes	1.703 (1.121–2.586)	0.012	1.666 (0.803–3.456)	0.171
First-line radiotherapy					
	No	Reference		Reference	
	Yes	0.256 (0.167–0.394)	< 0.001	0.223 (0.102–0.488)	< 0.001
chemotherapy regimen[b]					
	CE	Reference		Reference	
	PE	0.559 (0.363–0.860)	0.008	0.776 (0.409–1.472)	0.437
	Others	0.906 (0.577–1.423)	0.668	0.788 (0.317–1.961)	0.608
chemotherapy cycles[c]					
	<4	Reference		Reference	
	≥4	0.102 (0.063–0.164)	< 0.001	0.110 (0.041–0.290)	< 0.001
optimal efficacy[d]					
	CR	Reference		Reference	
	PR	0.947 (0.434–2.066)	0.891	0.444 (0.138–1.431)	0.174
	SD	2.874 (1.222–6.761)	0.016	1.019 (0.300–3.461)	0.976
	PD	19.835 (7.200–54.639)	< 0.001	3.786 (0.597–24.016)	0.158
LDH (U/L)					
	≤250	Reference		Reference	
	>250	1.666 (1.099–2.524)	0.016	1.511 (0.773–2.953)	0.227
NLR					
	≤2.97	Reference		Reference	
	>2.97	1.978 (1.351–2.894)	< 0.001	0.965 (0.535–1.740)	0.905

(*Continued*)

Table 2 (Continued).

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	P	HR (95% CI)	P
CEA (ug/L)					
	≤5.0	Reference		Reference	
	>5.0	1.568 (1.065–2.309)	0.023	1.472 (0.805–2.691)	0.209
NSE (ng/mL)					
	≤24	Reference		Reference	
	>24	2.093 (1.223–3.583)	0.007	3.246 (1.344–7.840)	0.009
Hypertension					
	No	Reference		Reference	
	Yes	1.812 (1.251–2.625)	0.002	1.833 (0.954–3.520)	0.069
Diabetes					
	No	Reference		Reference	
	Yes	1.789 (1.090–2.938)	0.021	0.807 (0.287–2.273)	0.685

Notes: a: Extra-mediastinal and extra-pulmonary hilar lymph node metastasis; b: First-line chemotherapy regimen; c: First-line chemotherapy cycles; d: First-line optimal efficacy.

Abbreviations: KPS, Karnofsky Performance Status; VALG, Veteran's Administration Lung Cancer Study Group; IASLC, International Association for the Study of Lung Cancer; LS, limited stage; ES, extensive stage; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron specific enolase.

Univariate and Multivariate Cox Analysis for OS in the Training Cohort

The results of the multivariate analysis showed that KPS score (HR = 42.168, 95% CI: 6.278–283.251, P < 0.001), VALG stage (HR = 3.324, 95% CI: 1.307–8.448, P = 0.012), First-line optimal efficacy (HR = 4.932, 95% CI: 1.387–17.541, P = 0.014), duration of optimal efficacy (HR = 0.394, 95% CI: 0.155–1.000, P = 0.049), CFI (HR = 2.710, 95% CI: 1.315–5.586, P=0.007), and NLR (HR = 3.170, 95% CI: 1.768–5.684, P < 0.001) were independent prognostic factors for OS (Table 3).

Table 3 Univariate and Multivariate Cox Analysis for OS in the Training Cohort

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	P	HR (95% CI)	P
KPS score					
	≥90	Reference		Reference	
	70–80	1.925 (1.289–2.872)	0.001	1.199 (0.611–2.351)	0.598
	<70	22.203 (10.705–46.051)	< 0.001	42.168 (6.278–283.251)	< 0.001
VALG stage					
	LS	Reference		Reference	
	ES	2.579 (1.667–3.989)	< 0.001	3.324 (1.307–8.448)	0.012
IASLC stage					
	LS	Reference		Reference	
	ES	2.093 (1.446–3.029)	< 0.001	0.838 (0.337–2.085)	0.704
lymph node metastasis[a]					
	No	Reference		Reference	
	Yes	1.421 (1.003–2.013)	0.048	1.161 (0.646–2.086)	0.617
Liver metastasis					
	No	Reference		Reference	
	Yes	2.869 (1.870–4.401)	< 0.001	1.564 (0.736–3.321)	0.245

(*Continued*)

Table 3 (Continued).

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	P	HR (95% CI)	P
Bone metastasis					
	No	Reference		Reference	
	Yes	2.182 (1.453–3.278)	< 0.001	1.675 (0.781–3.591)	0.185
First-line radiotherapy					
	No	Reference		Reference	
	Yes	0.481 (0.328–0.706)	< 0.001	0.714 (0.350–1.453)	0.352
chemotherapy cycles[b]					
	<4	Reference		Reference	
	≥4	0.321 (0.223–0.461)	< 0.001	1.828 (0.624–5.353)	0.271
optimal efficacy[c]					
	CR	Reference		Reference	
	PR	1.843 (0.843–4.030)	0.125	2.091 (0.673–6.495)	0.202
	SD	4.053 (1.711–9.598)	0.001	4.932 (1.387–17.541)	0.014
	PD	5.237 (2.051–13.369)	< 0.001	2.204 (0.386–12.582)	0.374
Duration of optimal efficacy (days)					
	≤84	Reference		Reference	
	>84	0.426 (0.294–0.618)	< 0.001	0.394 (0.155–1.000)	0.049
Duration of first-line treatment (days)					
	<77	Reference		Reference	
	≥77	0.406 (0.287–0.576)	< 0.001	0.671 (0.281–1.606)	0.371
CFI (days)					
	<45	Reference		Reference	
	≥45	0.592 (0.417–0.842)	0.003	2.710 (1.315–5.586)	0.007
PFS1 (days)					
	≤124	Reference		Reference	
	>124	0.376 (0.262–0.539)	< 0.001	0.690 (0.281–1.693)	0.418
Refractory recurrent type					
	No	Reference		Reference	
	Yes	2.869 (1.764–4.666)	< 0.001	1.315 (0.587–2.944)	0.506
LDH (U/L)					
	≤250	Reference		Reference	
	>250	2.351 (1.574–3.514)	< 0.001	1.272 (0.681–2.376)	0.450
NLR					
	≤2.97	Reference		Reference	
	>2.97	1.981 (1.379–2.845)	< 0.001	3.170 (1.768–5.684)	< 0.001
CEA (ug/L)					
	≤5.0	Reference		Reference	
	>5.0	1.459 (1.008–2.113)	0.045	0.820 (0.449–1.497)	0.518
CYFRA21-1 (ng/mL)					
	≤4.0	Reference		Reference	
	>4.0	1.913 (1.282–2.856)	0.001	1.593 (0.849–2.989)	0.147
aCCI					
	<8	Reference		Reference	
	≥8	1.742 (1.234–2.458)	0.002	0.642 (0.344–1.198)	0.164

Notes: a: Extra-mediastinal and extra-pulmonary hilar lymph node metastasis; b: First-line chemotherapy cycles; c: First-line optimal efficacy.
Abbreviations: KPS, Karnofsky Performance Status; VALG, Veteran's Administration Lung Cancer Study Group; IASLC, International Association for the Study of Lung Cancer; LS, limited stage; ES, extensive stage; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CFI, chemotherapy-free interval; PFS1, first-line progression free survival; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; CEA, carcinoembryonic antigen; CYFRA21-1, cytokeratin 19 fragment; aCCI, age-adjusted Charlson comorbidity index.

Establishment and Evaluation of the Nomogram Model in the Training Cohort

Establishment and Evaluation of the Nomogram Model for PFS1 in the Training Cohort

Based on the above analysis, NSE, first-line radiotherapy, and first-line chemotherapy cycles were ultimately included in the establishment of the nomogram model for PFS1 (Figure 2). Each variable was assigned a risk score ranging from 0 to 100. In the PFS1 nomogram model (Figure 2A), the score for first-line chemotherapy cycles had the highest weight, followed by first-line radiotherapy and NSE. Each patient could predict their corresponding tumor progression at 3 months, 6 months, and 12 months based on the PFS1 risk score. The higher the score, the worse the prognosis.

Based on the PFS1 risk score of each patient, the patients were divided into high- and low-risk groups using a median value of risk score (100.0). Kaplan–Meier survival curves showed significant differences in outcomes between different groups ($p < 0.001$, Figure 2B). AUC could be used to evaluate the discriminative ability of a model, meaning that the closer it was to 1, the better discriminative ability of the model. The AUC values (Figure 2C) for predicting progression at 3 months, 6 months, and 12 months were 0.919 (95% CI: 0.867–0.970, Sensitivity: 91.1%, Specificity: 86.9%), 0.908 (95% CI: 0.860–0.956, Sensitivity: 75.3%, Specificity: 88.9%), and 0.878 (95% CI: 0.798–0.958, Sensitivity: 77.0%, Specificity: 85.7%), indicating that the model had a good discriminative ability. Subsequently, the calibration curve indicated that the model's predictions of PFS1 (at 3 months, 6 months, and 12 months) were highly consistent with the actual outcomes, and the model had a good calibration (Figure 2D).

Establishment and Evaluation of the Nomogram Model for OS in the Training Cohort

KPS, VALG stage, first-line optimal efficacy, duration of optimal efficacy, CFI and NLR were ultimately included in the establishment of the nomogram model for OS. Figure 3 presented the nomogram prognostic model that was constructed. In the OS nomogram model (Figure 3A), the KPS score had the highest weightage, followed by the first-line optimal efficacy. Interestingly, the VALG stage and the duration of optimal efficacy had almost equal weights in predicting survival. Each patient could use the OS risk score to predict the corresponding 6-month, 12-month, and 24-month survival rates.

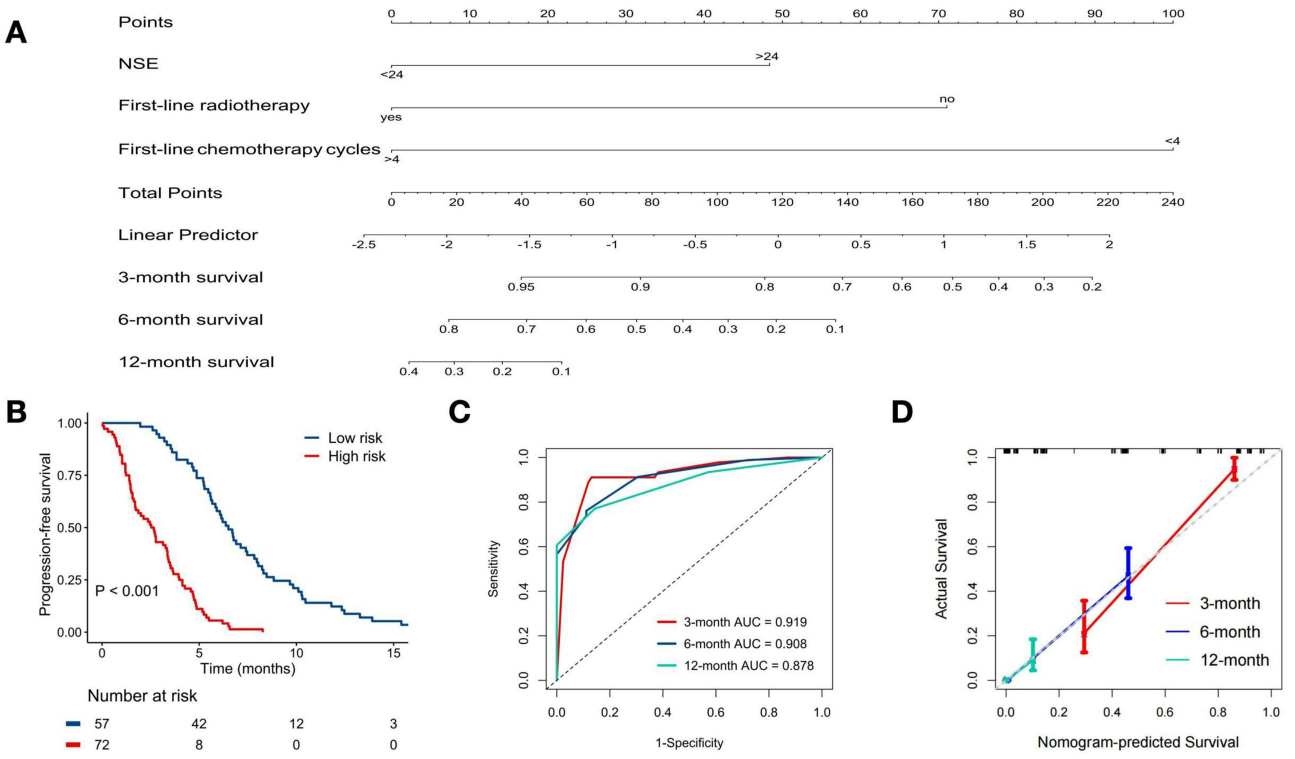

Figure 2 PFS1 nomogram of SCLC patients after standardized treatment and model assessment. (**A**) 3-, 6-, and 12-month PFS1 nomogram of SCLC patients after standardized treatment. (**B**) Kaplan–Meier curves using PFS1 risk scores. (**C**) ROC curves for the PFS1 model. (**D**) Calibration curves for the PFS1 model.

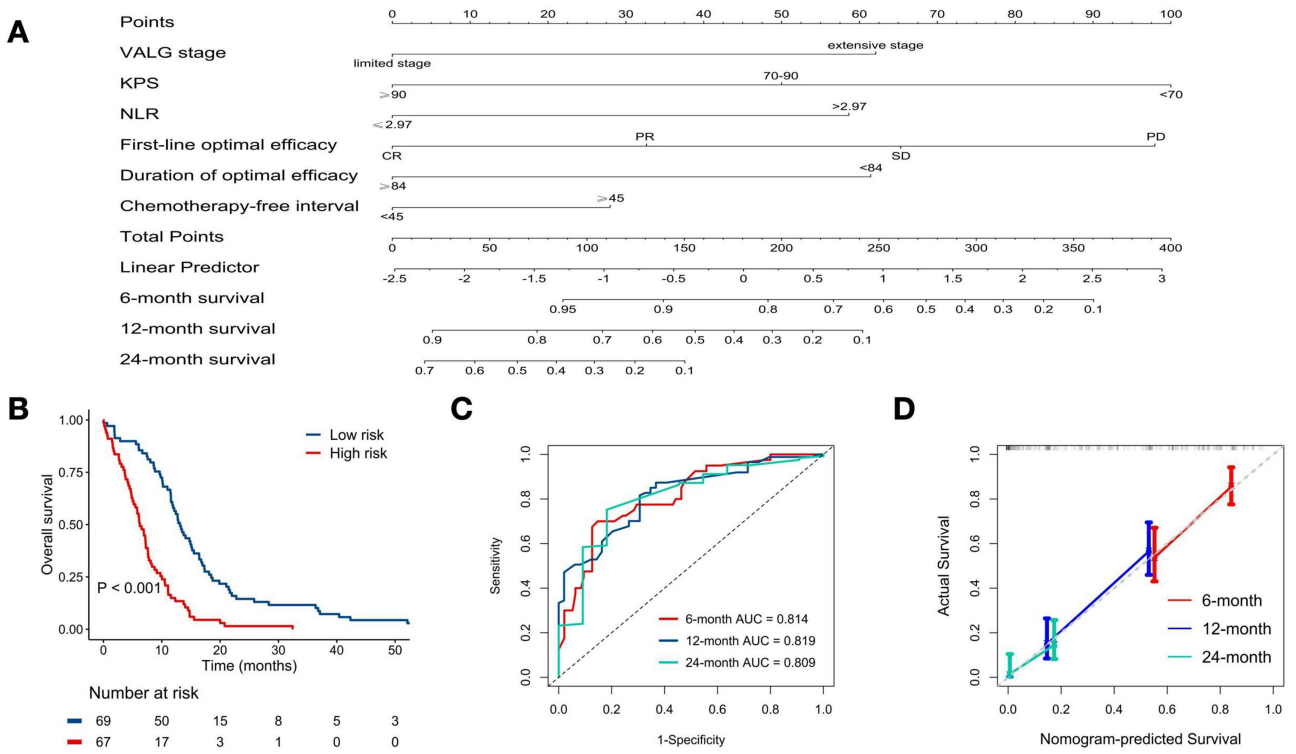

Figure 3 OS nomogram of SCLC patients after standardized treatment and model assessment. (**A**) 6-, 12-, and 24-month OS nomogram of SCLC patients after standardized treatment. (**B**) Kaplan–Meier curves using OS risk scores. (**C**) ROC curves for the OS model. (**D**) Calibration curves for the OS model.

Similarly, based on the OS risk score, patients were divided into high and low-risk groups using a median score of 172.7. The survival curves showed significant differences in prognosis between different groups ($p < 0.001$, Figure 3B). The AUC values (Figure 3C) for predicting survival at 6 months, 12 months, and 24 months were 0.814 (95% CI: 0.736–0.892, Sensitivity: 70.0%, Specificity: 85.1%), 0.819 (95% CI: 0.749–0.889, Sensitivity: 82.6%, Specificity: 69.4%), and 0.809 (95% CI: 0.678–0.941, Sensitivity: 75.8%, Specificity: 81.8%), indicating that the model had a good discriminative ability. The calibration curve of the model demonstrated a high consistency between the predicted OS (at 6, 12, and 24 months) and the actual OS, indicating good calibration of the model (Figure 3D).

Validation of the Nomogram Model in the Validation Cohort

To further evaluate the applicability of the two nomogram models, we proceeded to collect a validation cohort consisting of 106 SCLC patients diagnosed from 2014 to 2021 at the same hospital. The risk scores for each patient were calculated, and based on the cutoff values for high- and low-risk groups in the training cohort (PFS risk score = 100.0, OS risk score = 172.7), then the patients were divided into two groups. Survival curves showed significant differences in outcomes between different groups ($P < 0.001$) (Figure 4A and B). The AUC values for predicting progression at 3 months, 6 months, and 12 months using the nomogram models were 0.911 (95% CI: 0.875–0.947, Sensitivity: 81.3%, Specificity: 93.3%), 0.813 (95% CI: 0.773–0.853, Sensitivity: 87.5%, Specificity: 63.3%), and 0.792 (95% CI: 0.741–0.843, Sensitivity: 69.9%, Specificity: 83.3%) (Figure 4C). The AUC values for predicting 6-month, 12-month, and 24-month survival rates were 0.777 (95% CI: 0.658–0.895, Sensitivity: 66.7%, Specificity: 91.3%), 0.793 (95% CI: 0.749–0.837, Sensitivity: 71.0%, Specificity: 72.0%), and 0.656 (95% CI: 0.599–0.713, Sensitivity: 62.3%, Specificity: 62.1%) (Figure 4D).

Prognostic Factors Analysis for PFS1 and OS in the Validation Cohort

Next, we performed univariate and multivariate Cox regression analyses using PFS1 risk score and OS risk score as candidate variables in the validation cohort.

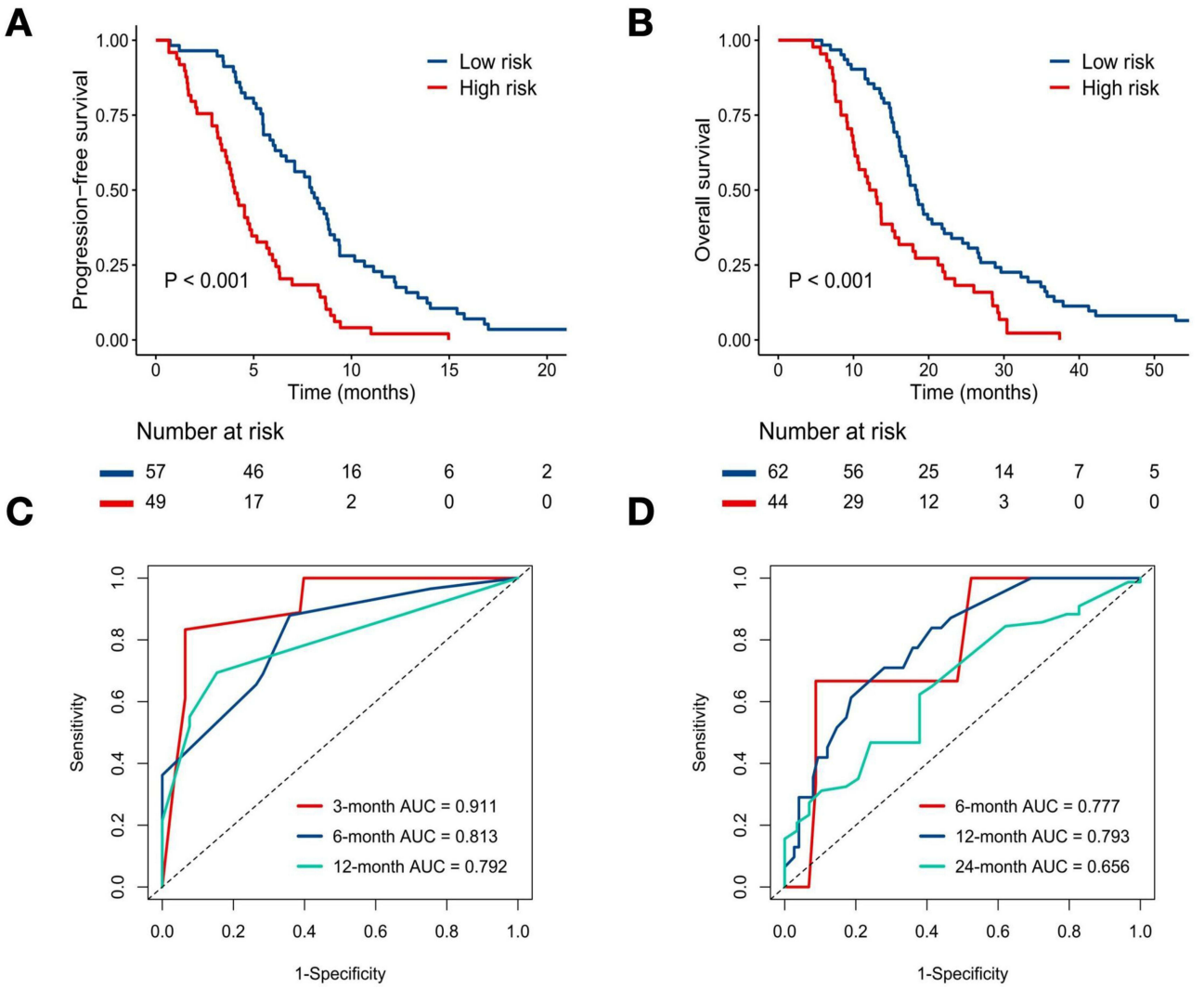

Figure 4 Validation of the nomogram models in the validation cohort. (**A**) Kaplan–Meier curves using risk scores to compare PFS. (**B**) Kaplan–Meier curves using risk scores to compare OS. (**C**) ROC curves for the models to validate PFS. (**D**) ROC curves for the models to validate OS.

Univariate and Multivariate Cox Analysis for PFS1 in the Validation Cohort

The results of univariate and multivariate cox analysis for PFS1 in the validation cohort indicated a significant association between PFS1 risk score and prognosis. Body surface area (HR = 0.602, 95% CI: 0.388–0.933, P=0.023) and PFS1 risk score (HR = 2.693, 95% CI: 1.789–4.055, P < 0.001) were identified as independent prognostic factors for PFS1 (Table 4).

Univariate and Multivariate Cox Analysis for OS in the Validation Cohort

The results of univariate and multivariate Cox analysis for OS in the validation cohort also indicated a significant correlation between the OS risk score and prognosis. Age (HR = 1.548, 95% CI: 1.022–2.346, P = 0.039), smoking status (HR = 1.973, 95% CI: 1.206–3.229, P = 0.007), liver metastasis (HR = 2.445, 95% CI: 1.599–3.737, P < 0.001), and OS risk score (HR = 1.956, 95% CI: 1.278–2.995, P = 0.002) were identified as independent prognostic factors for OS (Table 5).

The validation results demonstrated that the two nomogram models still had a good predictive ability in a completely independent validation cohort.

Table 4 Univariate and Multivariate Cox Analysis for PFS1 in the Validation Cohort

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)					
	<65	Reference			
	≥65	1.417 (0.942–2.131)	0.095		
Gender					
	Male	Reference			
	Female	0.909 (0.495–1.671)	0.760		
Body surface area (m^2)					
	≤1.73	Reference		Reference	
	>1.73	0.601 (0.389–0.930)	0.022	0.602 (0.388–0.933)	0.023
KPS score					
	≥90	Reference			
	70–80	1.112 (0.632–1.958)	0.712		
Smoking status					
	No	Reference			
	Yes	1.305 (0.823–2.069)	0.258		
Smoking index					
	≤400	Reference			
	>400	1.340 (0.898–2.001)	0.152		
Alcohol consumption					
	No	Reference			
	Yes	0.986 (0.666–1.461)	0.945		
Surgery					
	No	Reference			
	Yes	0.979 (0.309–3.104)	0.971		
Liver metastasis					
	No	Reference			
	Yes	1.325 (0.897–1.958)	0.158		
Bone metastasis					
	No	Reference			
	Yes	1.422 (0.950–2.131)	0.087		
Brain metastasis					
	No	Reference			
	Yes	1.066 (0.658–1.727)	0.794		
PFS1 risk score					
	Low risk	Reference		Reference	
	High risk	2.690 (1.789–4.044)	< 0.001	2.693 (1.789–4.055)	< 0.001

Abbreviations: KPS, Karnofsky Performance Status; PFS1, first-line progression free survival.

Table 5 Univariate and Multivariate Cox Analysis for OS in the Validation Cohort

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)					
	<65	Reference		Reference	
	≥65	1.640 (1.097–2.451)	0.016	1.548 (1.022–2.346)	0.039
Gender					
	Male	Reference			
	Female	0.687 (0.375–1.257)	0.223		

(*Continued*)

Table 5 (Continued).

Characteristics		Univariate Cox Regression		Multivariate Cox Regression	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Body surface area (m^2)					
	≤1.73	Reference			
	>1.73	0.772 (0.505–1.179)	0.231		
KPS score					
	≥90	Reference			
	70–80	1.161 (0.660–2.044)	0.605		
Smoking status					
	No	Reference		Reference	
	Yes	1.644 (1.035–2.612)	0.035	1.973 (1.206–3.229)	0.007
Smoking index					
	≤400	Reference			
	>400	1.462 (0.975–2.191)	0.066		
Alcohol consumption					
	No	Reference			
	Yes	1.097 (0.742–1.621)	0.642		
Surgery					
	No	Reference			
	Yes	0.546 (0.173–1.727)	0.303		
Liver metastasis					
	No	Reference		Reference	
	Yes	2.191 (1.464–3.278)	< 0.001	2.445 (1.599–3.737)	< 0.001
Bone metastasis					
	No	Reference		Reference	
	Yes	1.575 (1.061–2.338)	0.024	1.146 (0.755–1.739)	0.521
Brain metastasis					
	No	Reference			
	Yes	1.127 (0.694–1.831)	0.629		
OS risk score					
	Low risk	Reference		Reference	
	High risk	2.071 (1.379–3.110)	< 0.001	1.956 (1.278–2.995)	0.002

Abbreviations: KPS, Karnofsky Performance Status; OS, Overall survival.

Discussion

The treatment of SCLC has now achieved a longer median survival, reaching 15.9 months in recent Phase III trials.[28] Currently, the choice of first-line treatment is guided by staging and the functional status of the patients, with the aim of achieving maximum tumor shrinkage for potentially resectable or symptomatic patients.[29] For patients with LS-SCLC who are eligible for surgery, surgical treatment should be performed firstly, followed by systemic treatment.[30,31] In recent years, first-line treatment for ES-SCLC has been approved to include platinum-based doublet chemotherapy combined with ICIs for all eligible patients.[31] Radiation therapy can be combined with systemic treatment at an appropriate time to reduce tumor burden or used as palliative treatment to improve patient symptoms, playing a crucial role in the management of SCLC patients.[32]

In general, clinical trials evaluate the efficacy of chemotherapy based on OS, PFS and objective response rate (ORR),[33] and clinicians widely use these standards to adjust patient treatment strategies. OS is considered the gold standard in tumor research and is the best endpoint when sufficient time is available for evaluation. It has a clear definition and is easy to measure, without bias from endpoint events. PFS is an artificial endpoint based on the assessment of disease progression, but it has limitations such as subjectivity and potential bias in evaluation, and it cannot determine the impact on patient survival as it is evaluated prior to disease changes. However, an advantage of PFS

is that it has a shorter observation period, with results observed within 1–2 years, requiring a smaller sample size for studies. In addition, due to the complexity of the mechanisms of resistance, different treatment regimens may be chosen for second-line or third-line treatment after tumor progression in different patients. Furthermore, some patients may discontinue treatment after first-line therapy due to economic or psychological reasons, which may mask the efficacy of first-line treatment in subsequent analyses. In terms of specific drugs, PFS is less affected by confounding factors and provides a more accurate assessment of efficacy compared to OS. PFS can be obtained more quickly, facilitating the routine approval of new drugs and reducing patient's waiting time. Therefore, the Guideline on the evaluation of anticancer medicinal products in man issued by the European Medicines Agency state that accurate evaluation of OS may not be necessary for approval when there is a substantial improvement in PFS and a long survival period after disease progression or when there are clear safety characteristics.

However, the actual benefit to patients is always the goal pursued by clinicians. For highly malignant tumors like SCLC, if only improving PFS without translating into OS benefits can be achieved, it may not have significant value for patients overall and can lead to a certain degree of wastage of medical resources. For example, studies such as KEYNOTE-604[34] and NEJ026[35] have brought significant PFS benefits to patients, but the final reported OS values were similar and did not reach statistical significance. The validity of PFS as an substitute endpoint to OS was questioned.[36] Numerous studies have been conducted both domestically and internationally, but consensus has not been reached ultimately. For example, in gastrointestinal stromal tumors (GISTs), a study[37] showed a moderate-linear correlation between median progression free survival (mPFS) and median overall survival (mOS). In a subsequent study published in 2014, the relationship between mOS and mPFS was evaluated in all treatment combinations for GISTs. The study suggested an overall positive correlation between mOS and mPFS, with a stronger correlation observed in backline treatments.[38] The strong correlation between PFS and OS had also been demonstrated in clinical studies for metastatic colorectal cancer (mCRC),[39] advanced breast cancer (ABC),[40] and squamous cell cancer of the head and neck (SCCHN).[41] Conversely, a study in 2011 exploring the relationship between OS and PFS in metastatic breast cancer (MBC) failed to prove a correlation between PFS and OS, and this lack of correlation was particularly evident for second-line or third-line treatment of MBC.[42] Similarly, in advanced hepatocellular carcinoma (HCC),[43] advanced melanoma (AM)[44] and multiple myeloma (MM),[45] PFS had been shown to not be a good substitute for OS.

Taking into account the different results from various studies, the relationship between PFS and OS may vary depending on tumor type, treatment regimen, and even study quality.[46] In light of these characteristics, ongoing researches continue to explore the correlation between PFS and OS in specific treatment regimens, mutation statuses, and particular tumor types. In addition, researchers have attempted to establish new efficacy evaluation indicators or make improvements to PFS[47] as new substitute endpoints.[48] From a clinically observable perspective, we studied the random process of patients from achieving the optimal efficacy to experiencing disease progression until death after standardized treatment. Clinical indicators such as optimal efficacy, time to optimal efficacy, and duration of optimal efficacy, which were easily obtainable, were used to describe patients' response to treatment. We analyzed whether these indicators representing treatment response could serve as independent prognostic factors for SCLC patients and then established a nomogram prediction model in combination with other factors. In our PFS1 nomogram model, retained variables were NSE,[49] first-line radiotherapy, first-line chemotherapy cycles. In the OS nomogram model, retained variables were VALG stage, KPS score, NLR, optimal efficacy in first-line treatment, duration of optimal efficacy, and CFI. Previous studies have confirmed the impact of these variables, including tumor markers such as NSE, inflammatory markers such as NLR,[50,51] tumor stage, and KPS score on the survival outcomes of SCLC patients. The importance of chemotherapy combined with radiotherapy[12,13] and the number of chemotherapy cycles[52] in improving the prognosis of SCLC patients has also been demonstrated in recent years. However, the predictive value of initial response to tumor treatment for OS has not been thoroughly and systematically studied. Our statistical results indicated that the better the optimal efficacy achieved in the first-line treatment and the longer the duration of the optimal efficacy, the better the prognosis of patients. However, there was insufficient evidence to support a correlation between the time to optimal efficacy and survival in this study, possibly due to the bias caused by the small number of cases, which could be further investigated by including more patients in future research. Consistent with some previous studies, PFS1 did not show a direct correlation trend with OS. As expected, patients with a shorter CFI, who received second-line treatment soon

after the completion of first-line chemotherapy, had lower OS risk score, indicating the importance of timely and regular follow-up and prompt initiation of second-line treatment when necessary. Additionally, the PFS1 nomogram model predicted longer PFS for patients receiving chemotherapy combined with radiotherapy and those who completed ≥4 cycles of chemotherapy. However, it is not recommended to directly use the risk scores as treatment selection guidelines, as clinical treatment decisions should be based on multiple factors such as tumor stage, patient performance status, comorbidities, and economic conditions. The risk scores should be used as a reference to provide assistance in clinical decision-making.

This study used a patient cohort diagnosed from 1992 to 2018 for modeling, during which first-line treatment mainly consisted of platinum-based doublet chemotherapy without the use of ICIs. However, in the immunotherapy era, the subsequent OS extension would be more prominent due to the tail effect of immunotherapy.[53] Although our established models had high predictive value, we were concerned about whether these models were equally applicable to patients receiving immunotherapy, especially those receiving ICIs in first-line treatment.[54] Therefore, we collected patients receiving first-line ICIs, second-line ICIs, and backline ICIs as a validation cohort to verify the model. The validation results showed that both nomogram models had good predictive ability, indicating that these models were also applicable to patients receiving immunotherapy. This also further suggested that tumor treatment response had great predictive value, and our nomogram models had good applicability in individuals with different treatment regimens. However, we also found that the AUC value for predicting 24-month survival rate in the validation cohort was low, which may be due to the tail effect of immunotherapy. On one hand, this result demonstrated the important role of ICIs combined with chemotherapy as first-line treatment in improving survival in ES-SCLC patients, and immunotherapy may become the key to achieving long-term survival in SCLC patients.[54] On the other hand, it also suggested that we should further include real-world data of SCLC patients receiving ICIs to optimize the models. Subsequently, further comparison can be made to determine whether the same risk patients have significantly different survival outcomes due to different subsequent treatments and to identify relevant factors. This has very high clinical value for cancer with limited treatment options that may be cured by chemotherapy. In addition, this study is a single-center study with a large time span for patient diagnosis and a small sample size, which may lead to selection bias. Moreover, the predictive indicators and specific values established in this study lack related basic experimental verification, and the biological mechanism is not yet clear, which still needs to be confirmed by larger sample and prospective studies.

Conclusion

We established two nomogram models using nearly 30 years of real-world data and could predict the PFS1 and OS of SCLC patients receiving standard therapy. We also demonstrated the importance of initial response to treatment in predicting overall survival outcomes in SCLC, and clinicians could predict the patient's survival by patient's first-line treatment efficacy, which may help SCLC patients develop treatment and follow-up strategies.

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Disclosure

The authors report no conflicts of interest in this work.

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