Research Square

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Nomogram for Individualized Prediction of Survival after Immunotherapy for Extensive-Stage Small Cell Lung Cancer

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Abstract

Purpose

This study aimed to develop and validate a nomogram utilizing non-invasive baseline features to predict survival in patients with extensive-stage small cell lung cancer (ES-SCLC) undergoing immunotherapy.

Methods

This retrospective study included patients with ES-SCLC admitted to Shandong Provincial Hospital Affiliated to Shandong First Medical University between May 2020 and May 2023. Baseline clinical, radiological, serological, and pathological data were collected, with illness status monitored at regular intervals. Survival prediction nomograms were constructed using multivariate Cox regression analysis of the training cohort and validated in an independent internal cohort. Model performance was evaluated through Receiver Operating Characteristic (ROC) curves, C-indices, calibration curves, and Decision Curve Analysis (DCA).

Results

A total of 183 immunotherapy-treated ES-SCLC patients were included in the analysis. They were assigned to either a training cohort (n = 128) or a validation cohort (n = 55) through randomization based on a 7:3 ratio. Multivariate Cox regression analysis identified liver metastasis, elevated neuron-specific enolase (NSE), and increased pro-gastrin-releasing peptide (Pro-GRP) as independent risk factors for poor progression-free survival (PFS) and overall survival (OS) in the training cohort ($P < 0.05$). A prognostic nomogram was developed based on these factors. The risk scoring system revealed a significant association between risk categories and patient survival, with low-risk cases having more favorable PFS and OS outcomes than their high-risk counterparts.

Conclusion

The nomogram, based on non-invasive screening, effectively predicts survival outcomes in patients with ES-SCLC receiving immunotherapy, offering a tool for pre-treatment risk stratification and informed treatment decision-making.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality globally, including in China[1, 2]. Small cell lung cancer (SCLC) constitutes approximately 15% of lung cancer cases, with two-thirds of patients diagnosed at the extensive stag. At diagnosis, these patients often exhibit poor differentiation, high malignancy, and early metastasis, leading to an exceptionally poor prognosis and a 5-year survival

rate of under 7%[3–5]. Recent advances in immune combination therapies, particularly immune checkpoint inhibitors (ICIs), have markedly improved survival for patients with extensive-stage small cell lung cancer (ES-SCLC) compared to chemotherapy alone. Notable trials such as ASTRUM-005 (median overall survival [mOS]: 15.4 vs. 10.9 months; P < 0.001), CAPSTONE-1 (mOS: 15.3 vs. 12.8 months; P < 0.001), IMpower133 (mOS: 12.3 vs. 10.3 months; P = 0.0154), and CASPIAN (mOS: 12.9 vs. 10.5 months; P = 0.0032) have demonstrated significant survival benefits[6–9]. Following these results, regulatory approvals for several agents were granted. The National Medical Products Administration (NMPA) authorized serplulimab, adebrelimab, atezolizumab, and durvalumab as initial therapy for ES-SCLC. Meanwhile, the Food and Drug Administration (FDA) provided clearance for atezolizumab and durvalumab, reflecting a similar endorsement[8–12].

Clinical trials in SCLC have generally enrolled unselected patients, which may explain why adding immunotherapy to first-line chemotherapy offers limited survival benefits. This situation differs from non-small cell lung cancer (NSCLC), where biomarker-driven patient selection has led to substantially better treatment outcomes[13]. Consequently, it is crucial to screen patients in advance to identify those who are likely to benefit from immunotherapy.

Numerous studies have suggested that tumor mutation burden (TMB) and programmed cell death ligand 1 (PD-L1) may serve as potential predictors for ES-SCLC. Additionally, an increasing body of research indicates that specific epigenetic features of SCLC, such as transcription factor (TF) subtypes, neuroendocrine pathway gene expression, and Notch pathway activity, could function as reliable biomarkers for predicting immunotherapy efficacy. A low neuroendocrine score and activation of the Notch signaling pathway have been linked to better clinical outcomes with immunotherapy[14–17]. However, practical limitations, such as technical challenges, cost, and sample restrictions, significantly hinder the clinical application of these biomarkers[18–20]. Thus, several research groups are exploring novel biomarkers to predict immunotherapy response in patients with ES-SCLC. For instance, patients with a low Pan-Immune-Inflammation Value (PIV) exhibit significantly longer progression-free survival (PFS) and overall survival (OS) compared to those with high PIV (PFS: P = 0.012; OS: P = 0.020). Elevated PILE, a score derived from PIV, lactate dehydrogenase (LDH), and Eastern Cooperative Oncology Group Performance Status (ECOG PS), correlates with worse clinical outcomes (median PFS [mPFS]: 4.75 vs. 5.53 months, P = 0.043; mOS: 7.13 vs. 15.93 months, P = 0.002)[21]. In a retrospective study by Xiong et al., the prognostic significance of the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) for immunotherapy response in SCLC was evaluated. Their findings revealed that patients exhibiting an NLR below 5 at the six-week mark notably experienced a longer mPFS (P = 0.04)[22].

However, these studies have predominantly focused on single biomarkers, which limits their clinical predictive power. Furthermore, the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) analysis for identifying biomarkers in ES-SCLC ranged from 0.60 to 0.70, which falls short of the clinical requirements for early-stage immunotherapy efficacy screening. Combining multiple biomarkers could significantly enhance their predictive accuracy compared to a single marker[23, 24].

In recent years, nomograms have gained widespread use in clinical decision-making for cancer treatment, demonstrating significant practical value[25, 26]. This study aimed to develop and validate a nomogram based on non-invasive baseline features to predict survival in patients with ES-SCLC undergoing immunotherapy. This nomogram is expected to aid in patient stratification before treatment and inform clinical decision-making and execution.

2. Patients and methods

2.1. Patients

This retrospective real-world clinical study was conducted at the Cancer Treatment Center of Shandong Provincial Hospital Affiliated to Shandong First Medical University. It involved the collection of clinical data, serum tumor markers, and computed tomography (CT) imaging of patients with ES-SCLC admitted and treated between May 30, 2020, and May 30, 2023. Staging was performed using the Veterans Administration Lung Study Group criteria (2017 NCCN guidelines) to reassess and confirm the ES-SCLC status of every patient in the cohort.

Patients were required to meet the following criteria: (1) histologically confirmed SCLC; (2) clinical stage ES-SCLC; (3) expected survival time ≥ 3 months; (4) receipt of both immunotherapy and chemotherapy; and (5) availability of clinical and serological data. The exclusion criteria covered: (1) a concurrent primary tumor; (2) age < 18 years. Based on these criteria, 183 individuals with ES-SCLC were included in this analysis.

2.2. Ethical considerations

This research received approval from the Biomedical Research Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (SWYX: NO.2022-075) and was conducted according to the Declaration of Helsinki. All participants provided written consent, and necessary permissions were secured. All authors underwent Good Clinical Practice training. No industry funding was received for this study.

2.3. Data collection

Patient information was gathered from two primary sources. Clinical details such as age, sex, smoking history, tumor stage, metastasis locations, and immunotherapy outcomes came from electronic health records. Meanwhile, laboratory metrics like routine blood tests, liver function, blood biochemistry, and tumor markers were sourced from the Clinical Laboratory Report Inquiry System. Tumor histology was defined based on the 2004 World Health Organization criteria, while cancer staging was assessed following the American Joint Committee on Cancer (AJCC) 7th edition lung cancer staging guidelines. Patient follow-up commenced at immunotherapy initiation and continued until death or the final contact. Objective response rate (ORR) was calculated as the percentage of subjects achieving a sustained tumor volume reduction of at least 30% for more than four weeks. Both PFS and OS were evaluated by reviewing clinical records and conducting telephone interviews, with all data updated until July 31, 2023.

2.4. Treatment plan

All patients received chemotherapy in combination with immunotherapy. The ICIs used included durvalumab (Imfinzi, Medimmune), camrelizumab (Airuika, Jiangsu Hengrui Pharmaceuticals Co., Ltd.), atezolizumab (Tecentriq, Genentech), sintilimab (Daboshu, Innovent Biologics), and tislelizumab (Baizean, BeiGene). Chemotherapy drugs included etoposide, carboplatin, and irinotecan.

2.5. Efficacy evaluation

To establish baseline status before regular immunotherapy, all subjects underwent CT scans, cranial magnetic resonance imaging (MRI), and whole-body single-photon emission computed tomography (SPECT) imaging. Tumor response was assessed following every two cycles of treatment. Based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, we categorized therapeutic outcomes as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). PR was defined as a ≥ 30% reduction in tumor size sustained for four weeks; SD was defined as a decrease of < 30% or stable illness, or an increase of < 20%; PD was defined as a ≥ 20% increase in tumor size.

2.6 Statistical analyses

This study used both PFS and OS as its main endpoints, and independent factors affecting these outcomes were evaluated with univariate and multivariate Cox regression. A nomogram and risk classification system were developed based on the factors included in the final model. Model calibration was assessed by comparing predicted survival times with observed survival rates. We used ROC curve analysis to assess the nomogram's predictive accuracy. The validation cohort was then divided into low-risk and high-risk prognostic categories according to the total scores calculated for each subject. Survival analysis was performed using Kaplan-Meier curves with log-rank testing for comparisons. The data were analyzed in R software version 4.2.1 and Statistical Product and Service Solutions (SPSS) version 26.0. A two-tailed approach was used for all analyses except univariate regression, and P values below 0.05 were considered significant.

3. Results

3.1. Patient characteristics

This study analyzed 183 patients with ES-SCLC who received a combination of immunotherapy and chemotherapy. The cohort was split into training and validation groups in a proportion of seven to three (Supplementary Fig. 1). The median age at diagnosis for patients receiving immunotherapy was 55 years (range: 33–81 years), with the majority of participants being male (77.0%). Liver, brain, and bone metastases were reported in 32.7%, 13.6%, and 29.5% of the cohort, respectively. All patients were diagnosed with ES-SCLC according to the staging criteria of the American Veterans Lung Cancer Association. The training and validation groups showed comparable clinical features at baseline (Table 1).

Table 1 Clinicopathological characteristics of patients with ES-SCLC (n = 183).

Characteristic	All Patients (n=183) No. (%)	Training Cohort (n=128) No. (%)	Validation Cohort (n=55) No. (%)	P □P□0.05□
Median age (range) — yr	55(33-81)	68(43-81)	65(33-78)	
Gender				0.039
Female	141□77□	104□81.2□	37□67.2□	
Male	42□23□	24□17.8□	18□32.8□	
Hypertension				0.385
Yes	55□30□	36□28.1□	19□34.5□	
No	128□70□	92□71.9□	36□65.5□	
Diabetes				0.492
Yes	32□17.4□	24□18.7□	8□14.5□	
No	151□82.6□	104□81.3□	47□85.5□	
Smoking status				0.771
Current/former	127□69.3□	88□68.7□	39□71.0□	
Never	56□30.7□	40□31.3□	16□29.0□	
Drinking				0.087
Yes	79□43.1□	50□39.0□	29□52.7□	
No	104□56.8□	78□61.0□	26□47.3□	
Brain metastasis				0.809
Yes	25□13.6□	18□14.0□	7□12.7□	
No	158□86.3□	110□86.0□	48□87.3□	
Liver metastasis				0.740
Yes	60□32.7□	41□32.0□	19□34.5□	
No	123□67.2□	87□68.0□	36□65.5□	
Bone metastasis				0.664
Yes	54□29.5□	39□30.4□	15□27.2□	
No	129□70.4□	89□69.6□	40□72.8□	

ES-SCLC, Extensive stage small cell lung cancer.

3.2. Hematological characteristics

Sun et al. identified that among patients with gastric cancer treated with immunotherapy, indirect bilirubin (IDBIL) (OS: P = 0.032), human carbohydrate antigen 724 (CA724) (OS: P = 0.019), and TNM stage (OS: P = 0.010) were independent prognostic factors for OS[23,27-19]. Building on this existing literature, various hematological indices in the training cohort of patients were retrospectively analyzed, including blood routine parameters (hemoglobin [HGB], mean corpuscular hemoglobin, platelet, lymphocyte, monocyte, neutrophil, and eosinophil [EO] counts, PIV, SII, NLR, and PLR); liver function markers (albumin [ALB], albumin-to-globulin ratio [A/G], and LDH); and tumor markers (neuron-specific enolase [NSE] and pro-gastrin-releasing peptide [Pro-GRP]) (Supplementary Table 1). The cut-off values for each index used in the prognosis prediction of ES-SCLC were based on their respective grouping criteria (Supplementary Table 2).

3.3. Risk factors for PFS

In the training cohort, 100 progression events were recorded, with a median follow-up time of 7.0 months (range: 1-25 months). The relationship between 27 clinicopathological factors and PFS was assessed. Univariate analysis revealed significant associations between PFS and liver metastasis (P < 0.001, HR = 2.43, 95% CI: 1.58-3.73), A/G (P < 0.033, HR = 0.60, 95% CI: 0.38-0.96), age (P < 0.016, HR = 1.65, 95% CI: 1.10-2.47), LDH (P < 0.001, HR = 2.33, 95% CI: 1.54-3.53), NSE (P < 0.001, HR = 3.10, 95% CI: 1.68-5.74), and Pro-GRP (P = 0.006, HR = 1.76, 95% CI: 1.19-2.70) (Table 2). Gender, smoking status, and TNM stage were not significant predictors of PFS. Based on the univariate results, a multivariate Cox regression model was constructed, which included five variables. Multivariate analysis identified liver metastasis (P < 0.021, HR = 1.75, 95% CI: 1.09-2.80), LDH (P = 0.026, HR = 1.68, 95% CI: 1.06-2.64), NSE (P = 0.013, HR = 2.24, 95% CI: 1.19-4.22), and Pro-GRP (P = 0.038, HR = 1.56, 95% CI: 1.02-2.38) as independent risk factors for PFS (Table 2).

Table 2 Univariate and Multivariate Cox regression analyses of multiple variables for PFS in ES-SCLC treated with ICIs (n = 128).

characteristics	PFS					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	P.value	HR	95%CI	P.value
Hypertension	1.14	0.74-1.75	0.549	-	-	-
Liver metastasis	2.43	1.58-3.73	<0.001	1.75	1.09-2.80	0.021
Bone metastasis	0.98	0.64-1.49	0.922	-	-	-
Brain metastasis	0.73	0.41-1.32	0.298	-	-	-
Age	1.65	1.1-2.47	0.016	-	-	-
Diabetes	0.71	0.41-1.22	0.212	-	-	-
Gender	0.93	0.55-1.57	0.786	-	-	-
Smoking	0.66	0.44-1.01	0.057	-	-	-
Drinking	0.85	0.56-1.28	0.433	-	-	-
Transfers	1.31	0.86-2	0.215	-	-	-
A/G	0.60	0.38-0.96	0.033	-	-	-
ALB	0.68	0.45-1.02	0.059	-	-	-
EO	1.82	0.74-4.5	0.193	-	-	-
HGB	1.25	0.78-1.98	0.383	-	-	-
LDH	2.33	1.54-3.53	<0.001	1.68	1.06-2.64	0.026
LYMPH	0.74	0.45-1.21	0.224	-	-	-
MCH	0.74	0.42-1.31	0.307	-	-	-
MONO	0.83	0.55-1.27	0.396	-	-	-
NEUT	1.26	0.83-1.9	0271	-	-	-
NLR	1.31	0.76-2.24	0.327	-	-	-
NSE	3.1	1.68-5.74	<0.001	2.24	1.19-4.22	0.013
PIV	1.43	0.89-2.28	0.136	-	-	-
PLR	0.94	0.56-1.56	0.798	-	-	-
PLT	1.38	0.91-2.11	0.134	-	-	-
ProGRP	1.79	1.19-2.71	0.006	1.56	1.02-2.38	0.038
SII	1.44	0.88-2.36	0.149	-	-	-

A/G: albumin-globulin ratio; ALB: albumin; EO: eosinophil; HGB: hemoglobin; LDH: lactate dehydrogenase; LYMPH: lymphocyte; MCH: mean corpuscular hemoglobin; MONO: monocytes; NEUT: neutrophil; NLR: neutrophil-to-lymphocyte ratio; NSE: neuron specific enolase; PIV: pan-immune-inflammation value; PLR: platelet to lymphocyte ratio; PLT: platelet; Pro-GRP: pro-gastrin-releasing peptide; SII: systemic immune-inflammation index.

3.4. Risk factors for OS

In the training cohort, 68 death events were recorded, with a median follow-up time of 12 months (range: 2-38 months). The relationship between 27 clinicopathological factors and OS was assessed. Univariate analysis identified significant associations between OS and LDH (P = 0.003, HR = 4.60, 95% CI: 1.67-12.66), NSE (P < 0.001, HR = 4.45, 95% CI: 2.52-7.86), and Pro-GRP (P = 0.001, HR = 2.65, 95% CI: 1.48-4.76) (Table 3). Based on these univariate results, a multivariate Cox regression model was constructed, which included three variables. Multivariate analysis revealed that LDH (P = 0.008, HR = 4.04, 95% CI: 1.44-11.33), NSE (P < 0.001, HR = 3.60, 95% CI: 2.03-6.40), and Pro-GRP (P < 0.001, HR = 2.77, 95% CI: 1.51-5.05) were independent risk factors for OS (Table 3).

Table 3 Univariate and Multivariate Cox regression analyses of multiple variables for OS in ES-SCLC treated with ICIs (n = 75).

characteristics	OS					
	Univariate analysis			Multivariate analysis		
	HR	95%CI	HR	HR	HR	P.value
Hypertension	0.95	0.56-1.62	0.853	-	-	-
Liver metastasis	1.41	0.85-2.31	0.081	-	-	-
Bone metastasis	1.09	0.66-1.79	0.739	-	-	-
Brain metastasis	1.33	0.57-3.09	0.505	-	-	-
Age	0.88	0.45-1.72	0.705	-	-	-
Diabetes	1.17	0.72-1.9	0.523	-	-	-
Gender	0.76	0.39-1.5	0.434	-	-	-
Smoking	0.87	0.46-1.62	0.653	-	-	-
Drinking	1.05	0.62-1.77	0.852	-	-	-
Transfers	1.17	0.72-1.89	0.532	-	-	-
Hypertension	1.24	0.73-2.11	0.428	-	-	-
A/G	0.84	0.43-1.66	0.618	-	-	-
ALB	1.34	0.82-2.2	0.242	-	-	-
EO	0.67	0.41-1.09	0.108	-	-	-
HGB	1.26	0.74-2.15	0.394	-	-	-
LDH	4.60	1.67-12.66	0.003	4.04	1.44-11.33	0.008
LYMPH	0.56	0.29-1.06	0.076	-	-	-
MCH	1.20	0.48-2.99	0.701	-	-	-
MONO	1.20	0.71-2.01	0.495	-	-	-
NECT	1.51	0.92-2.49	0.101	-	-	-
NLR	1.78	0.93-3.41	0.083	-	-	-
NSE	4.45	2.52-7.86	<0.001	3.60	2.03-6.40	<0.001
PIV	1.74	1.03-2.94	0.038	-	-	-
PLR	1.76	0.91-3.38	0.092	-	-	-
PLT	1.38	0.84-2.26	0.203	-	-	-
ProGRP	2.65	1.48-4.76	0.001	2.77	1.51-5.05	<0.001

SII	1.84	0.98-3.46	0.057	-	-	-

3.5. Predicted probability of ES-SCLC progression

In the training cohort, a nomogram model was developed to predict the risk of PFS at 6 and 12 months in ES-SCLC, incorporating the variables of liver metastasis, NSE, Pro-GRP, and LDH. The corresponding risk scores for each factor are presented in Fig. 1A. The total score was calculated by integrating the patient's data into the risk score table to estimate the likelihood of disease progression at 6 and 12 months.

Similarly, a nomogram was applied to predict OS probabilities at 12 and 18 months in ES-SCLC, based on the same dataset, including NSE, Pro-GRP, and LDH. The risk scores associated with each factor are outlined in Fig. 1B. The total score was determined by incorporating patient data into the risk score table, providing the predicted probability of disease-related death at 12 and 18 months.

3.6. Validation performance of the nomogram

The time-dependent AUCs for 6-month and 12-month PFS were 0.792 and 0.840, respectively, in the training cohort, while the 12-month and 18-month OS time-dependent AUCs were 0.924 and 0.918. In the validation cohort, the 6- and 12-month PFS and 12- and 18-month OS probabilities were 0.760, 0.860, 0.864, and 0.862, respectively (Fig. 2A, B; Fig. 3A, B). These results indicate that the nomogram effectively distinguishes patient outcomes.

Additionally, calibration plots for PFS prediction at 6 and 12 months and OS prediction at 12 and 18 months were generated using the training cohort (Supplementary Fig. 2A-D). These plots reflect the agreement between the nomogram's predictions and actual patient outcomes. The results demonstrate that the model has robust overall predictive efficacy.

3.7. Clinical application of the nomogram

The clinical applicability of the disease progression risk prediction nomogram was assessed using detrended correspondence analysis (DCA), based on net benefits and threshold probabilities. The DCA indicated that the nomogram provided significant net benefits in both the training and validation cohorts (Supplementary Fig. 3A–B).

3.8. Application of risk

Using a total score derived from the nomogram's factor-based points system, we stratified patients into high- and low-risk categories. Subsequent analysis revealed that the low-risk stratum had more favorable PFS and OS outcomes than the high-risk group. In the training cohort, the PFS rates at 5 and 10 months were 73.8% and 36.9% for the low-risk group, and 60.3% and 6.3% for the high-risk group, respectively. The OS rates at 10 and 20 months were 71.6% and 22.5% in the low-risk group, compared to 20.0% and 0% in the high-risk group (Fig. 4A, 4C).

In the validation cohort, the PFS rates at 5 and 10 months were 71.4% and 14.3% for the low-risk group, and 37.0% and 7.4% for the high-risk group. The OS rates at 10 and 20 months were 37.5% and 4.2% in the low-risk group, and 14.3% and 0% in the high-risk group (Fig. 4B, 4D).

The low-risk group showed better outcomes from immunotherapy than the high-risk group in survival analysis.

4. Discussion

Following the results of the ASTRUM-005, CAPSTONE-1, IMpower133, and CASPIAN trials, the NMPA has approved serplulimab, adebrelimab, atezolizumab, and durvalumab for the first-line treatment of ES-SCLC, while the FDA has approved only two PD-L1 inhibitors, atezolizumab and durvalumab, for the same indication. The clinical value of combining PD-1 blockade with chemotherapy for ES-SCLC continues to be debated[30–33]. In the KEYNOTE-604 trial, pembrolizumab combined with chemotherapy prolonged OS, although the result was not statistically significant (P = 0.016)[30]. In contrast, the ASTRUM-005 study[8] showed a significant improvement in OS for patients receiving serplulimab in combination with chemotherapy compared to the placebo group (15.4 vs. 10.9 months, P < 0.001).

PD-1 blockers prevent the binding of PD-1 to both PD-L1 and PD-L2, while PD-L1 blockers only stop PD-1 from connecting with PD-L1. Consequently, tumors may evade anti-tumor immune responses when treated with PD-L1 inhibitors *via* the PD-1/PD-L2 axis[34]. In this study, among 183 patients with ES-SCLC who received immunotherapy and met the inclusion criteria, no significant survival difference was observed between PD-1 and PD-L1 inhibitors (median PFS: 7.0 vs. 7.0 months, P = 0.796; median OS: 14.0 vs. 16.0 months, P = 0.614). Potential explanations for this finding include the unique immune microenvironment of SCLC, where PD-L1 expression is often absent or low[35]. Additionally, PD-L1 binds to two receptors, PD-1 and B7.1 (CD80). B7.1 on tumor-associated dendritic cells (DCs) plays a pivotal role in T cell activation through the CD28-B7.1 interaction, suggesting that PD-L1 inhibitors may be more effective than PD-1 inhibitors by blocking PD-L1 on DCs, thereby modulating T cell responses[36]. Further well-defined animal models are needed to elucidate the mechanistic differences between PD-L1 and PD-1 inhibitors in SCLC. Although ICIs have shown some success in treating ES-SCLC and improving survival outcomes, the benefits are limited to a small subset of patients (CheckMate-032 trial: ORR = 11.6%; CheckMate-331 trial: nivolumab vs. chemotherapy: ORR = 13.7% vs. 16.5%)[37, 38]. Identifying a reliable method to select patients who are most likely to benefit from immunotherapy remains a critical challenge.

An immunotherapy effectiveness prediction nomogram for ES-SCLC was developed and validated in this study by dividing patients into training and validation cohorts. The nomogram, which incorporates demographics, disease staging, and baseline hematology tests routinely available before treatment, demonstrated adequate discriminatory power and calibration accuracy in both cohorts. It serves as the foundation for our risk stratification approach, successfully differentiating between patients with varying risks for OS and PFS.

Our nomogram model offers several advantages compared to similar studies. First, all markers selected for the model are noninvasive and can be obtained through routine clinical testing. In contrast, biopsy samples from SCLC are typically small and often consist mostly of necrotic tissue. For example, in the IMpower133 study, only 137 out of 403 patients had assessable tissue samples, highlighting the challenges of obtaining adequate biopsy material[6]. Therefore, the use of noninvasive markers in our nomogram is not only clinically feasible but also offers advantages in terms of cost-effectiveness, convenience, and practicality compared to traditional histopathology-based methods. Second, the nomogram incorporates multiple markers for a comprehensive evaluation, making it more robust than single-marker predictions. This enables personalized treatment prognosis assessments based on individual patient conditions, enhancing specificity and stability. To our knowledge, this is the first noninvasive efficacy nomogram model for ES-SCLC prior to immunotherapy, which can assist clinicians in making informed treatment decisions.

Additionally, this study revealed that two tumor markers, NSE and Pro-GRP, are independent predictors of immunotherapy ineffectiveness in patients with ES-SCLC. Both NSE and Pro-GRP are well-established SCLC tumor markers[39, 40], linked to disease progression and the effectiveness of immunotherapy in various cancers, including Merkel cell carcinoma and NSCLC[41]. van Veenendaal et al. found that NSE levels could help differentiate responders from non-responders during immunotherapy[42]. Furthermore, a decline in NSE levels at 6 weeks (HR = 0.619, 95% CI: 0.386–0.994) and 12 weeks (HR = 0.578, 95% CI: 0.353–0.947) after treatment was associated with prolonged survival in patients with NSCLC undergoing immunotherapy, as reported by Chen et al.[43]. These findings support our conclusion that elevated NSE and Pro-GRP levels are associated with a poor immunotherapy prognosis in SCLC. This may be explained by the fact that silencing NSE inhibits SCLC cell migration, proliferation, and colony formation, and reduces the S-phase population. Moreover, the knockdown of NSE leads to the overexpression of E-cadherin and NM23 and the downregulation of VEGF[44]. However, the exact mechanisms linking NSE and Pro-GRP levels with immunotherapy effectiveness in patients with ES-SCLC remain unclear and warrant further investigation.

Several constraints should be considered in this research. The analysis relies on retrospective data from a single institution's clinical practice, which may lead to potential selection bias. Moreover, as immune checkpoint inhibitors gained approval for ES-SCLC just recently, we included cases treated between May 2020 and May 2022, which limited the total number of cases available for analysis. Extending the follow-up period would likely have yielded more robust and comprehensive results. Additionally, due to the constraints of our study design, the nomogram was not validated with an external cohort. To improve the generalizability of the nomogram in clinical practice, it must be validated using a larger, external cohort. Moreover, due to the limitations of retrospective data collection, this study could not assess the predictive value of imaging and pathology-related parameters. Including these indicators would likely have enhanced the predictive accuracy of the model.

Conclusion

Overall, real-world ES-SCLC patients receiving ICI-based combination therapy showed notable improvements in both PFS and OS. By collecting baseline information and performing univariate and multivariate Cox regression analyses, this study developed a nomogram based on independent prognostic variables. This nomogram is the first to utilize non-invasive screening tests to predict survival in patients with ES-SCLC receiving immunotherapy, showing great potential for risk stratification prior to treatment and guiding clinical decision-making.

Declarations

Competing interests:

The authors declare no relevant financial or non-financial interests.

Consent to publish:

Not applicable.

Ethics approval and consent to participate:

All participants provided written informed consent to take part in the study. This study was conducted in accordance with the Declaration of Helsinki, and the scheme was reviewed and approved by the Biomedical Research Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong First Medical University (Approval number: SWYX: NO.2022-075). Patients' personal information is protected and will not be disclosed.

Author Contribution

Investigation: Jing Zhao, Lei Liu, Fengxian Jiang, Jingjiang Lai and Yang Shu. Methodology: Jing Zhao and Jingliang Wang. Writing – original draft: Jing Zhao. Software: Xiaodi Xie, Wei Xu and Pancen Ran. Writing – review and editing: Xiaodi Xie. Formal analysis: Xiaodi Xie, Fengxian Jiang and Jingjiang Lai. Data curation: Lei Liu and Pancen Ran. Supervision: Lei Liu, Jingliang Wang, Cuiyan Wang and Guobin Fu. Validation: Wei Xu, Fengxian Jiang, Zhizhao Zhang and Yang Shu. Visualization: Jun Ma and Guobin Fu. Project administration: Cuiyan Wang and Guobin Fu. Conceptualization: Guobin Fu.

Data Availability

The data used to support the findings of this study are available from the corresponding authors upon request.

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Figures

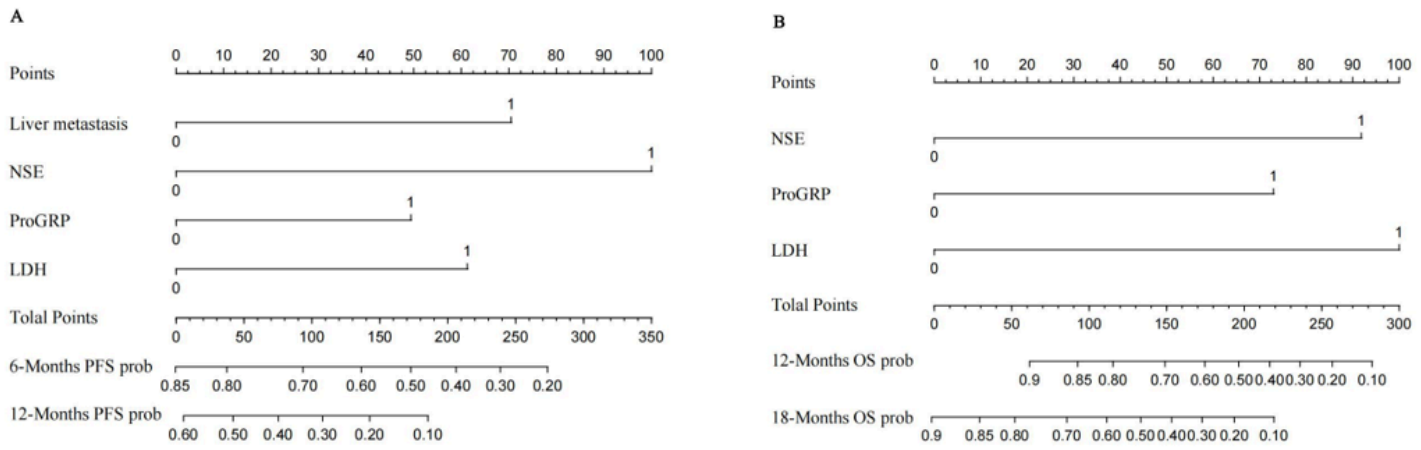


Figure 1

Nomogram predicting 6- and 12-month PFS in patients with ES-SCLC (Fig. 1A). Nomogram predicting 12- and 18-month OS in patients with ES-SCLC (Fig. 1B). The nomogram is applied by summing the points assigned to each variable on the point scale. The total points on the bottom scale indicate the patient's probabilities of PFS and OS.

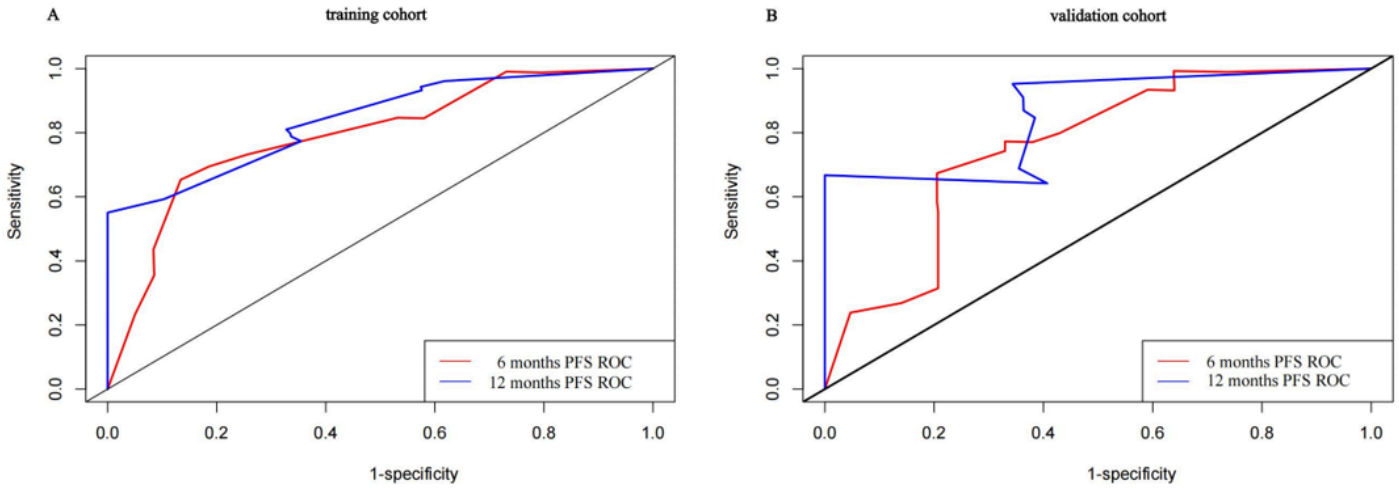


Figure 2

(A) ROC curves and AUC for nomograms predicting PFS rates at 6 months (AUC = 0.792) and 12 months (AUC = 0.840) for the training cohort. (B) ROC curves and AUC for nomograms predicting PFS rates at 6 months (AUC = 0.760) and 12 months (AUC = 0.860) for the validation cohort.

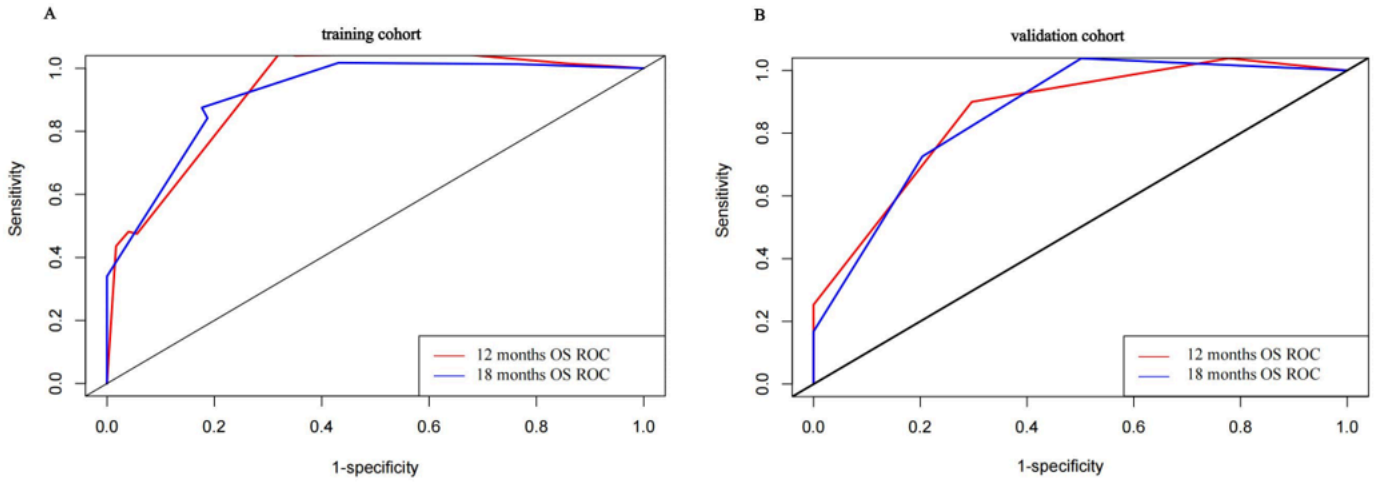


Figure 3

(A) ROC curves and AUC for nomograms predicting OS rates at 12 months (AUC = 0.924) and 18 months (AUC = 0.918) for the training cohort. (B) ROC curves and AUC for nomograms predicting OS rates at 12 months (AUC = 0.864) and 18 months (AUC = 0.862) for the validation cohort.

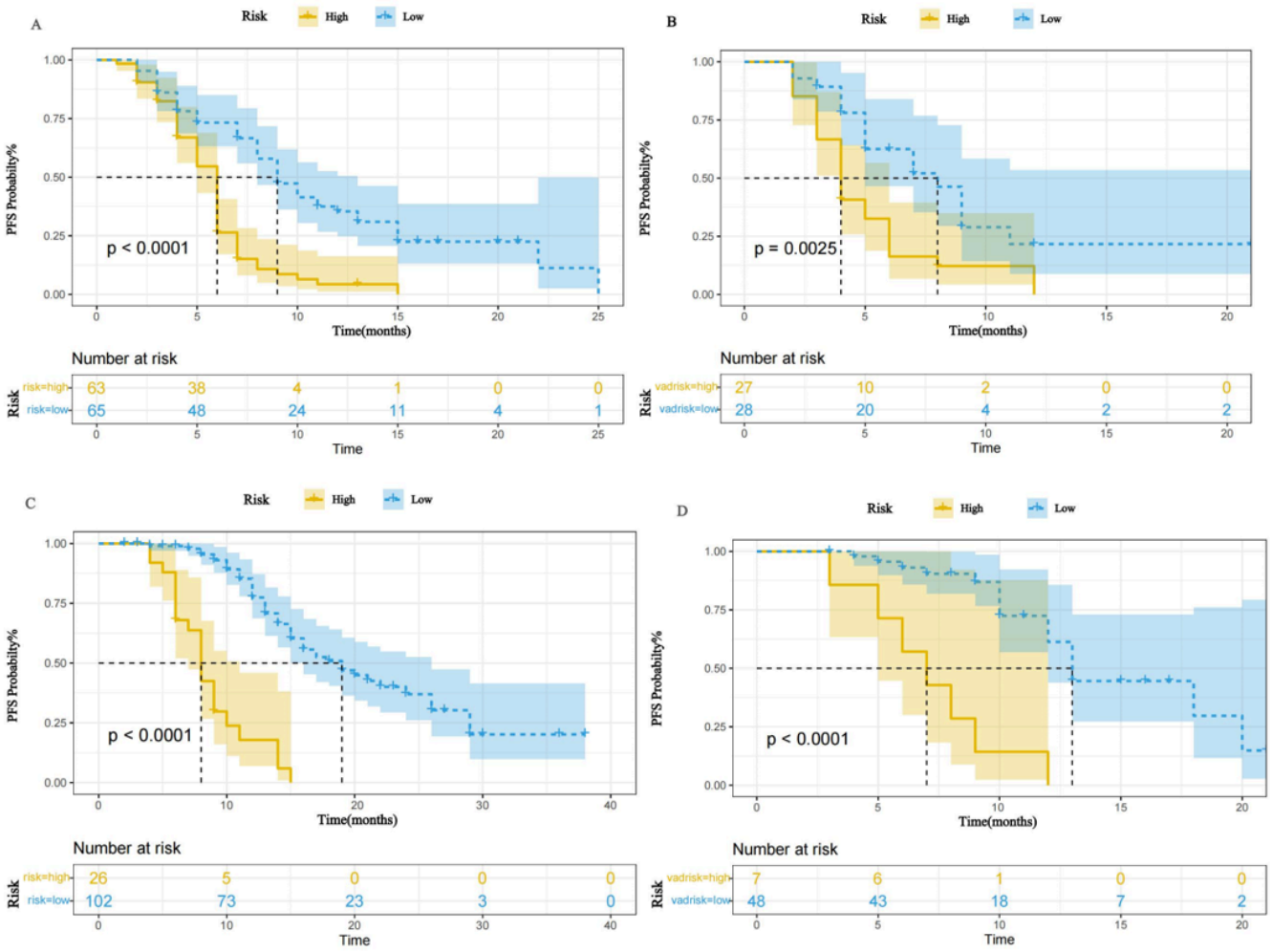


Figure 4

(A, B) Kaplan–Meier curves showing PFS with risk stratification in the training and validation cohorts. (C, D) Kaplan–Meier curves showing OS with risk stratification in the training and validation cohorts.

Supplementary Files

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