

ORIGINAL ARTICLE

An Eosinophil-Incorporated Multi-Parameter Model for Predicting Immunotherapy Efficacy in Extensive-Stage Small Cell Lung Cancer

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ABSTRACT

Background: Despite improved outcomes with immune checkpoint inhibitors (ICIs), patient responses in extensive-stage small cell lung cancer (ES-SCLC) remain heterogeneous. However, reliable predictors of immunotherapy efficacy remain elusive. This study aimed to systematically investigate the association of various blood biomarkers with immunotherapy efficacy and develop a predictive model.

Methods: Data were retrospectively collected from 254 ES-SCLC patients treated with immunotherapy at the First Affiliated Hospital of University of Science and Technology of China (training cohort; January 2020 - March 2025) and from 77 patients at the First Affiliated Hospital of Bengbu Medical University (validation cohort; January 2020 - May 2025). Patient blood parameter levels at baseline (T0) and on treatment (T2), as well as their dynamic changes (T2/T0), were collected. Independent predictors from Cox regression were used to construct prediction models, which were evaluated through ROC curves and validated with Kaplan-Meier/log-rank tests.

Results: Among the three predictive models, the T2 model and the dynamic model (T2/T0) demonstrated comparably promising predictive performance. The T2 model achieved AUCs of 0.814 (180-day PFS, 95% CI: 0.757, 0.87) and 0.824 (540-day PFS, 95% CI: 0.738, 0.911), while the dynamic model (T2/T0) achieved AUCs of 0.779 (180-day PFS, 95% CI: 0.713, 0.845) and 0.83 (540-day PFS, 95% CI: 0.74, 0.919), respectively. These findings were validated in an independent cohort. Besides, we identified a significant association between immunotherapy outcomes and eosinophils (EOS), which was further substantiated by its role as an independent prognostic factor in all three predictive models.

Conclusions: This study developed an effective predictive model for small cell lung cancer (SCLC) immunotherapy efficacy. Furthermore, the study observed an association between EOS dynamics and clinical outcomes in patients receiving immunotherapy, highlighting the need for further mechanistic investigations to explore the biological role of these cells.

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KEYWORDS

small cell lung cancer, immunotherapy efficacy, prediction model, eosinophil; biomarkers

LIST OF ABBREVIATIONS

ES-SCLC - Extensive-stage small cell lung cancer
SCLC - Small cell lung cancer
ICI - Immune checkpoint inhibitor
PFS - Progression-free survival
OS - Overall survival
EOS - Eosinophil(s)
AUC - Area under the curve
ROC - Receiver operating characteristic
HR - Hazard ratio
CI - Confidence interval
mPFS - Median progression-free survival
LDH - Lactate dehydrogenase
NSE - Neuron-specific enolase
TP - Total protein
NLR - Neutrophil-to-lymphocyte ratio
PLR - Platelet-to-lymphocyte ratio
LMR - Lymphocyte-to-monocyte ratio
CBC - Complete blood count
WBC - White blood cell count
PLT - Platelet count
HGB - Hemoglobin
ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
ALB - Albumin
GLB - Globulin
PA - Prealbumin
TBIL - Total bilirubin
SCr - Serum creatinine
BUN - Blood urea nitrogen
ProGRP - Pro-gastrin-releasing peptide
CEA - Carcinoembryonic antigen
SCC - Squamous cell carcinoma A
CA211 - Cytokeratin 19 fragment antigen 21-1
TSH - Thyroid-stimulating hormone
FT3 - Free triiodothyronine
FT4 - Free thyroxine
PD-1 - Programmed cell death protein 1
PD-L1 - Programmed death-ligand 1
TMB - Tumor mutational burden
ctDNA - Circulating tumor DNA
CTC - Circulating tumor cell

irAE - Immune-related adverse event
RECIST - Response Evaluation Criteria in Solid Tumors
CR - Complete response
PR - Partial response
SD - Stable disease
PD - Progressive disease
ECOG PS - Eastern Cooperative Oncology Group Performance Status
AJCC - American Joint Committee on Cancer
VALG - Veterans Administration Lung Study Group
CSCO - Chinese Society of Clinical Oncology
K-M - Kaplan-Meier
scRNA-seq - Single-cell RNA sequencing
bTMB - Blood-based tumor mutational burden
STARD - Standards for Reporting Diagnostic Accuracy Studies

INTRODUCTION

Small cell lung cancer (SCLC) represents 15 - 20% of all lung cancer cases. As a highly aggressive malignancy, the majority of SCLC patients are diagnosed at an extensive stage (ES), with a 2-year survival rate of less than 5% [1]. For decades, etoposide-platinum has been the first-line standard for ES-SCLC, yielding high initial response rates but poor long-term outcomes [2]. Recently, clinical trials have demonstrated the therapeutic efficacy of immune checkpoint inhibitors (ICIs) in ES-SCLC [3,4]. The combination of immunotherapy and chemotherapy has been formally endorsed as a first-line standard-of-care regimen in the Chinese Society of Clinical Oncology (CSCO) treatment guidelines. However, there are approximately 70% of patients failing to achieve the desired clinical outcomes while remaining susceptible to immune-related adverse events (irAEs) that confer both unnecessary health risks and substantial economic burdens. However, no established predictive biomarker is available to guide the use of ICIs in patients with SCLC. Therefore, exploring predictive biomarkers for accurately identifying ES-SCLC patients who may benefit from immunotherapy is crucial for achieving personalized treatment and improving prognosis.

Although PD-L1 expression and tumor mutational burden (TMB) represent the most widely validated predictive biomarkers for immunotherapy, their clinical utility in ES-SCLC remains suboptimal [4-7]. For example, in IMpower133, OS benefit from atezolizumab was observed in PD-L1-low and PD-L1-high subgroups but not in PD-L1-intermediate patients, suggesting a non-linear relationship between PD-L1 expression and therapeutic response in ES-SCLC [5]. In the KEYNOTE-604 trial, the hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) were similar, regardless of PD-L1 expression [4]. Liquid biopsy has emerged as a promising alternative to tissue biopsy due to its non-invasive nature and ability to overcome the

spatial limitations of single-site tissue sampling. More importantly, it enables real-time monitoring of tumor dynamics during treatment, capturing critical molecular changes that influence therapeutic response. As a result, researchers are increasingly focusing on liquid biopsy technologies including circulating tumor DNA (ct-DNA), circulating tumor cells (CTCs), inflammation-related parameters, or blood-based tumor mutational burden (bTMB) [8]. However, individual biomarkers often capture only a single aspect of tumor biology and exhibit limited predictive power, failing to comprehensively reflect the complexity of the disease.

To overcome the limitations of single-parameter analysis, composite models integrating multiple biomarkers have emerged and can significantly enhance the predictive performance. For instance, Zhao et al. developed a radiomic-clinical nomogram for predicting immunotherapy efficacy in ES-SCLC, which demonstrated high accuracy (AUC 0.744 at 6 months and 0.836 at 12 months) [9]. However, the model by Zhao et al. mostly relies on specialized imaging infrastructure, limiting its applicability for dynamic monitoring. Xie et al. established a plasma protein-based risk score that enabled patient risk stratification, with the low-risk group showing a significant 6-month improvement in median progression-free survival (mPFS) [10]. This model depends on costly multiplex protein detection technologies. In our study, we intended to systematically investigate whether indicators from routine clinical examinations can be utilized to build an effective and accessible predictive model. This strategy would not impose additional economic or procedural burdens on patients yet could provide valuable auxiliary information for clinical decision-making.

During our investigation of peripheral blood parameters for predicting immunotherapy outcomes in ES-SCLC, eosinophil dynamics emerged as a particularly significant factor closely associated with treatment response. EOS are multifunctional white blood cells whose physiological and pathological roles have been extensively studied. Growing evidence highlights their interactions with tumors [11] and their potential influence on immunotherapy efficacy and adverse events [12,13]. Multiple studies suggest that EOS levels are closely associated with cancer patient prognosis and treatment response. For instance, a high pretreatment peripheral eosinophil count has been identified as a predictive biomarker for favorable response to immunotherapy in melanoma patients [14-17], whereas a low baseline count is associated with inferior outcomes in metastatic urothelial carcinoma patients receiving ICI treatment [18]. Nevertheless, the role of eosinophils (EOS) in SCLC immunotherapy remains underexplored, despite their established prognostic value in other solid tumors. This study systematically examines the relationship between Eos dynamics and clinical outcomes in SCLC patients receiving immunotherapy, with particular focus on their potential as a readily accessible biomarker.

In this study, we developed and validated an effective model for assessing immunotherapy response in patients with ES-SCLC. The model transforms routine blood parameters into a practical tool which may help doctors make better personalized decisions for ES-SCLC patients. Meanwhile, we identified a significant correlation between eosinophil levels and immunotherapy outcomes, potentially driving further investigation into their specific role within the tumor immune micro-environment.

MATERIALS AND METHODS

Study design and patients

Data were retrospectively collected from 254 ES-SCLC patients who received immunotherapy at the First Affiliated Hospital of University of Science and Technology of China (training cohort, January 2020 - March 2025) and from 77 ES-SCLC patients at the First Affiliated Hospital of Bengbu Medical University (validation cohort, January 2020 - May 2025). Inclusion criteria were: 1) Histologically confirmed ES-SCLC according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system combined with the Veterans Administration Lung Study Group (VALG) two-stage classification; 2) treatment with PD-1/PD-L1 inhibitors; 3) absence of contraindications or drug allergies; and 4) complete clinical data. Exclusion criteria were: 1) Concurrent other malignancies; presence of non-neoplastic inflammatory diseases, autoimmune disorders, cardiovascular/cerebrovascular diseases, hepatic/renal diseases, or hematologic system diseases; 2) age < 18 years; and 3) use of antibiotics or corticosteroids within 2 weeks prior to treatment initiation [19,20]. This study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (2025-RE-147). Due to the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was waived by the ethics committee.

Biomarker selection

Guided by previous research and cancer nutrient metabolism theories [21-27], and also taking advantage of the easy accessibility of routine peripheral blood tests from our laboratory medicine practice, we selected 34 laboratory biomarkers for analysis in this study. To comprehensively assess the prognostic value of these biomarkers, biomarker data were obtained before initiating immunotherapy (T0) and after two cycles of immunotherapy (T2).

The specific biomarkers analyzed primarily included: 1) Complete blood count (CBC) parameters: Eosinophils (EOS), neutrophils (Neut), lymphocytes (Lymph), monocytes (Mono), white blood cell count (WBC), platelet count (PLT), hemoglobin (HGB), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio

(PLR), lymphocyte-to-Monocyte ratio (LMR); 2) biochemical markers: lactate dehydrogenase (LDH), glucose (GLU), sodium (Na^+), potassium (K^+), alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT ratio, prealbumin (PA), globulin (GLB), albumin (ALB), total protein (TP), albumin-to-globulin ratio (A/G ratio), total bilirubin (TBIL), serum creatinine (SCr), blood urea nitrogen (BUN); 3) coagulation marker: D-dimer; 4) tumor markers: pro-gastrin-releasing peptide (ProGRP), neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), cytokeratin 19 fragment antigen 21-1 (CA211); and 5) thyroid function tests: thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4).

CBC analysis was performed using the Mindray BC-6800Plus automated hematology analyzer with its proprietary reagents, employing the sheath flow impedance method for cell counting and flow cytometry with laser scattering and fluorescent staining for differential leukocyte counts. Coagulation tests (e.g. PT, APTT) were measured by the clotting method using the STAGO STA-R MAX analyzer with original reagents. Biochemical parameters were measured by electrochemiluminescence immunoassay using the Roche Diagnostics Cobas 8000 automated analyzer with Roche original reagents. Tumor biomarkers were detected by chemiluminescence immunoassay using the Abbott Alinity automated analyzer with Abbott original reagents. Thyroid function tests were performed by direct chemiluminescence technology using the Siemens Healthineers Atellica IM 1600 Analyzer with its proprietary reagents. Our laboratory has always adhered to stringent quality control practices and performs daily internal quality control (IQC) with Westgard rules. Although the acceptable CV thresholds vary across different biomarkers, they were consistently required to be below 7.5% to ensure data quality and analytical validity.

Immunotherapy and chemotherapy regimens

Administered ICIs included: 1) PD-L1 inhibitors: Atezolizumab (Roche), Durvalumab (AstraZeneca), Envafohimab (KN035; Tracoon Pharmaceuticals/3S Bio), Adebrelimab (SHR-1316; Hengrui Pharmaceuticals), Sugemalimab (CS1001; CStone Pharmaceuticals); 2) PD-1 inhibitors: Nivolumab (Bristol Myers Squibb), Camrelizumab (SHR-1210; Hengrui Pharmaceuticals), Sintilimab (Tyvyt®; Innovent Biologics), Serplulimab (HANSIZHUANG; Henlius Biotech), Tislelizumab (BGB-A317; BeiGene), Toripalimab (JS001; Junshi Biosciences), Pembrolizumab (Merck & Co.); and 3) chemotherapy regimens: according to the current NCCN guidelines [28], platinum-etoposide served as the standard regimen; alternative platinum-based regimens (e.g. irinotecan or paclitaxel + platinum) were permitted. Immunotherapy duration: ≥ 4 cycles.

Treatment response evaluation

PFS was selected as the primary endpoint as overall survival (OS) data were not yet mature at the time of analysis. The median follow-up duration for the training cohort was 189 days (range: 31 - 941), and for the validation cohort, it was 200 days (range: 37 - 652). PFS was defined as the time from immunotherapy initiation to the first documented disease progression or death from any cause, whichever occurred first. Patients who were alive or without documented clinical/radiological disease progression at the last follow-up were censored in the survival analysis. With reference to previous studies [29], the responding groups were defined as patients who achieved complete response, partial responses, or stable disease control in response to immunotherapy. Non-responding groups were patients who had progressive disease. From a clinical management perspective, patients achieving SD, like those achieving CR/PR, continue treatment without changing treatment regimens, whereas patients with progressive disease (PD) were promptly switched to alternative therapies. Therefore, grouping CR/PR/SD as the "non-progression" group aligns with the clinical question we sought to address. These treatment response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [30]. All imaging assessments were performed independently by two senior radiologists, who were blinded to patients' clinical information, treatment allocation, and biomarker results.

Construction and validation of the prediction model

By using univariate screening, LASSO Cox regression with 10-fold cross-validation ($\lambda_{\min}$), and multivariable Cox proportional hazards regression analyses, we identified independent prognostic factors significantly associated with immunotherapy outcomes in ES-SCLC patients. The proportional hazards assumption was formally tested for all Cox models using the Schoenfeld residual method, and the results showed that all variables included in the final models satisfied the proportional hazards assumption ($p > 0.05$, Supplemental Figure 1). Based on the multivariable regression results, predictive models for immunotherapy prognosis in ES-SCLC patients were constructed and graphically represented as clinically practical nomogram. The formula for each model presents the linear combination of predictors weighted by their respective Cox regression coefficients. Risk score was calculated from the predictive models, and the median values were chosen to stratify patients into low-risk and high-risk groups. To assess the model's discriminative ability, we calculated time-dependent AUC values at key clinical timepoints (180 days and 540 days). Furthermore, we evaluated the model's prognostic performance through Kaplan-Meier survival analysis with log-rank testing, stratifying patients according to risk groups derived from the nomogram. It is important to note that all biomarkers and risk scores were modeled as continuous variables in the Cox proportional hazards regression analyses. Median-based

dichotomization was applied exclusively for Kaplan-Meier survival analyses, as required for categorical grouping to facilitate visualization and log-rank comparison. In the training cohort, a total of 157 PFS events were observed. Our final multivariable model included a maximum of five predictors, yielding an events-per-variable (EPV) of $157/4 = 39.25$. This substantially exceeds the widely accepted threshold of 10 EPV.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 10.0 and R Studio (version 4.2.3). The normality of continuous variables was assessed using the Shapiro-Wilk test. Parametric tests (paired or unpaired *t*-tests) were applied to normally distributed variables, whereas non-parametric tests (Wilcoxon signed-rank test for paired data or Wilcoxon rank-sum test for independent samples) were used for non-normally distributed variables. Kaplan-Meier analyses for single indicators were conducted using GraphPad Prism. Multivariable Cox proportional hazards regression models and time-dependent receiver operating characteristic (ROC) curves were developed using R, with key packages including survival, timeROC, ggplot2, survminer, forestplot, and regplot. A *p*-value < 0.05 was considered statistically significant. Detailed R code is provided in Supplemental Material 2. The Cox proportional hazards regression model was applied for univariate and multivariate analysis. In univariate Cox regression, laboratory indicators with *p* < 0.1 were included in the multivariate Cox regression model to screen for independent risk factors (*p* < 0.05) affecting the prognosis of ES-SCLC patients. By using the median value of each indicator as the cutoff, patients were divided into high and low groups, the Kaplan-Meier method was employed to estimate survival rates, and the log-rank test was used to analyze differences in patient survival rates. Time-dependent receiver operating characteristic (ROC) curve with 180 days and 540 days as cutoffs were used to evaluate the model performance. Variables with missing values were examined prior to analysis. For continuous variables with less than 30% missing data, missing values were imputed using multiple imputation. Categorical variables had no missing data (Supplemental Table 1).

RESULTS

Patient information

As shown in Figure 1, this study initially enrolled 389 ES-SCLC patients who received immunotherapy. After screening, 331 patients were included in the final analysis, comprising 254 cases in the training cohort and 77 cases in the external validation cohort. The baseline characteristics of patients are listed in Table 1. The training cohort, consisting of 202 males (79.5%) and 52 females (20.5%), had a mean age of 63.1 years. In terms of smoking, 33.5% (85/254) of patients had a smoking history. Regarding performance status, the majority of

patients had an ECOG score of 0 - 1 (228 patients, 89.8%), while 26 patients (10.2%) had an ECOG score of 2. Among these patients, 12.6% (32/254) of patients did not have metastases, 70.9% (180/254) of patients had 1 - 2 metastases, and 16.5% (42/254) of patients had ≥ 3 metastases. Following 4 cycles of immunotherapy, treatment response assessment identified 189 responders (74.4%) and 65 non-responders (25.6%) in the training cohort. This response distribution provides a robust data foundation for subsequent development of predictive models.

Peripheral blood biomarker levels at baseline (T0) for predicting immunotherapy outcomes

By using PFS as the outcome variable, we performed univariate Cox regression analysis in the training cohort to investigate the association between clinical features and PFS. This preliminary screening (*p* < 0.1) identified metastases number and other nine baseline peripheral blood biomarkers with potential predictive value for immunotherapy outcomes in ES-SCLC (Figure 2A). Multivariate Cox regression analysis of these candidates revealed four independent prognostic factors: EOS_{T0} (HR = 1.52, 95% CI: 1.05 - 2.19, *p* = 0.0247), LDH_{T0} (HR = 1.95, 95% CI: 1.29 - 2.96, *p* = 0.0016), Lymph_{T0} (HR = 0.55, 95% CI: 0.39 - 0.79, *p* = 0.0012), and metastases (HR = 1.31, 95% CI: 1.13 - 1.52, *p* = 0.0004; Figure 2B). These factors were also significantly associated with PFS (*p* = 0.0032, *p* < 0.001, and *p* = 0.0069, respectively; Figure 2C-E). Compared with non-responders, immunotherapy responders revealed significantly lower baseline eosinophil (EOS) levels (*p* = 0.0059) (Supplemental Figure 2A). However, possibly because the response status after four treatment cycles does not fully align with the final progression-free survival (PFS), LDH did not show significant differences here. Other indicators that showed significant differences between the responder and non-responder groups - such as lymphocyte count (*p* = 0.0022) - are also summarized in Supplemental Figure 2.

By using the identified independent prognostic factors (EOS_{T0}, LDH_{T0}, Lymph_{T0}, and metastases) with their respective Cox regression coefficients as weights, we constructed a prognostic risk score model (risk score = $(0.420 \times \text{EOS}_{T0}) + (0.669 \times \text{LDH}_{T0}) + (-0.592 \times \text{Lymph}_{T0}) + (0.269 \times \text{metastases})$). The prognostic model yielded significantly elevated risk scores in non-progression group versus progression group in the training set (*p* < 0.001; Figure 3A). Here, the progression group encompasses patients who experienced disease progression or died from any cause during immunotherapy. The non-progression group comprises those alive without progression at the final follow-up. Subsequently, patients were stratified into high-risk and low-risk groups using the median risk score of the training cohort as the cutoff. Kaplan-Meier analysis revealed a significant shorter mPFS in high-risk group (174 days; 95% CI: 156 - 207) compared to the low-risk group (321 days; 95% CI: 281 - 491; HR = 3.17 [2.25 - 4.46]), demon-

Table 1. Summary of ES-SCLC patient outcomes and treatment information.

Characteristics	Training cohort (n = 254)	Validation cohort (n = 77)
Age, mean (SD), years	63.1 (8.8)	66.0 (9.3)
Gender (%)		
Male	202 (79.5)	62 (80.5)
Female	52 (20.5)	15 (19.5)
Smoking (%)		
Yes	85 (33.5)	11 (14.3)
No	169 (66.5)	66 (85.7)
ECOG (%)		
0 - 1	228 (89.8)	67 (87.01)
2	26 (10.2)	10 (12.99)
Metastases (%)		
0	32 (12.6)	13 (16.9)
1 - 2	180 (70.9)	35 (45.4)
≥ 3	42 (16.5)	29 (37.7)
Bone metastases (%)		
Yes	86 (33.9)	17 (22.1)
No	168 (66.1)	60 (77.9)
Brain metastases (%)		
Yes	100 (39.4)	13 (16.9)
No	154 (60.6)	64 (83.1)
Liver metastases (%)		
Yes	54 (21.3)	18 (23.4)
No	200 (78.7)	59 (76.6)
Clinical efficacy (%)		
CR	0	1 (1.3)
SD	98 (38.6)	27 (35.0)
PR	91 (35.8)	22 (28.6)
PD	65 (25.6)	27 (35.1)

Responders: CR + PR + SD, non-responders: PD.

strating the model's clinical utility for risk stratification in ES-SCLC patients receiving immunotherapy (Figure 3B). To further validate the model, we applied it to an independent cohort of patients from a separate medical center. In the external validation cohort, the low-risk group also maintained superior mPFS (330 days; 95% CI: 233 - 460 vs. 120 days; 95% CI: 93 - 224; HR = 4.24 [2.34 - 7.69]; $p < 0.001$; Figure 3E). Based on the established model, we constructed a clinically applicable nomogram that visually translates predictor values into individualized risk estimates (Figure 3C). However, calibration curve reveals unstable predictions of the T0 model in training and validation sets (Supplemental Figures 3A, B and 4A, B), possibly owing to short follow-up and limited sample size. Consistent with these

calibration findings, decision curve analysis for the T0 model revealed that the clinical net benefit was limited, only observed within a narrow range of threshold probabilities (Supplemental Figure 5A). To further validate the model's predictive performance, we conducted time-dependent ROC analysis at 180-day and 540-day time-points. In the training cohort, the model achieved AUCs of 0.717 (180 days, 95% CI: 0.648, 0.785) and 0.818 (540 days, 95% CI: 0.709, 0.927) (Figure 3D), while maintaining robust performance in the independent validation cohort with corresponding AUCs of 0.764 and 0.923 (Figure 3F). Collectively, these results demonstrate that our risk model, incorporating baseline biomarker profiles, effectively predicts immunotherapy efficacy and progression-free survival in ES-SCLC pa-

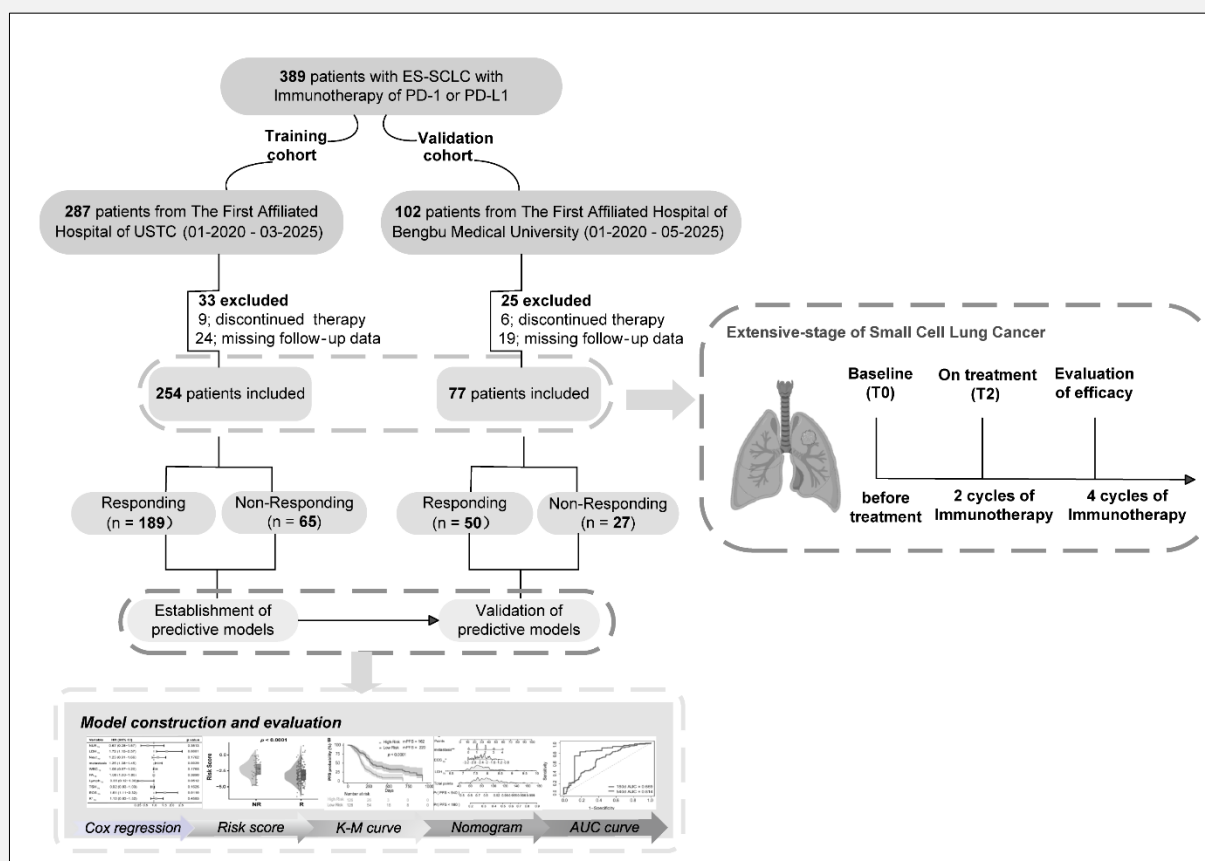


Figure 1. Study design workflow for developing a prognostic model in ES-SCLC patients undergoing immunotherapy.

The study included ES-SCLC patients receiving immunotherapy (targeted PD-1 or PD-L1). A prognostic model was developed using a training cohort and was validated in an independent external cohort. Clinical features associated with therapeutic efficacy were identified through Cox regression analysis. AUC: area under the curve, ES-SCLC: extensive-stage small cell lung cancer, K-M: Kaplan-Meier.

tients.

Dynamic changes during initial treatment in peripheral blood biomarkers (T2/T0) for predicting immunotherapy outcomes in ES-SCLC

Given that baseline measurements represent static pre-treatment states while immunotherapy efficacy may depend on dynamic immune reprogramming, we evaluated biomarker kinetics by comparing pre-treatment (T0) with on-treatment (T2) levels. Here, sequential Cox regression analyses identified four independent predictors of PFS: $\text{EOS}_{\text{T2/T0}}$ (HR = 0.65, 95% CI: 0.58 - 0.74, $p < 0.001$), $\text{TP}_{\text{T2/T0}}$ (HR = 0.29, 95% CI: 0.09 - 0.89, $p = 0.0309$; although the confidence interval is relatively wide, bootstrap internal validation showed a consistently protective direction in 98.8% of the resamples, see Supplemental Table 2), metastases (HR = 1.45, 95% CI: 1.25 - 1.68, $p < 0.001$), and $\text{NSE}_{\text{T2/T0}}$ (HR = 1.17, 95% CI: 1 - 1.35, $p = 0.0431$; Supplemental Figure

6B). Notably, EOS dynamics demonstrated the strongest protective effect among all predictors, highlighting its pivotal role in the model. T-test analysis revealed that two cycles of immunotherapy significantly increased EOS levels in responders ($p < 0.001$; Supplemental Figure 6C) but decreased them in the non-responders ($p < 0.001$; Supplemental Figure 6D). The result reinforced the crucial importance of EOS dynamics in treatment response assessment. NSE levels decreased significantly in the responder group ($p < 0.001$; Supplemental Figure 6C), while a slight decreasing trend was also observed in non-responders ($p = 0.0078$; Supplemental Figure 6D). Kaplan-Meier survival analysis showed the dynamics of EOS and NSE were significantly associated with PFS ($p < 0.001$ and $p = 0.0260$, respectively; Supplemental Figure 6E, F). However, the level of TP exhibited neither significant changes after two cycles of immunotherapy nor a significant correlation with PFS (data not shown). Other indicators that

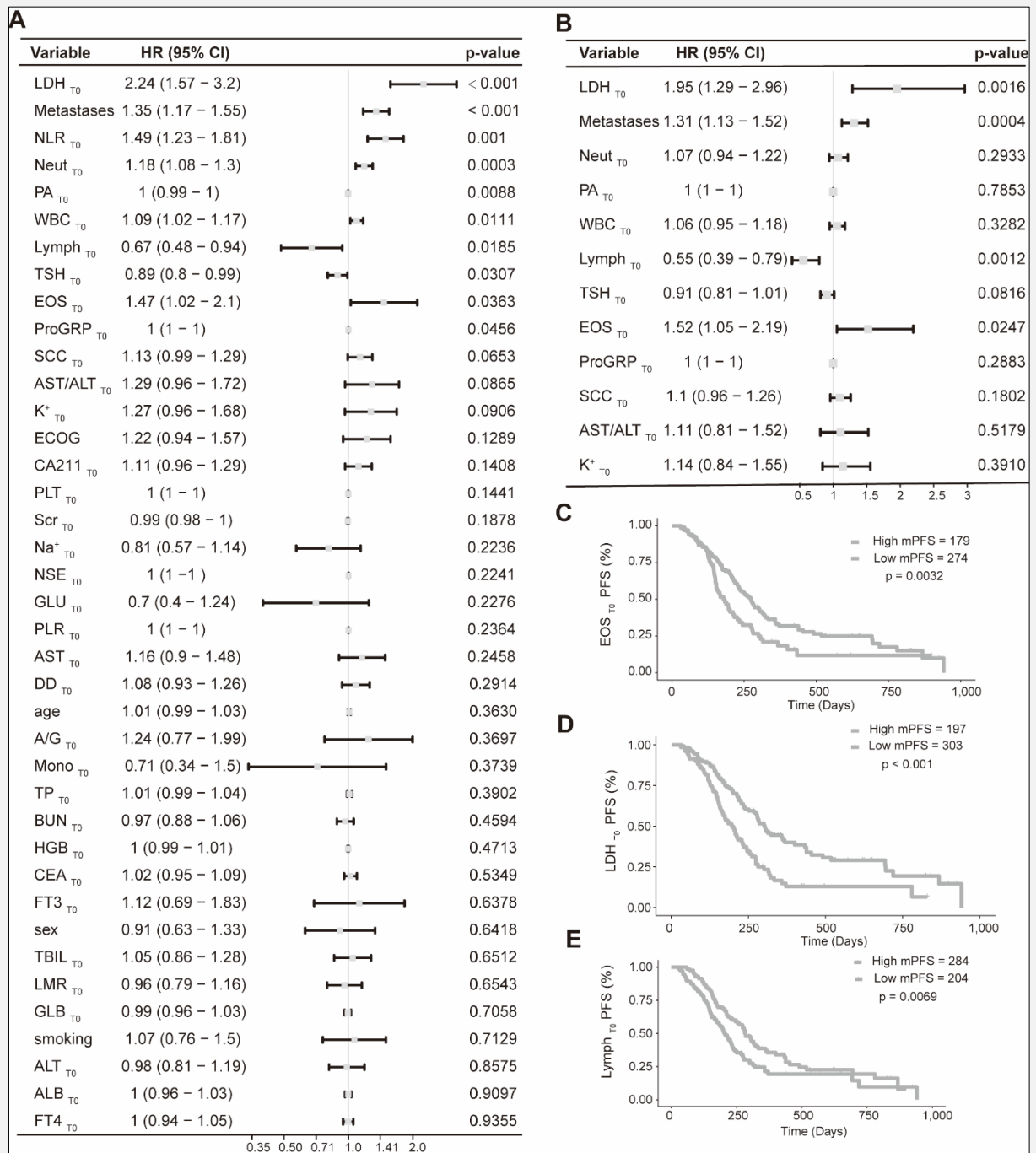


Figure 2. Association between baseline clinical variables and immunotherapy efficacy in ES-SCLC patients.

A and B: Forest plots display, **A:** univariate and **B:** multivariate Cox proportional hazard regression analyses of PFS. **C – E:** Kaplan-Meier survival curves for PFS stratified by baseline levels of **C:** EOS, **D:** LDH, and **E:** Lymph (dichotomized at median values). T0 indicates baseline measurements. Variables showing marginal association ($p < 0.1$) in univariate analysis were advanced to multivariate modeling, where $p < 0.05$ in multivariate analysis defined statistically significant independent predictors for model construction. PFS: progression-free survival, EOS: eosinophil, LDH: lactate dehydrogenase, Lymph: lymphocytes. Cox proportional hazard models were fitted using the survival package in R. Kaplan-Meier analyses for single indicators were conducted using GraphPad Prism.

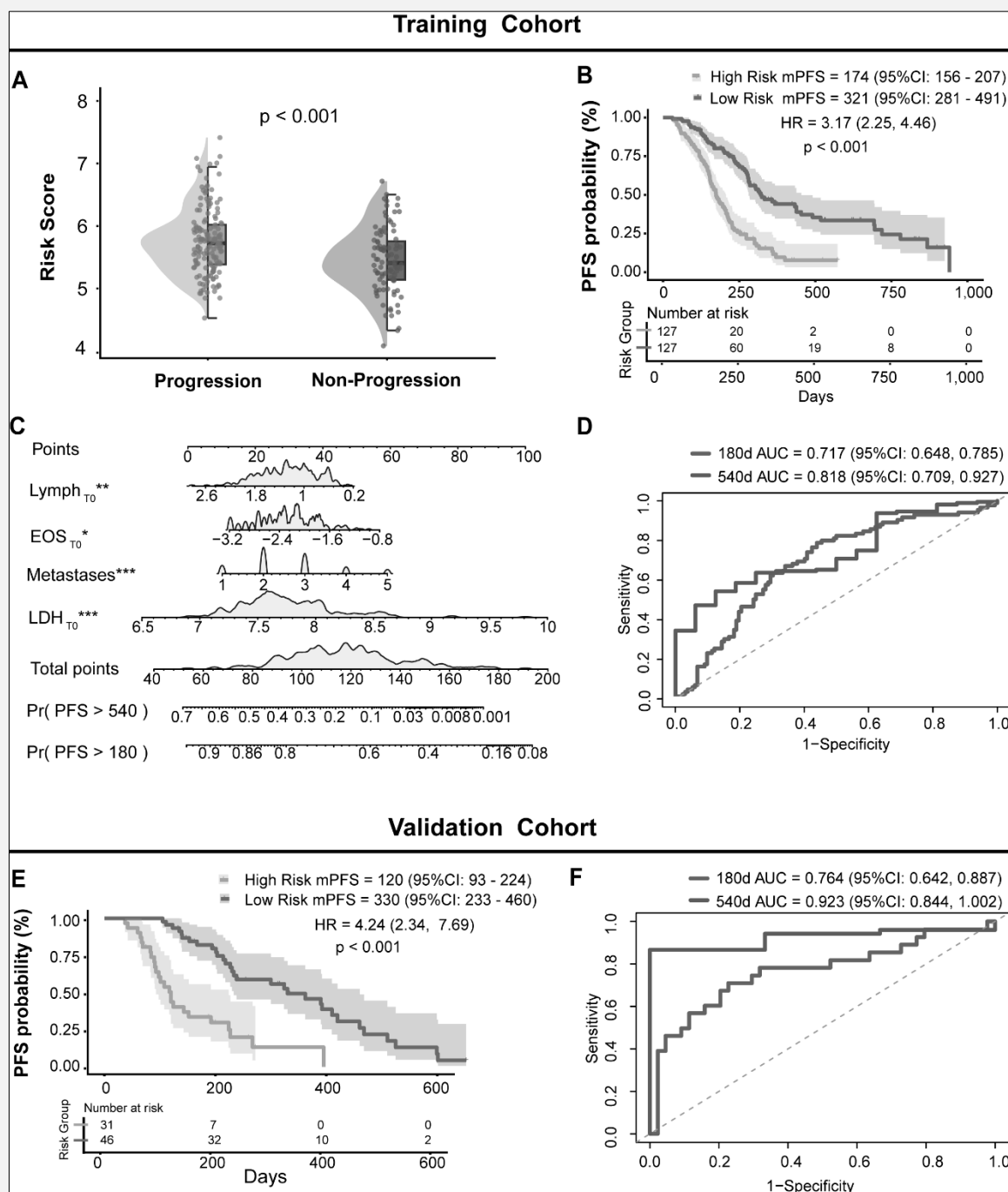


Figure 3. Development and validation of the baseline model for predicting immunotherapy response in ES-SCLC.

A - D: Training cohort analysis: A: Risk score distribution stratified by treatment outcomes (progression vs. non-progression), B: PFS analysis by Kaplan-Meier curves (high-risk vs. low-risk groups, stratified by median risk score [cutoff: 5.5227]), C: Nomogram for predicting PFS probabilities at 180 and 540 days post-immunotherapy, and D: time-dependent ROC curves assessing model performance at 180 and 540 days. **E and F: Validation cohort analysis:** E: Kaplan-Meier PFS analysis, F: ROC curves evaluating predictive performance at 180 and 540 days. PFS: progression-free survival. All figures were generated using R software (version 4.2.3) with the following packages: Kaplan-Meier curves and risk tables: survival (for survival object and model fitting) and survminer (for visualization); Raincloud plots (distribution of risk score): ggplot2, gghalves, ggpubr, and dplyr; time-dependent ROC curves: timeROC; nomogram: regplot.

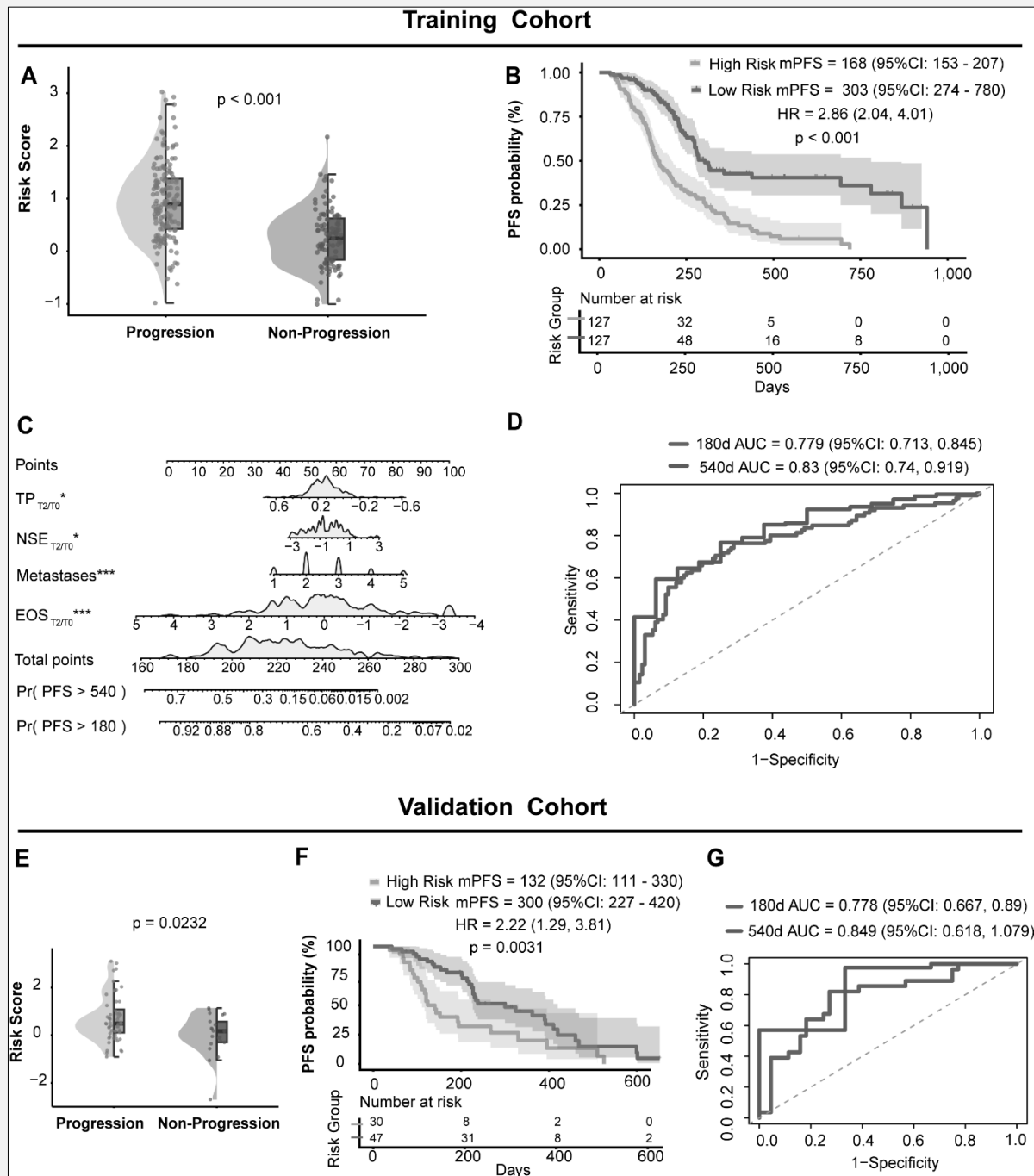


Figure 4. Development and validation of the model based on dynamic changes (T2/T0) for immunotherapy response in ES-SCLC patients.

A - D: Training cohort analysis: A: Risk score distribution stratified by treatment outcomes (progression vs. non-progression), B: Kaplan-Meier survival analysis comparing high-risk (≥ 0.6418) and low-risk groups, C: nomogram predicting progression-free survival (PFS) probabilities at 180 and 540 days post-immunotherapy, and D: time-dependent receiver operating characteristic (ROC) curves evaluating model performance at 180 and 540 days. T2/T0: Ratio of post-treatment (after two cycles) to baseline values. All figures were generated using R software (version 4.2.3) with the following packages: Kaplan-Meier curves and risk tables: survival (for survival object and model fitting) and survminer (for visualization); Raincloud plots (distribution of risk score): ggplot2, gghalves, ggpubr, and dplyr; time-dependent ROC curves: timeROC; nomogram: regplot.

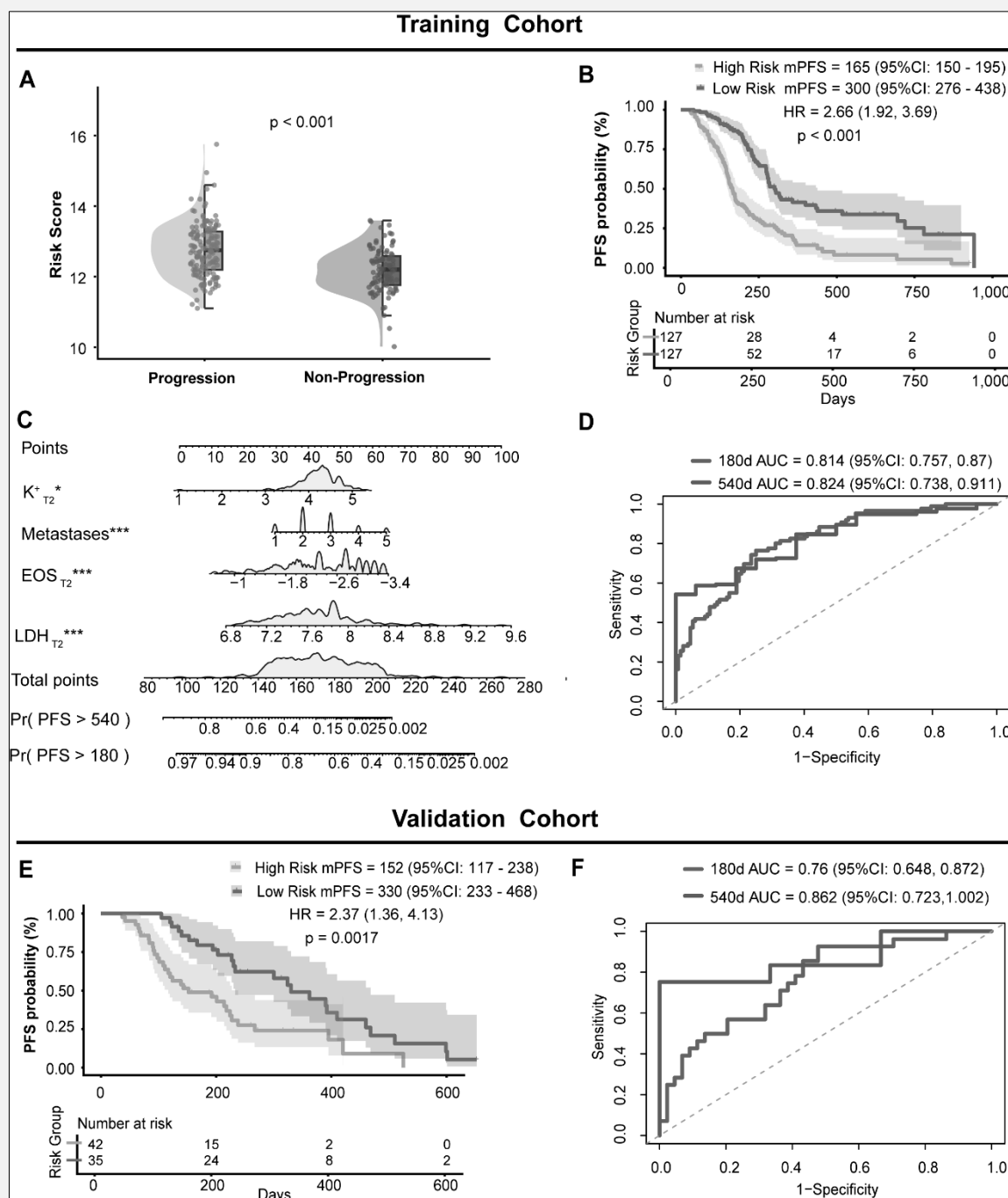


Figure 5. Development and validation of the on-treatment model for predicting immunotherapy response in ES-SCLC.

A - D: Training cohort analysis: **A:** Risk score distribution stratified by treatment response (progression vs. non-progression), **B:** Kaplan-Meier progression-free survival (PFS) curves comparing high-risk (≥ 12.4891) and low-risk groups, **C:** nomogram for predicting 180- and 540-day PFS probabilities following immunotherapy, and **D:** time-dependent receiver operating characteristic (ROC) curves evaluating model performance at 180 and 540 days. **E and F:** Validation cohort analysis: **E:** Kaplan-Meier PFS analysis of high-risk (≥ 12.4891) and low-risk groups, **F:** ROC curves assessing predictive accuracy at 180 and 540 days. All figures were generated using R software (version 4.2.3) with the following packages: Kaplan-Meier curves and risk tables: survival (for survival object and model fitting) and survminer (for visualization); Raincloud plots (distribution of risk score): ggplot2, gghalves, ggpubr, and dplyr; time-dependent ROC curves: timeROC; nomogram: regplot.

showed significant differences between the responder and non-responder groups are summarized in Supplemental Figure 7 and Supplemental Figure 8.

Here, the newly developed scoring model (risk score = $(-1.251 \times TP_{T2/T0}) + (-0.425 \times EOS_{T2/T0}) + (0.371 \times \text{metastases}) + (0.154 \times NSE_{T2/T0})$) also yielded significant higher risk scores in progression group compared to non-progression group in both training set and validation set ($p < 0.001$ and $p = 0.0232$ respectively; Figure 4A, 4E). Kaplan-Meier analysis confirmed significantly shorter mPFS in high-risk patients in both training (168 days; 95% CI: 153 - 207 vs. 303 days; 95% CI: 274 - 780; HR = 2.86 [2.04 - 4.01]; $p < 0.001$; Figure 4B) and validation cohorts (132 days; 95% CI: 111 - 330 vs. 300 days; 95% CI: 227 - 420; HR = 2.22 [1.29 - 3.81]; $p = 0.0031$; Figure 4F). Based on the dynamic peripheral blood model, we developed a clinically applicable nomogram (Figure 4C). For the T2/T0 model, short-term (180-day) calibration shows better performance than long-term (540-day) predictions, with good agreement between predicted probabilities and observed risks in both the training and validation sets, despite a mild systematic tendency to overestimate survival (Supplemental Figures 3C, D and 4C, D). Here, the DCA results demonstrated that the net benefit of the T2/T0 model at both 180 days and 540 days was significantly superior to the simple strategies of "treat all" or "treat none" across a decision threshold range of 10% - 80% (Supplemental Figure 5B), indicating a clear advantage in guiding clinical intervention. Time-dependent ROC analysis demonstrated enhanced predictive performance, with training cohort AUC increasing from 0.779 at 180 days (95% CI: 0.713, 0.845) to 0.83 at 540 days (95% CI: 0.74, 0.919 Figure 4D), and validation cohort achieving AUCs of 0.778 and 0.849 at 180 and 540 days, respectively (Figure 4G). These results represent a substantial improvement over the baseline model's performance.

On-treatment biomarker levels (T2) for predicting immunotherapy outcomes in ES-SCLC

Following univariable analysis (Supplemental Figure 9A), the multivariable Cox regression analysis identified metastases number and other four on-treatment biomarker levels with independent predictive value for immunotherapy outcomes in Supplemental Figure 9B: EOS_{T2} (HR = 0.47, 95% CI: 0.35 - 0.62, $p < 0.001$), K^+_{T2} (HR = 1.68, 95% CI: 1.1 - 2.57, $p = 0.0165$), metastases (HR = 1.34, 95% CI: 1.14 - 1.56, $p = 0.0003$), and LDH_{T2} (HR = 2.27, 95% CI: 1.55 - 3.35, $p < 0.001$). Compared to non-responders, the responder group demonstrated significant higher EOS_{T2} levels ($p < 0.001$; Supplemental Figure 9C) but lower LDH_{T2} level ($p < 0.001$; Supplemental Figure 9D) in the training cohort. Other indicators that showed significant differences between the responder and non-responder groups - such as lymphocyte count ($p = 0.0001$) - are also summarized in Supplemental Figure 10. Kaplan-Meier curves illustrate the significant associations between the

on-treatment biomarker levels (EOS_{T2} and LDH_{T2}) and PFS ($p = 0.0019$, $p < 0.001$, respectively; Supplemental Figure 9E, F). The prognosis prediction model (risk score = $(-0.765 \times EOS_{T2}) + (0.822 \times LDH_{T2}) + (0.519 \times K^+_{T2}) + (0.290 \times \text{metastases})$) constructed here demonstrated robust differentiation capacity between progression group and non-progression group ($p < 0.001$) in the training set (Figure 5A), but this effect was not statistically significant in the validation cohort (data not shown). Nevertheless, when patients were stratified into high and low-risk groups using the optimal cutoff derived from the training cohort, the Kaplan-Meier analysis demonstrated a significant difference in progression-free survival ($p = 0.0017$, Figure 5E). Specifically, low-risk patients experienced significantly prolonged progression-free survival compared to high-risk patients in both the training cohort (300 days; 95% CI: 276 - 438 vs. 165 days; 95% CI: 150 - 195; HR = 2.66 [1.92 - 3.69]; $p < 0.001$; Figure 5B) and the validation cohort (330 days; 95% CI: 233 - 468 vs. 152 days; 95% CI: 117 - 238; HR = 2.37 [1.36 - 4.13]; $p = 0.0017$; Figure 5E). The nomogram identified LDH_{T2} as the primary contributor to risk stratification (Figure 5C). Furthermore, the T2 model also shows good short-term (180-day) calibration performance in both the training and validation sets (Supplemental Figures 3E, F and 4E, F). In addition, DCA confirmed that the T2 model also offered a significantly better net benefit at both 180 and 540 days compared with the "treat all" or "treat none" strategies across a wide threshold range (10 - 80%, Supplemental Figure 5C), pointing to a clear advantage for clinical intervention guidance. Time-dependent ROC analysis demonstrated excellent differentiation ability for 180-day PFS in the training cohort (AUC = 0.814; 95% CI: 0.757, 0.87) but declined at 540 days (AUC = 0.824; 95% CI: 0.738, 0.911) (Figure 5D). In the validation cohort, the model achieved AUCs of 0.76 and 0.862 at 180 days and 540 days, respectively (Figure 5F).

DISCUSSION

Immunotherapy has achieved breakthrough progress in the treatment of ES-SCLC, yet the population benefiting clinically remains relatively limited [31]. Currently, accurately identifying patients who may potentially benefit from immunotherapy remains a major clinical challenge. Existing predictive biomarkers (such as PD-L1 expression and TMB) face difficulties in widespread clinical application due to either high testing complexity or insufficient predictive efficacy [32].

During the evaluation of various peripheral blood parameters (including complete blood count, biochemistry, and thyroid function) at different time points in relation to immunotherapy outcomes in ES-SCLC patients, we demonstrate that EOS levels serve as a potential biomarker predictive of treatment efficacy. Multivariate Cox regression analysis identified EOS levels as inde-

pendent prognostic factors for immunotherapy efficacy across all three datasets (baseline levels, on-treatment levels, and treatment-induced changes). Moreover, we found that EOS levels significantly increased post-immunotherapy in responders but decreased in non-responders. This divergent pattern underscores a potential active role for EOS in the efficacy of ES-SCLC immunotherapy. However, an intriguing finding emerged from our analysis: higher baseline eosinophil levels were correlated with poorer treatment response. It is plausible that these paradoxical dynamics reflect a dual role of EOS in the context of immunotherapy. While elevated pre-treatment EOS levels may potentially be associated with a tumor microenvironment conducive to immune evasion, therapy-induced EOS expansion could be linked to the augmentation of anti-tumor immune responses. There is substantial evidence regarding the heterogeneity of EOS. For example, a breast cancer-driven lung metastasis model identified two distinct EOS subpopulations: CD125^{int}/Siglec-F^{low} cells, which are tissue-resident, and CD125^{int}/Siglec-F^{high} cells, which are recruited [33]. In a murine allergy model, CD101⁺ EOS exhibit anti-inflammatory properties, while CD101⁻ subsets drive pro-inflammatory reactions [34]. Although direct evidence is currently lacking in the context of ES-SCLC immunotherapy, we speculate that this dual role of EOS may also be present in ES-SCLC immunotherapy. Baseline EOS may resemble the CD101⁺ subtype, which exhibits anti-inflammatory properties and could potentially favor tumor progression. In contrast, immunotherapy-expanded EOS may be analogous to the CD101⁻ subset, possibly contributing to treatment efficacy by enhancing anti-tumor immunity. This interpretation remains speculative and would require validation through functional studies. For example, it would be necessary to analyze paired tissue sections from ES-SCLC patients before and after immunotherapy, using single-cell RNA sequencing (scRNA-seq) to characterize differences in infiltrating EOS subtypes. Alternatively, scRNA-seq of peripheral blood EOS could offer a less invasive approach. However, such analyses have not been feasible due to limited sample availability. In the future, suitable mouse models may be developed to further investigate the phenotypic and functional distinctions between these EOS subpopulations in the context of cancer immunotherapy.

In this study, based on biomarker levels at different time points and their dynamic changes, we constructed three distinct models to predict immunotherapy efficacy in ES-SCLC. Although median-based dichotomization used here for Kaplan-Meier curves is data-driven and may entail information loss, it was employed solely for descriptive visualization and had no impact on the Cox regression findings. Moreover, the robustness of our conclusions is supported by sensitivity analyses using tertile-based grouping (Supplemental Figure 11). The results showed that the T0 model exhibited poor-to-fair differentiation ability, whereas the T2 model and the dynamic model (T2/T0) demonstrated comparably

promising predictive performance, as reflected by their similar C-index values (Supplemental Table 3) and ROC analysis results. The scoring system incorporates both baseline individual variations and dynamic changes during early treatment, enabling comprehensive evaluation of initial immunotherapy response. The on-treatment model based on biomarker profiles after two-cycle treatment time (T2) may represent a critical window for evaluating whether immunotherapy successfully elicits systemic anti-tumor responses. Studies indicate that the efficacy of ICI depends on T-cell clonal expansion and myeloid phenotypic switching, a process typically requiring 1 - 2 treatment cycles (corresponding to the T2 time point) for completion [35]. Based on this reason, biomarker levels after the two-cycle immunotherapy may more directly reflect whether treatment has successfully overcome the tumor's immunosuppressive barrier, thereby enabling immunotherapy efficacy. In contrast, while the baseline model shows relatively lower predictive accuracy, its reliance solely on pre-treatment data makes it inherently suitable for initial decision support. At therapy initiation, it could help identify patients most likely to benefit from the specific immunotherapy regimen, aiding in stratification and initial patient counseling. Therefore, these models may function sequentially: the baseline model offers a preliminary risk assessment, while the dynamic model refines this prognosis using early treatment response data, enabling a more personalized and adaptive management strategy throughout the care continuum. Future integration of other clinical data such as imaging information is anticipated to substantially improve predictive power, thereby boosting clinical utility.

We observed notable differences in baseline clinical characteristics between the training and validation cohorts, reflecting the inherent heterogeneity of multi-center retrospective data. As shown in Supplemental Table 4, the standardized mean differences (SMDs) for many baseline variables exhibited SMDs > 0.1 (e.g. smoking and metastases patterns), indicating meaningful cross-cohort heterogeneity. This heterogeneity, while reflective of real-world clinical diversity, may influence the generalizability of our model. Although multivariable analyses adjusted for these factors, residual confounding cannot be entirely excluded. To further evaluate whether the heterogeneity of immune checkpoint inhibitor (ICI) regimens influenced the predictive performance of our model, we conducted a stratified analysis by ICI class (PD-1 vs. PD-L1 inhibitors). The results, presented in Supplemental Table 5 and Supplemental Figure 12, demonstrated that the model maintained robust predictive performance in the PD-L1 inhibitor subgroup, with 540-day AUC values comparable to or slightly exceeding those of the overall cohort. In contrast, predictive accuracy was somewhat lower in the PD-1 inhibitor subgroup. However, the relatively limited sample size in the PD-1 group may have led to unstable performance estimates and may not reflect a true biological distinction between the two ICI classes. In

general, future studies with larger, balanced cohorts are warranted to validate our results.

This study has several other limitations. First, the retrospective design carries a risk of selection bias. While the use of an independent validation cohort mitigates this bias to some extent, the exclusion of patients who stopped treatment early (before the first scheduled assessment) may have resulted in an over-optimistic performance estimation. Furthermore, irAEs were not systematically collected or analyzed as patients with early severe irAEs were excluded from our efficacy cohort (which required completion of four treatment cycles), and mild-to-moderate events were not consistently documented in medical records. Consequently, the potential association between irAEs and treatment efficacy could not be evaluated, which may limit the comprehensiveness of the clinical interpretation of our findings. Future prospective studies with longer standardized follow-up and systematic documentation of all grades of irAEs are warranted to better address these important clinical outcomes. Secondly, our biomarker selection was restricted to a core set of baseline clinical variables (e.g. age, gender, smoking status, metastasis) and blood parameters - we intentionally focused on these easily accessible indicators to improve model availability and clinical applicability. Other key parameters, including tumor mutational burden (TMB), the expression of PD-L1, and detailed imaging features, were not included. Specifically, radiological features such as tumor size, radiomics, and early response by RECIST were not systematically available or collected in this cohort and thus could not be included in the model. We believe incorporating these could significantly enhance the model's clinical utility. Third, to ensure a sufficient number of enrolled patients with extensive-stage SCLC, this study included cases from the period 2020 - 2025. However, over this relatively long time span, gradual changes in treatment strategies, supportive care, and clinical practice may have introduced temporal confounding, and such bias cannot be completely adjusted for in the analysis. Additionally, our model, particularly the eosinophil kinetic parameters, requires external validation in larger, multi-center prospective cohorts.

CONCLUSION

In summary, this study developed three models for predicting immunotherapy efficacy in patients with ES-SCLC, utilizing routinely available blood-based indicators measured at baseline, during early treatment, and throughout their dynamic changes over time. Among these, the model incorporating dynamic changes - which innovatively integrates pre-treatment baseline heterogeneity with early-phase response - demonstrated superior predictive performance. This integrated, multidimensional framework overcomes the limitations of conventional static, single-parameter biomarkers and enables

more timely and precise prediction of patients' response to immunotherapy.

By providing a clinically applicable tool for risk stratification, this model may help guide personalized immunotherapy strategies, optimize healthcare resource allocation, and reduce unnecessary treatment-related toxicity and costs for patients unlikely to benefit. To translate this promise into practice, further large-scale, multi-center prospective studies are essential.

Beyond the development of the predictive model, our investigation revealed a clinically significant and biologically intriguing association between EOS level and treatment outcomes. We observed a dual and seemingly paradoxical role of EOS: while a high baseline EOS level was correlated with poorer prognosis, an increase in EOS during the initial phase of immunotherapy was associated with favorable therapeutic response. This heterogeneity underscores the complex, dynamic nature of the immune response elicited by treatment. This finding not only enriches our understanding of EOS as a potential dynamic biomarker but also opens new avenues for research. Future studies should focus on elucidating the underlying immunological mechanisms driving this dichotomy, which could lead to novel strategies for modulating the immune response to enhance treatment efficacy and personalize patient management in ES-SCLC immunotherapy.

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The authors declare that no AI tool was used.

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Ethical Approval Statement:

The authors state that this study was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (2025-RE-147).

Data Availability Statement:

The data that support the findings of this study are available from the corresponding author, Ming Li, upon reasonable request.

Declaration of Interest:

The authors declare that they have no competing financial interests.

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