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ORIGINAL ARTICLE

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

Kaili Wang [1, 2, 3, *], Lingyu Zhang [4, *], Ying Yan [5], Shengyu Feng [6], Lili Chen [1, 2, 3], Haonan Chen [4], Qiunan Zhu [4], Mingyang Dou [4], Yan Hua [2, 3], Ming Li [2, 3]

[*] *These authors contributed equally to this work and share first authorship*
[1] *Anhui University of Science and Technology, Huainan, Anhui, China*
[2] *Department of Laboratory Medicine, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China*
[3] *Department of Laboratory Medicine, Anhui Provincial Cancer Hospital, Hefei, Anhui, China*
[4] *Department of Laboratory Medicine, The First Affiliated Hospital of Bengbu Medical University, Bengbu, China*
[5] *Department of Medical Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China*
[6] *Institute for Regenerative Medicine, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China*

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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Correspondence:
Yan Hua
Department of Laboratory Medicine
The First Affiliated Hospital of USTC
Division of Life Sciences and Medicine
University of Science and Technology of China
Hefei
Anhui, 230031
China
Email: huayan@mail.ustc.edu.cn

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Ming Li
Department of Laboratory Medicine
The First Affiliated Hospital of USTC
Division of Life Sciences and Medicine
University of Science and Technology of China
Hefei
Anhui, 230031
China
Email: lm831216@ustc.edu.cn

Supplementary Data

Table S1: Parameter Missing Rates in the Training Cohort.

Parameter	Missing data rate (%)	
	T0 (n = 254)	T2 (n = 254)
DD	6 (2.36)	15 (5.91)
LDH	4(1.57)	
PA	2 (0.79)	2 (0.79)
NLR		2 (0.79)
A/G		1 (0.39)
HGB		1 (0.39)
GLU		1 (0.39)
TSH	17 (6.69)	22 (8.66)
FT4	28 (11.02)	32 (12.6)
FT3	28 (11.02)	31 (12.2)
AST/ALT	2 (0.79)	
SCC	64 (25.2)	84 (33.07)
NSE	21 (8.27)	25 (9.84)
CA125	85 (33.46)	89 (35.04)
CEA	27 (10.63)	33 (12.99)
CA211	60 (23.62)	73 (28.74)
ProGRP	73 (28.74)	81 (31.89)

Table S2. Bootstrap validation for $TP_{T2/T0}$.

Metric	Value
Original HR (95% CI)	0.286 (0.092 - 0.892)
Bootstrap median HR (95% CI)	0.282 (0.090 - 0.846)
Direction consistency (negative, HR < 1)	98.8% (988/1,000)
Direction consistency (positive, HR > 1)	1.2% (12/1,000)

Table S3. Harrell's C-index (95% confidence interval) for each prediction model after bootstrap internal validation.

Model	C-index (95% CI)
T0	0.66 (0.62 - 0.71)
T2	0.71 (0.67 - 0.75)
T2/T0	0.70 (0.66 - 0.74)

Table S4. Standardized Mean Differences for Baseline Characteristics.

Characteristics	SMD
Age, mean (SD), years	0.32
Gender (%)	0.025
Smoking (%)	0.461
ECOG (%)	0.086
Metastases (%)	
0	0.121
1~2	0.533
≥ 3	-0.489
Bone metastases (%)	0.265
Brain metastases (%)	0.517
Liver metastases (%)	0.051
Clinical efficacy (%)	
CR	0.163
SD	0.073
PR	0.156
PD	-0.207

SMD: standardized mean difference. SMD > 0.1 indicates a meaningful difference between cohorts.

Table S5. The predictive performance of the Models in the training cohort and PD-1/PD-L1 inhibitor subgroups.

	PD-1 (n = 68)		PD-L1 (n = 186)		Total (n = 254)	
	AUC at 180 days	AUC at 540 days	AUC at 180 days	AUC at 540 days	AUC at 180 days	AUC at 540 days
Baseline (T0)	0.619	0.727	0.647	0.793	0.717	0.818
Dynamic (T2/T0)	0.68	0.722	0.758	0.884	0.779	0.83
On-treatment (T2)	0.722	0.792	0.775	0.71	0.814	0.824

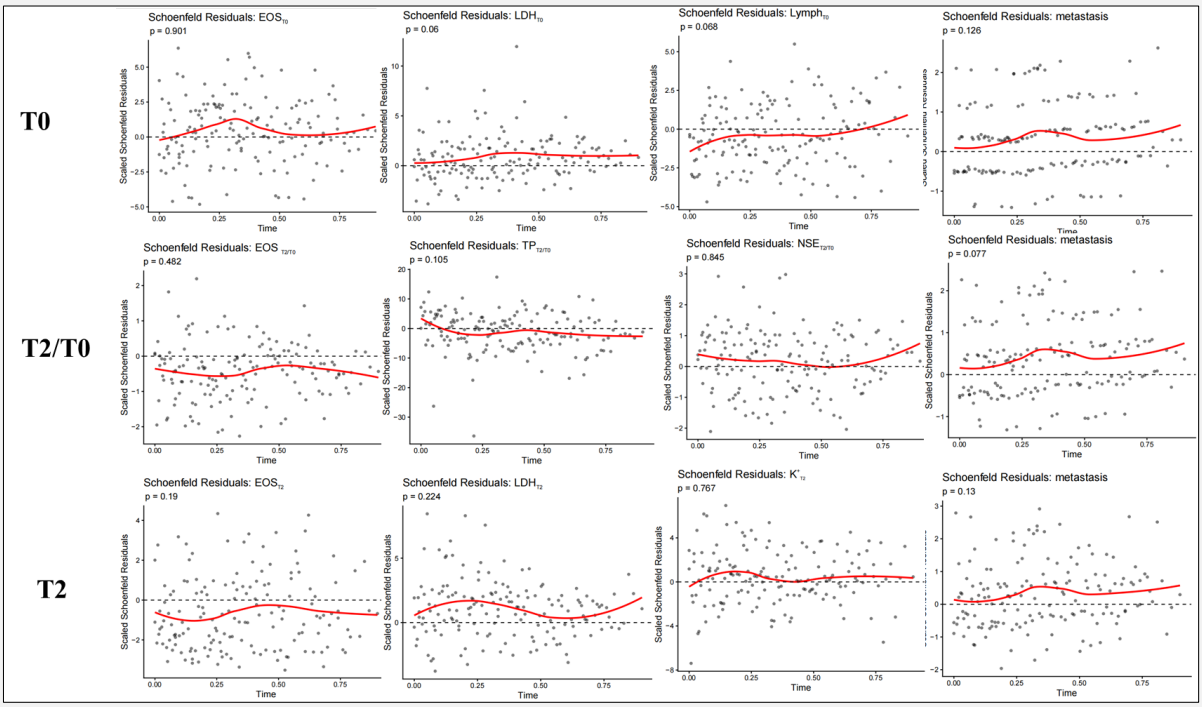

Figure S1. Schoenfeld residual plots for each variable in the T0, T2/T0, and T2 models. The proportional hazards assumption was tested using Schoenfeld residuals. p > 0.05 indicates no violation. All variables in the three models showed p > 0.05, confirming the assumption. All tests were performed in R.

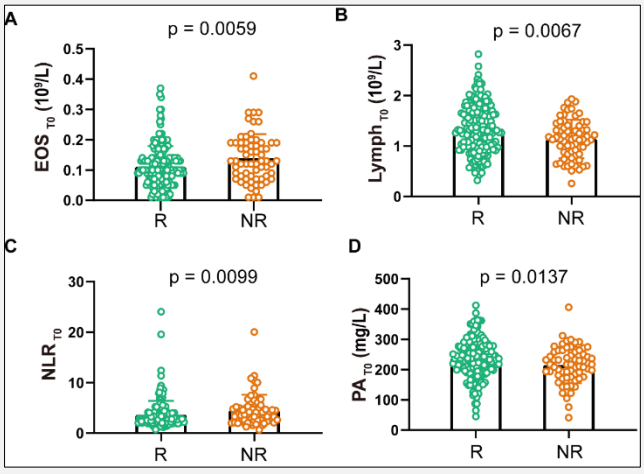

Figure S2. Baseline levels (T0) of laboratory parameter associated with the response of immunotherapy in patients with ES-SCLC.

A - D: A: EOS, B: Lymph, C: NLR, D: PA. EOS: Eosinophils, Lymph: Lymphocytes, NLR: Neutrophil-to-lymphocyte ratio, PA: Prealbumin, R: responders, NR: non-responders. The Shapiro-Wilk test was used to assess normality. Prealbumin (PA) was normally distributed, and between-group comparisons were performed using independent samples t-test. Eosinophils (EOS), lymphocytes (Lymph), and neutrophil-to-lymphocyte ratio (NLR) were non-normally distributed, and between-group comparisons were performed using the Mann-Whitney U test. All statistical analyses were conducted using GraphPad Prism.

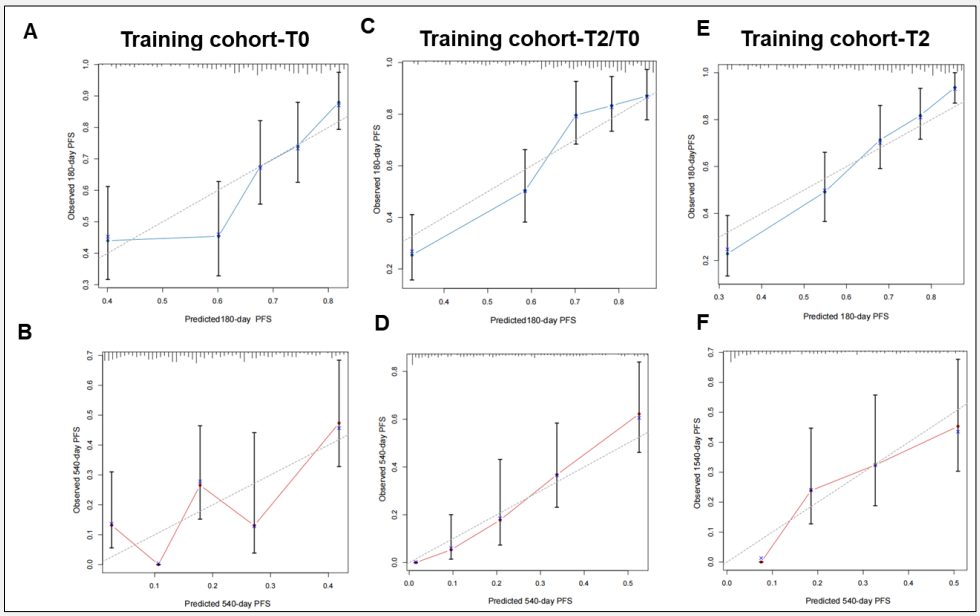

Figure S3. Calibration plots for the T0, T2/T0, and T2 models in the training cohort at 180 days and 540 days.

A - B: Training cohort of T0 (180-day and 540-day), C - D: Training cohort of T2/T0 (180-day and 540-day), E - F: Training cohort of T2 (180-day and 540-day). All tests were performed in R.

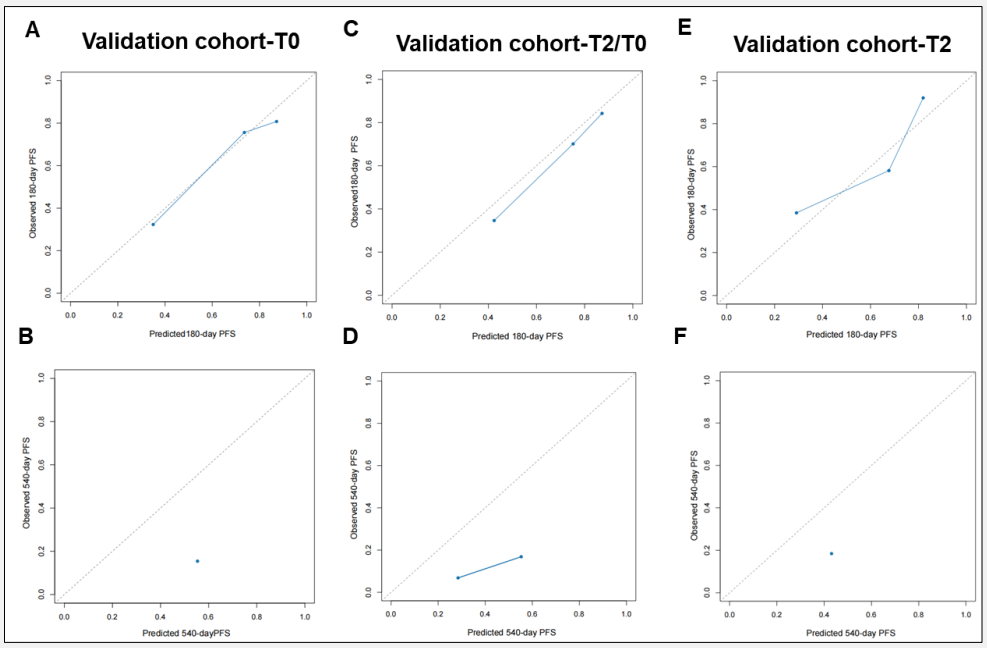

Figure S4. Calibration plots for the T0, T2/T0, and T2 models at 180 days and 540 days in the validation cohort.

A - B: Validation cohort of T0 (180-day and 540-day), C - D: Validation cohort of T2/T0 (180-day and540-day), E - F: Validation cohort of T2 (180-day and 540-day). All tests were performed in R.

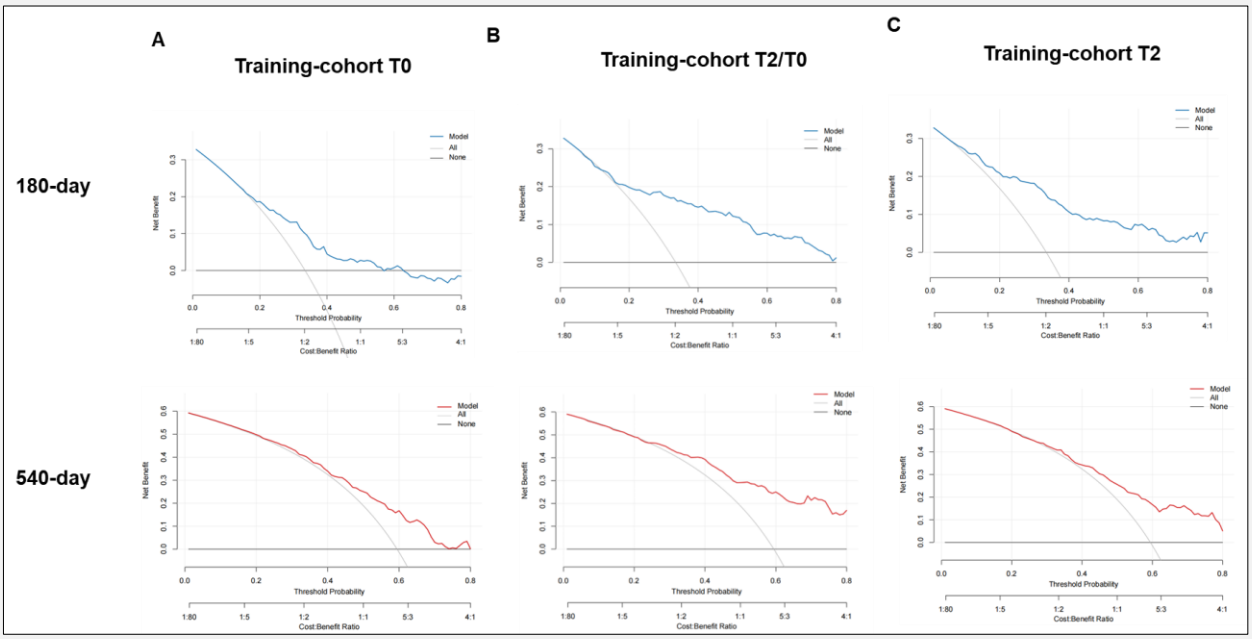

Figure S5. Decision curve analysis (DCA) of the nomogram for predicting 180-day and 540-day progression-free survival (PFS) in the training set.

A: DCA of the nomogram based on the T0 model for predicting 180-day and 540-day PFS in the training set. B: DCA of the nomogram based on the T2/T0 model for predicting 180-day and 540-day PFS in the training set. C: DCA of the nomogram based on the T2 model for predicting 180-day and 540-day PFS in the training set. All tests were performed in R.

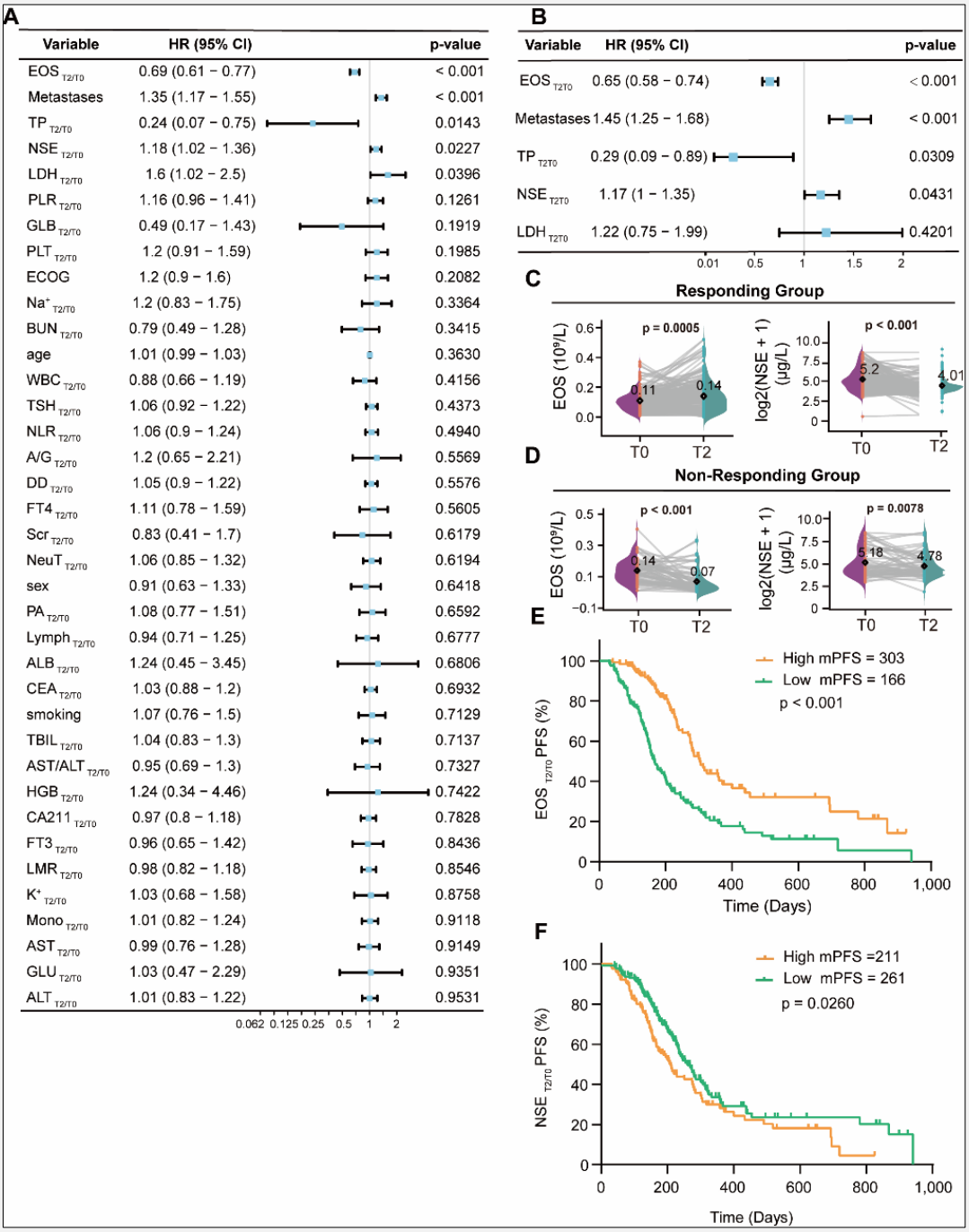

Figure S6. Dynamic Changes during treatment in Peripheral Blood Biomarkers (T2/T0) associated with Immunotherapy response in ES-SCLC.

A - B: Forest plots display A: univariate and B: multivariate Cox proportional hazards regression analyses of progression-free survival (PFS). C - D: Paired longitudinal analysis at T0 and T2 in C: responders and D: non-responders. Normality assessed by Shapiro-Wilk test. In Responding Group: EOS (normal, paired t-test), NSE (non-normal, Wilcoxon Wilcoxon signed-rank test). In Non-Responding Group: both EOS and NSE (non-normal, Wilcoxon). E - F: Kaplan-Meier survival curves stratified by dynamic changes in: E: eosinophil (EOS $_{T2/T0}$) and F: NSE (NSE$_{T2/T0}$). EOS: Eosinophils, NSE: Neuron-Specific Enolase, PFS: progression-free survival. T2/T0 represents the percentage change after two immunotherapy cycles relative to baseline. Connecting lines indicate paired samples from individual patients. 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. Cox proportional hazards models (using the survival package) and paired comparisons were performed in R, while Kaplan-Meier analyses for single indicators were conducted using GraphPad Prism.

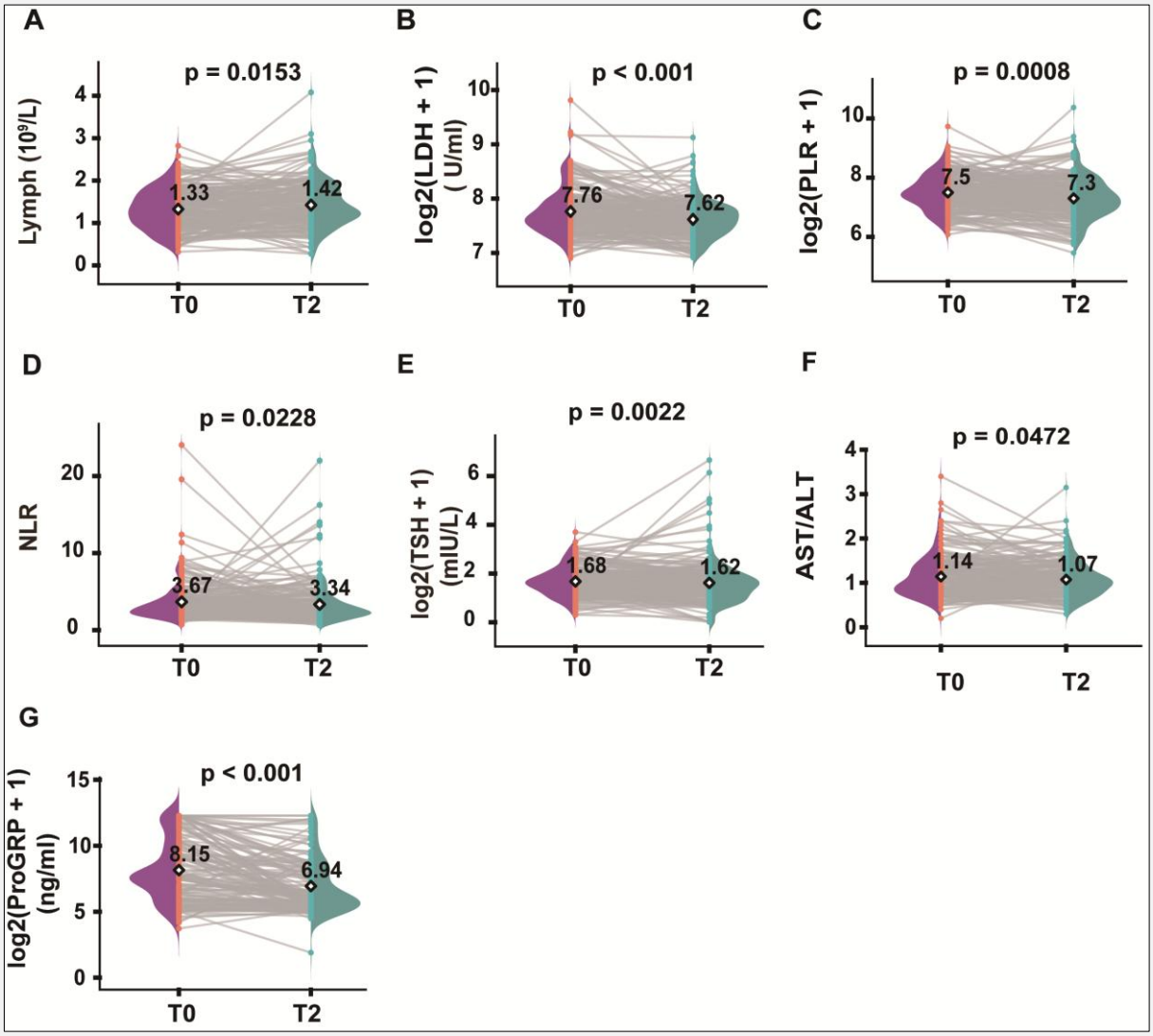

Figure S7. Paired Analysis of dynamic changes in laboratory parameters from Baseline to On-Treatment in Responders.

A - L: A: Lymph, B: LDH, C: PLR, D: NLR, E: TSH, F: AST/ALT, G: ProGRP, Laboratory Parameters processed by log2(x + 1) included LDH, PLR, TSH, ProGRP. Lymph: Lymphocytes, LDH: Lactate Dehydrogenase, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophils-to-lymphocyte ratio, TSH: Thyroid-Stimulating Hormone, AST/ALT: AST/ALT Ratio, ProGRP: Pro.gastrin.releasing Peptide, T0: pre-treatment, T2: on-treatment. The Shapiro-Wilk test was used to assess normality. In the Responding Group, Lymph was normally distributed (paired t-test), while LDH, PLR, NLR, TSH, AST/ALT and ProGRP were non-normally distributed (Wilcoxon signed-rank test). All t-tests were performed in R.

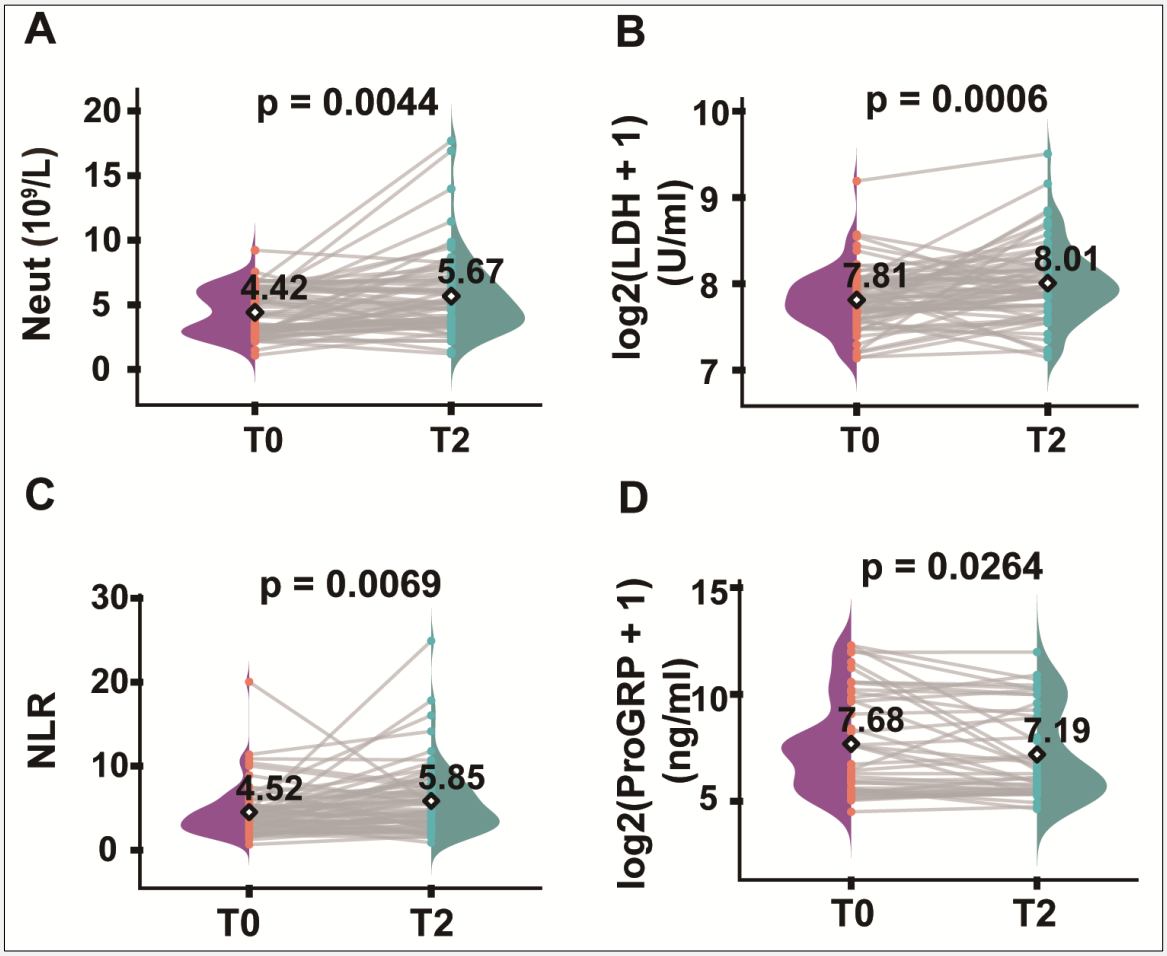

Figure S8. Paired Analysis of dynamic Changes in laboratory parameters from Baseline to On-Treatment in Non-responders.

A - D: A: Neut, B: LDH, C: NLR, D: ProGRP, LDH and ProGRP were processed by log2(x + 1). Neut: Neutrophils, Mono: Monocytes, LDH: Lactate Dehydrogenase, NLR: Neutrophil-to-lymphocyte ratio, ProGRP: Pro.gastrin.releasing Peptide, T0: pre-treatment, T2: on-treatment. The Shapiro-Wilk test was used to assess normality. In the Non-Responding Group, Neut, LDH, NLR, and ProGRP were non-normally distributed (Wilcoxon signed-rank test). All t-tests were performed in R.

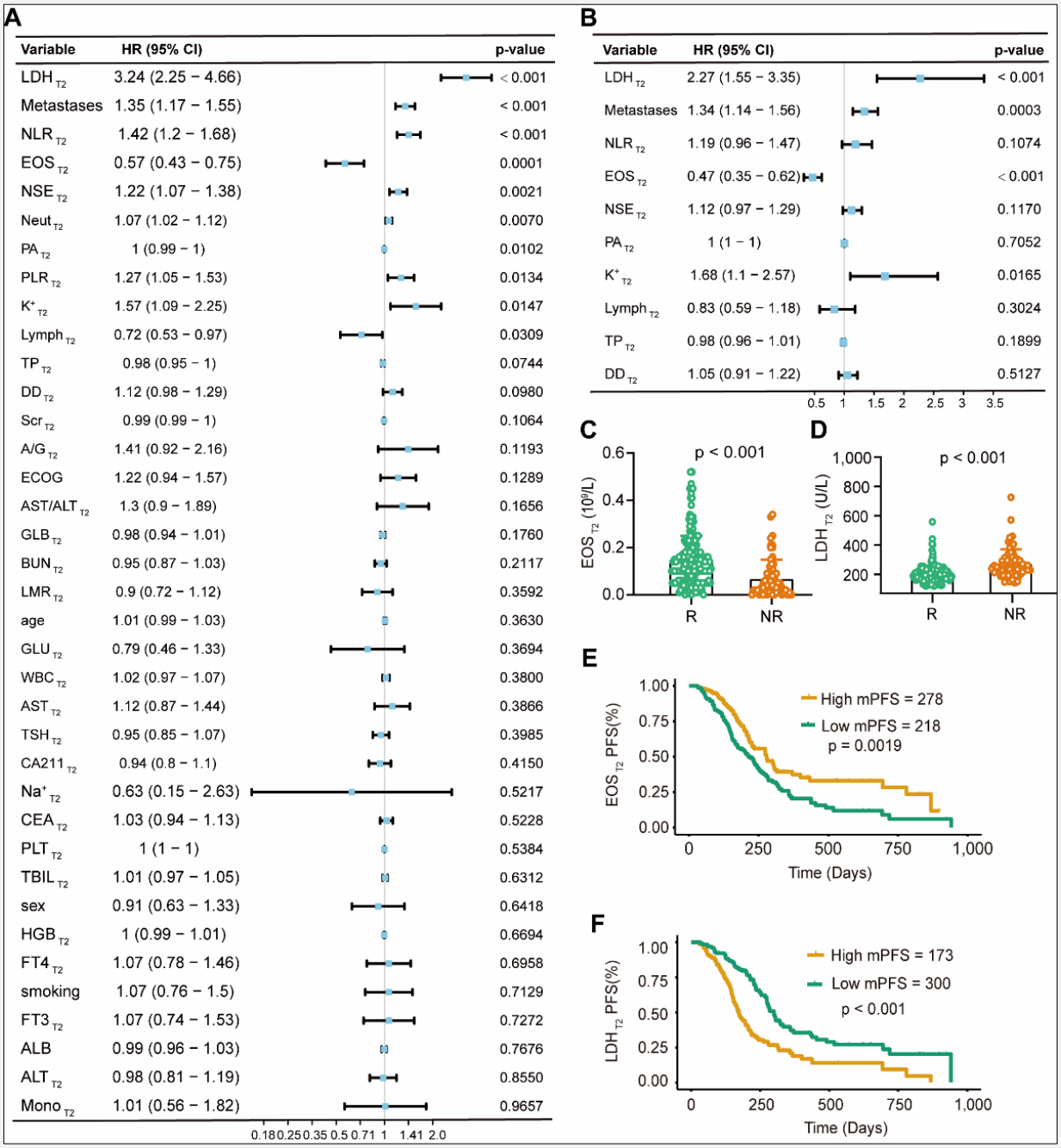

Figure S9. Association between on-treatment clinical variables and immunotherapy efficacy in ES-SCLC patients.

A - B: Forest plots display A: univariate and B: multivariate Cox proportional hazards regression analyses of PFS, C - D: Comparison of pretreatment laboratory parameters between responders (R) and non-responders (NR): C: EOS, D: LDH, E -F: Kaplan-Meier survival curves for PFS stratified by baseline levels of E: EOS, F: LDH, (dichotomized at median values). T2 indicates on-treatment; 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. HR: Hazard ratio, EOS: Eosinophils, LDH: Lactate Dehydrogenase, Metastases refers to the number of sites of tumor metastasis. The Shapiro-Wilk test was used to assess normality. In the comparison between responders and non-responders, EOS and LDH were all non-normally distributed, and the Mann-Whitney U test was applied. All such comparisons, along with Kaplan-Meier analyses for single indicators, were performed using GraphPad Prism. Cox proportional hazards models were fitted using the survival package in R.

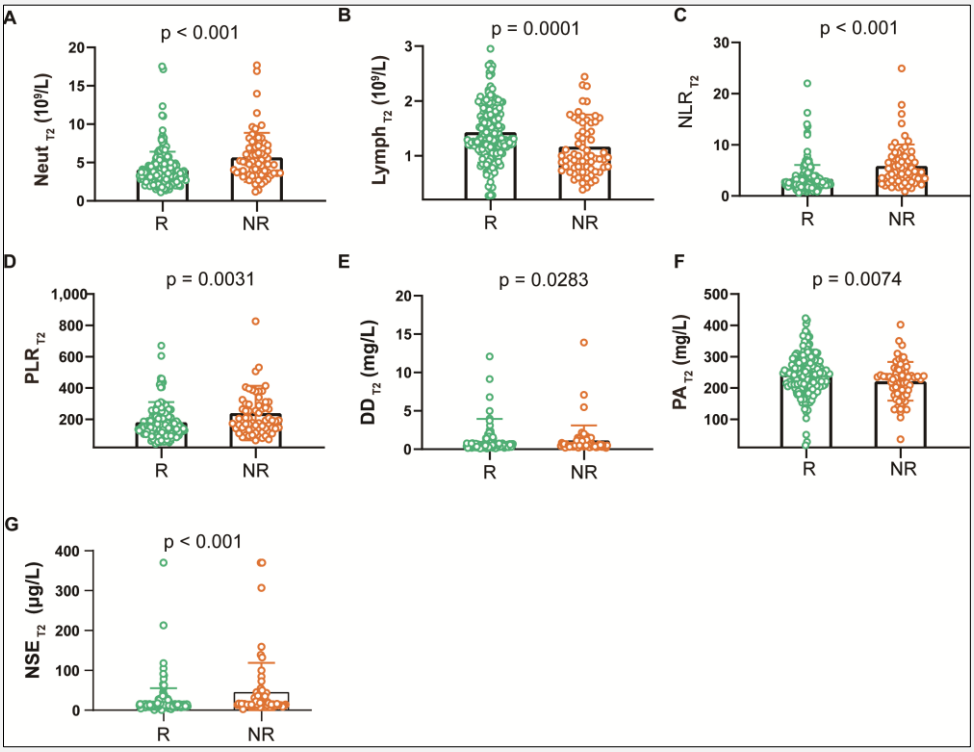

Figure S10. On-treatment levels (T2) of laboratory parameter associated with the response of immunotherapy in patients with ES-SCLC.

A - F: A: Neut, B: Lymph, C: NLR, D: PLR, E: DD, F: PA, G: NSE. Neut: Neutrophils, Lymph: Lymphocytes, NLR: Neutrophils-to-lymphocyte ratio, DD: D-Dimer, PA: Prealbumin, NSE: Neuron-Specific Enolase. R: responders, NR: non-responders. Normality assessed by Shapiro-Wilk test. Neut, Lymph, NLR, PLR, DD, PA and NSE were all non-normally distributed (Mann-Whitney U test). All analyses were performed using GraphPad Prism.

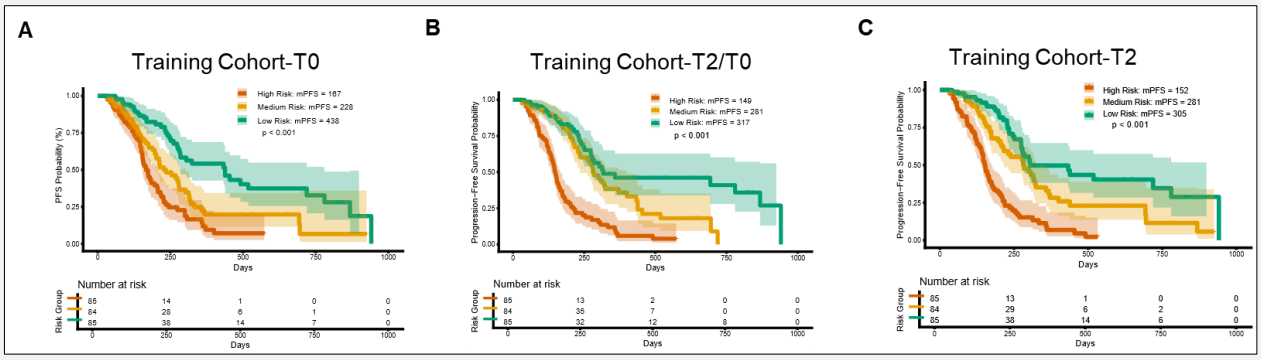

Figure S11. Kaplan-Meier survival curves from sensitivity analyses based on tertile grouping in the training set for the T0, T2/T0, and T2 models.

A - C: Corresponding curves for T0, T2/T0, and T2, respectively. The log-rank test showed statistically significant survival differences among the three risk groups across all models (p < 0.001). Kaplan-Meier survival curves were generated using R software (Version 4.2.3) with the survival package.

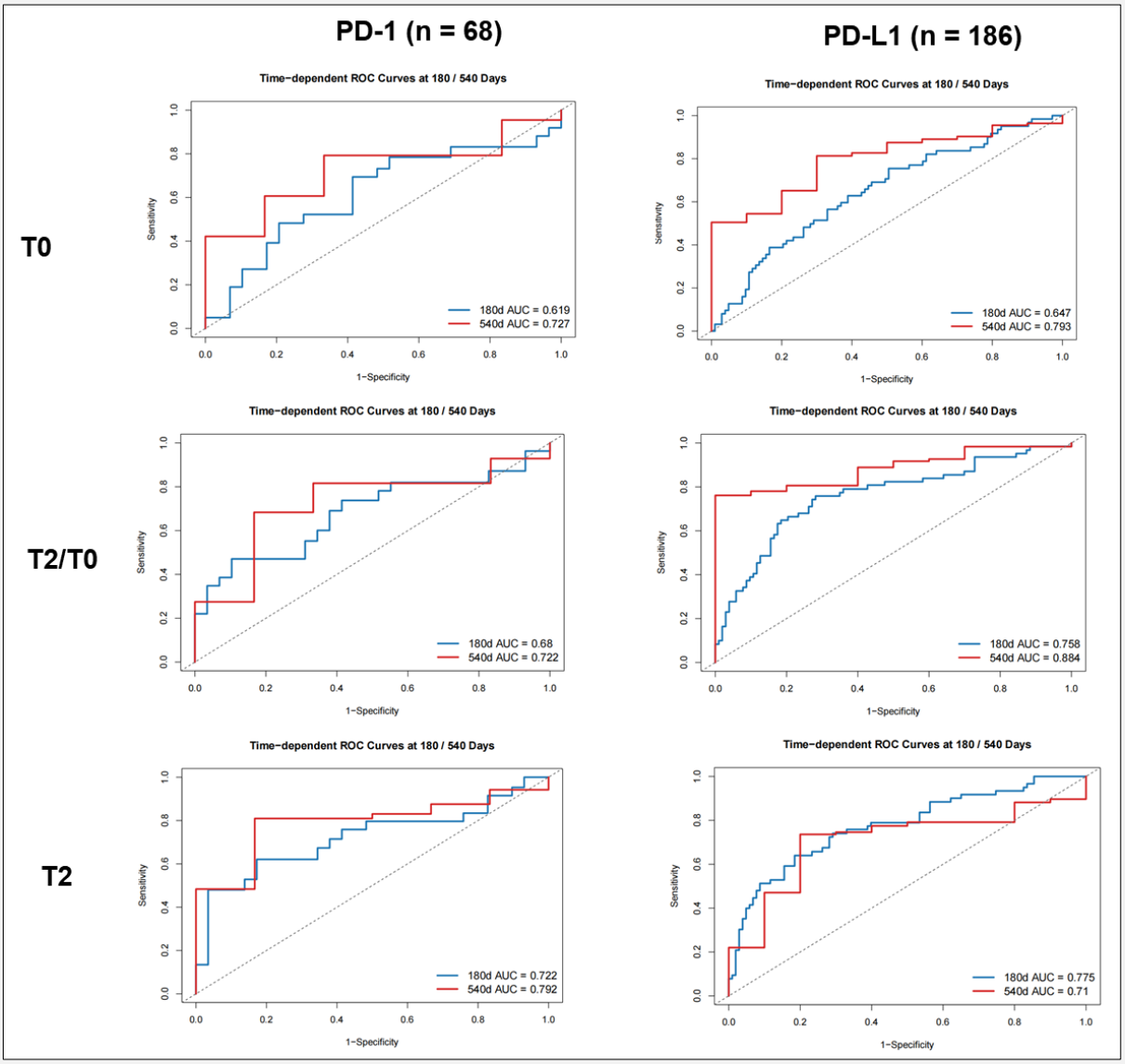

Figure S12. Time-dependent ROC curves for the predictive models stratified by ICI class. Time-dependent ROC curves were generated using R software (Version 4.2.3) with the timeROC package.