

A Prognostic Nomogram Combining Postoperative SII and PIV Improves Long-Term Survival Prediction in NSCLC

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Purpose: Systemic inflammation plays a crucial role in the progression and prognosis of non-small cell lung cancer (NSCLC), yet the prognostic value of perioperative inflammatory markers remains underexplored.

Patients and methods: We retrospectively analyzed 243 patients who underwent resection (2015–2019) at The Second Xiangya Hospital. Five inflammatory indices—neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and pan-immune-inflammation value (PIV)—were calculated from pre- and postoperative blood counts, and their changes (Δ values) were derived. Prognostic markers were identified using receiver operating characteristic (ROC) curve analysis, Cox regression, least absolute shrinkage and selection operator (LASSO), and stepwise selection. A nomogram was developed in a training cohort and internally validated using a 70/30 hold-out split from the same center.

Results: Postoperative SII and PIV, along with their perioperative changes (Δ SII and Δ PIV), showed superior prognostic performance compared to preoperative values. The final nomogram (POST_SII, POST_PIV, clinical tumor-node-metastasis stage, smoking history, preoperative albumin, age, and gender) achieved a concordance index (C-index) of 0.85 in the training cohort, with area under the curve (AUCs) of 0.86, 0.89, and 0.94 at 1-, 3-, and 5-year, and a C-index of 0.80 with AUCs of 0.74, 0.85, and 0.90 in the validation cohort. The model surpassed TNM and clinical models and showed greater net clinical benefit in decision-curve analysis.

Conclusion: Postoperative SII and PIV are strong inflammatory predictors of survival after NSCLC resection. A nomogram integrating these markers with clinical variables provides accurate, individualized risk stratification.

Keywords: nomogram, survival prediction, systemic immune-inflammation index, pan-immune-inflammation value, postoperative prognosis

Introduction

Non-small cell lung cancer (NSCLC) is one of the most prevalent malignancies worldwide, accounting for approximately 18.7% of total cancer deaths.¹ Surgical resection is the primary curative treatment for NSCLC; however, the postoperative prognosis varies significantly.² While traditional staging systems, such as TNM staging, provide prognosis estimates, they primarily focus on anatomical tumor characteristics and fail to fully capture the complex biological processes underlying tumor progression, including the patients' systemic immune-inflammatory status and dynamic perioperative changes.³

Mounting evidence highlights the pivotal role of systemic inflammation in tumor initiation, progression, and metastasis.^{4,5} Inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been extensively linked to poor prognosis in cancers.⁶ However, most NSCLC prognostic nomograms

have been derived from preoperative/baseline variables (clinicopathologic features and inflammatory measures), with postoperative and perioperative dynamics remaining under-represented.^{7,8} Surgical stress elicits a systemic inflammatory response, transient immune disequilibrium, and metabolic reprogramming that remodel the tumor microenvironment (TME) and dampen immune surveillance in the early postoperative period. Accordingly, capturing perioperative inflammatory dynamics may yield prognostic signals that are stronger and more clinically actionable than those provided by preoperative indices alone.⁹

In this study, we conducted retrospective study to comprehensively investigate the association between dynamic perioperative immune-inflammatory indices and survival. By quantifying both preoperative baseline and postoperative changes in inflammatory markers, this model seeks to enhance the precision of long-term survival prediction in NSCLC patients. The successful implementation of such a dynamic prognostic tool could significantly advance personalized medicine by enabling more stratified risk assessment and tailored therapeutic interventions.

Methods

Patients and Participants

This retrospective study included a total of 243 patients with non-small cell lung cancer (NSCLC) who underwent curative-intent surgical resection at The Second Xiangya Hospital of Central South University between January 2015 and December 2019. All patients were pathologically confirmed to have NSCLC and completed comprehensive clinical evaluations both preoperatively and postoperatively.

Inclusion Criteria: ① Patients with histopathologically confirmed NSCLC who received their initial diagnosis and underwent surgical resection at our institution; ② Availability of complete clinical, pathological, and imaging data, including peripheral blood test results within 3–5 days before and after surgery; ③ Availability of complete follow-up information on overall survival (OS).

Exclusion Criteria: ① Death within 30 days after surgery. ② Presence of chronic respiratory diseases (eg, bronchial asthma, chronic obstructive pulmonary disease, interstitial pulmonary fibrosis) or other severe comorbidities deemed by the attending physician to significantly impair surgical tolerance or long-term prognosis; ③ History of malignancies other than NSCLC; ④ Presence of clinically confirmed acute infections (eg, pneumonia, urinary tract infection, skin and soft tissue infections) within one month prior to surgery, or administration of antibiotics due to infection during the same period.

OS and Follow-Up

Overall survival (OS) was defined as the interval from the date of surgery to the date of death from any cause or the last follow-up. Patients who remained alive at the last follow-up were censored at 60 months. The follow-up duration was calculated from the date of surgery to the date of last contact or death.

Clinical Information

Clinical data were obtained from the hospital's electronic medical record system, outpatient follow-up records, and regular postoperative surveillance. The following variables were collected: gender, age, smoking history, body mass index (BMI), surgery type, clean node number, tumor location, lobe number, histology, clinical tumor-node-metastasis stage (cTNM stage), T stage, lymph node metastasis, and pathological features including pleural invasion, neural invasion, vascular invasion, and programmed death-ligand 1 expression (PD-L1 expression). The PD-L1 status was retrieved from pathology reports and recorded as the tumor proportion score (TPS, %).

Inflammatory Indices and Calculation

Peripheral blood samples collected within 3–5 days before and 3–5 days after surgery were used to assess routine hematological parameters, including neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MON), platelet count (PLT), and serum albumin level (ALB). Based on these values, five systemic inflammation-based composite indices were calculated as follows:

Neutrophil-to-lymphocyte ratio (NLR) = NEU / LYM

Platelet-to-lymphocyte ratio (PLR) = PLT / LYM

Systemic immune-inflammation index (SII) = (PLT × NEU) / LYM

Systemic inflammation response index (SIRI) = (NEU × MON) / LYM

Pan-immune-inflammation value (PIV) = (NEU × PLT × MON) / LYM

Each index was calculated at two timepoints: preoperatively and postoperatively, denoted respectively by the prefixes PRE_ (eg, PRE_SII) and POST_ (eg, POST_PIV). In addition, delta values (Δ) were derived to reflect perioperative changes, defined as the difference between postoperative and preoperative values (eg, Δ SII = POST_SII – PRE_SII). These Δ values were used to assess dynamic alterations in systemic inflammation during the perioperative period and to explore their potential prognostic implications.

Statistical Analysis

Continuous variables were presented as mean \pm standard deviation and compared using the Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. Categorical variables were summarized as counts and percentages and compared using the chi-squared test. Five inflammation-based composite indices (NLR, PLR, SII, SIRI, and PIV) were derived from preoperative (PRE_) and postoperative (POST_) peripheral blood values, including neutrophils (NEU), lymphocytes (LYM), monocytes (MON), platelets (PLT), and albumin (ALB). Perioperative changes (Δ values) were calculated as POST_ minus PRE_ (eg, Δ SII = POST_SII – PRE_SII). All patients (N = 243) were randomly divided into a training cohort (70%) and a validation cohort (30%). Unless otherwise specified, all modeling procedures were performed in the training cohort.

In the training cohort, conventional receiver operating characteristic (ROC) curves were first used to determine the optimal cutoff values of each inflammation index using the Youden index, which were then applied to stratify patients into high- and low-risk groups for Kaplan–Meier survival analysis. Prognostic performance of individual indices was further evaluated using time-dependent ROC curves (TIMEROC) and Harrell's concordance index (C-index). Subsequently, univariate Cox regression was performed to identify clinical variables associated with overall survival (OS). Each significant clinical variable ($P < 0.05$) was then individually included in multivariate Cox regression with each inflammation index to examine the independent prognostic value of each index. The area under the curve (AUC) and C-index were used to compare the discriminative performance of these multivariate models. Based on these analyses, four optimal indices (POST_SII, POST_PIV, Δ SII, and Δ PIV) were selected for model construction. To further explore potential non-linear associations between each inflammation-based index and overall survival, restricted cubic spline (RCS) functions with four knots were fitted in univariable Cox proportional hazards models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were plotted across the range of each continuous variable, and log-likelihood ratio tests were used to assess evidence of non-linearity.

All clinical variables with statistical significance in univariate Cox analysis, along with the selected four inflammation indices, were subjected to least absolute shrinkage and selection operator (LASSO) regression with the λ_{1se} criterion to reduce collinearity and avoid overfitting. The retained variables were further refined by stepwise multivariate Cox regression to determine the final predictors for model development.¹⁰ Age and gender were included in the model based on clinical relevance, regardless of statistical significance. Three hierarchical prognostic models were constructed: the TNM model (cTNM stage only), the Clinical model (cTNM plus clinical predictors), and the Nomogram model (Clinical model plus POST_SII and POST_PIV) (Table 1). Model performance was evaluated using time-dependent AUC and Harrell's C-index. Calibration plots and Kaplan–Meier curves were used to assess predictive accuracy and survival

Table 1 Model Characteristics

Model	Characteristics
TNM	cTNM Stage
Clinical	cTNM Stage, Age, Smoking History, Gender, Preoperative Albumin,
Nomogram	cTNM Stage, Age, Smoking History, Gender, Preoperative Albumin, Postoperative SII, Postoperative PIV

stratification. Decision curve analysis (DCA) was performed to assess clinical utility at 1, 3, and 5 years. Reclassification performance was further compared across models using net reclassification improvement (NRI) and integrated discrimination improvement (IDI), with the TNM model as the reference. The proportional hazards (PH) assumption for the final multivariable Cox model was assessed using Schoenfeld residuals and log–log survival plots to ensure that the PH assumption was not violated.

To address potential bias from a single 70/30 split and assess robustness, we applied two procedures using the final seven-variable Cox model (Smoking History, cTNM stage, Preoperative Albumin, POST_SII, POST_PIV, Age, and Gender): (i) 5-fold cross-validation in the training cohort and (ii) 100 repeated 70/30 random splits of the full cohort. Discrimination was summarized by Harrell's C-index and time-dependent AUCs at 1, 3, and 5 years; AUCs were estimated with Uno's method, and time points with insufficient events or at-risk subjects were treated as NA and excluded from averaging. Results are reported as mean \pm standard deviation across folds or splits.

All statistical analyses were conducted using R software (version 4.3.2), and a two-sided P value < 0.05 was considered statistically significant. The study design and patient selection process are summarized in [Supplementary Figure 1](#).

Results

Patient Baseline Characteristics

The study included the retrospective analysis of 243 patients with NSCLC who underwent curative-intent surgical resection at the Second Xiangya Hospital of Central South University from January 2015 and December 2019. The characteristics of the patients were displayed in [Table 2](#). The mean age was 58.0 ± 9.9 years, and the cohort included 152 (62.6%) males and 91 (37.4%) females. Prognosis was retrospectively evaluated through an analysis

Table 2 Clinical Characteristics

Characteristics	Live	Dead	Total	P value
	(N=137)	(N=106)	(N=243)	
Gender				<0.001
Female	65 (47.4%)	26 (24.5%)	91 (37.4%)	
Male	72 (52.6%)	80 (75.5%)	152 (62.6%)	
Age	57.3 \pm 10.3	58.9 \pm 9.3	58.0 \pm 9.9	0.219
Smoking History				<0.001
No	97 (70.8%)	48 (45.3%)	145 (59.7%)	
Yes	40 (29.2%)	58 (54.7%)	98 (40.3%)	
BMI(kg/m ²)	23.4 \pm 3.5	23.6 \pm 3.3	23.5 \pm 3.4	0.699
Surgery Type				0.074
Wedge Resection	13 (9.5%)	10 (9.4%)	23 (9.5%)	
Lobectomy	118 (86.1%)	83 (78.3%)	201 (82.7%)	
Thoracotomy	6 (4.4%)	13 (12.3%)	19 (7.8%)	
Clean Node Number	5.2 \pm 1.9	5.3 \pm 2.1	5.2 \pm 2.0	0.593
Tumor Location				1
Left	53 (38.7%)	41 (38.7%)	94 (38.7%)	
Right	84 (61.3%)	65 (61.3%)	149 (61.3%)	
Lobe Number				0.276
Multiple	10 (7.3%)	13 (12.3%)	23 (9.5%)	
Single	127 (92.7%)	93 (87.7%)	220 (90.5%)	
Histology				0.007
Adenocarcinoma	108 (78.8%)	66 (62.3%)	174 (71.6%)	
Non-Adenocarcinoma	29 (21.2%)	40 (37.7%)	69 (28.4%)	

(Continued)

Table 2 (Continued).

Characteristics	Live	Dead	Total	P value
	(N=137)	(N=106)	(N=243)	
cTNM Stage				<0.001
Clinical I	116 (84.7%)	36 (34.0%)	152 (62.6%)	
Clinical II	16 (11.7%)	42 (39.6%)	58 (23.9%)	
Clinical III	5 (3.6%)	28 (26.4%)	33 (13.6%)	
T Stage				<0.001
T1	97 (70.8%)	46 (43.4%)	143 (58.8%)	
T2	38 (27.7%)	53 (50.0%)	91 (37.4%)	
T3+	2 (1.5%)	7 (6.6%)	9 (3.7%)	
Lymph Node Metastasis				<0.001
No Lymph Node Metastasis	124 (90.5%)	63 (59.4%)	187 (77.0%)	
Single-Station Metastasis	8 (5.8%)	30 (28.3%)	38 (15.6%)	
Multi-Station Metastasis	5 (3.6%)	13 (12.3%)	18 (7.4%)	
Pleural Invasion				0.156
No	103 (75.2%)	70 (66.0%)	173 (71.2%)	
Yes	34 (24.8%)	36 (34.0%)	70 (28.8%)	
Neural Invasion				0.171
No	136 (99.3%)	102 (96.2%)	238 (97.9%)	
Yes	1 (0.7%)	4 (3.8%)	5 (2.1%)	
Vascular Invasion				0.184
No	134 (97.8%)	100 (94.3%)	234 (96.3%)	
Yes	3 (2.2%)	6 (5.7%)	9 (3.7%)	
PD-L1 expression(%)	2.6 ± 10.7	10.8 ± 23.8	6.2 ± 18.0	0.001

of varied 5-year survival rates. Among these 243 patients, 137 patients were alive at the last follow-up, while 106 patients had passed away (Table 2). Compared with the survival group, the death group showed significantly different distribution in gender (75.5% male vs 24.5% female, $P < 0.001$), smoking history (54.7% smokers vs 45.3% non-smokers, $P < 0.001$), and adenocarcinoma histology (62.3% vs 37.7% non-adenocarcinoma, $P = 0.007$). In the death group, advanced clinical stage (cTNM stage II–III: 66% vs 34%, $P < 0.001$), higher T stage ($P < 0.001$), and more frequent lymph node metastasis ($P < 0.001$) were more often seen, indicating a more advanced disease state.

We specifically evaluate the difference in systemic immune-inflammation indices (Table 3). Indicators from peripheral blood demonstrated that the death group had significantly elevated preoperative levels of neutrophil ($P = 0.013$),

Table 3 Inflammation-Related Indices' Characteristics

Characteristics	Live	Dead	P value
	(N=137)	(N=106)	
Preoperative Neutrophil($\times 10^9/L$)	3.7 ± 1.2	4.1 ± 1.4	0.013
Preoperative Lymphocyte($\times 10^9/L$)	1.8 ± 0.6	1.7 ± 0.6	0.476
Preoperative Platelet($\times 10^9/L$)	209.4 ± 61.7	232.1 ± 78.7	0.016
Preoperative Monocyte($\times 10^9/L$)	0.3 ± 0.2	0.4 ± 0.2	0.001
Preoperative Albumin(g/L)	40.0 ± 3.4	38.8 ± 3.9	0.009
Preoperative NLR	2.2 ± 0.9	2.6 ± 1.4	0.015
Preoperative PLR	126.8 ± 50.0	147.9 ± 66.1	0.007
Preoperative SII	479.6 ± 275.7	615.1 ± 385.8	0.003

(Continued)

Table 3 (Continued).

Characteristics	Live	Dead	P value
	(N=137)	(N=106)	
Preoperative SIRI	0.8 ± 0.7	1.1 ± 0.8	0.001
Preoperative PIV	178.5 ± 175.6	267.7 ± 219.2	0.001
Postoperative Neutrophil($\times 10^9/L$)	9.3 ± 3.3	11.2 ± 3.3	<0.001
Postoperative Lymphocyte($\times 10^9/L$)	1.3 ± 0.5	1.0 ± 0.4	<0.001
Postoperative Platelet($\times 10^9/L$)	211.6 ± 64.5	251.1 ± 98.7	<0.001
Postoperative Monocyte($\times 10^9/L$)	0.6 ± 0.2	0.8 ± 0.5	<0.001
Postoperative Albumin(g/L)	35.2 ± 3.4	34.3 ± 4.2	0.072
Postoperative NLR	8.0 ± 3.5	13.1 ± 6.5	<0.001
Postoperative PLR	181.1 ± 62.3	283.3 ± 139.1	<0.001
Postoperative SII	1606.7 ± 607.9	3133.5 ± 1870.8	<0.001
Postoperative SIRI	4.6 ± 2.8	10.1 ± 9.3	<0.001
Postoperative PIV	941.3 ± 564.4	2418.6 ± 2398.7	<0.001
Δ NLR	5.8 ± 3.7	10.3 ± 6.5	<0.001
Δ PLR	54.3 ± 64.3	135.4 ± 123.6	<0.001
Δ SII	1117.6 ± 634.5	2475.6 ± 1687.2	<0.001
Δ SIRI	3.8 ± 2.8	8.8 ± 9.4	<0.001
Δ PIV	758.5 ± 557.4	2127.9 ± 2326.6	<0.001

Abbreviations: PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value; Δ , postoperative value minus preoperative value.

platelet ($P = 0.016$), and monocyte ($P = 0.001$), along with reduced albumin levels ($P = 0.009$). The immunohistochemical test showed that the death group had notably increased PD-L1 expression levels (10.8 ± 23.8 vs 2.6 ± 10.7 , $P = 0.001$). This indicates that the baseline inflammation status might negatively influence the postoperative prognosis of lung cancer patients, while immune nutritional status has positive impacts.

After the operation, systemic inflammation is commonly seen in most patients, which is a usual response to surgical trauma. After the operation, the patients showed increased neutrophils and decreased lymphocytes and albumin. Compared to the survival group, the death group had significantly increased levels of neutrophils ($P < 0.001$), platelets ($P < 0.001$), and monocytes ($P < 0.001$), along with notably reduced levels of lymphocytes ($P < 0.001$). This indicates that the occurrence of inflammation after operation might negatively influence the postoperative prognosis of lung cancer patients. Several established inflammation indices are recognized as superior prognostic indicators compared to single inflammatory cell counts. Consistent with this, we revealed significantly higher preoperative and postoperative levels of five inflammatory indices, including NLR, PLR, SII, SIRI, and PIV, in the death group than in the survival group (Table 3). Importantly, the postoperative and Δ (change) values of these indices revealed greater differences between the two groups than their preoperative values, underscoring the significance on prognosis of perioperative inflammatory status. These results suggest that heightened inflammatory activity, particularly when sustained postoperatively or rising perioperatively, is closely linked to adverse long-term prognosis.

Inflammation-Based Indices as Predictors of Long-Term Survival

We subsequently examined the prognostic performance of these preoperative, postoperative, and Δ (post-pre) inflammation-related indices using time-dependent ROC curves and the concordance index (C-index). After determining optimal cutoff values via ROC analysis (Youden's index), we conducted univariate Cox regression for clinical variables and each inflammation marker. Significant clinical variables ($P < 0.05$) and individual inflammation markers were then included in multivariate Cox models. To reduce overfitting, the cohort ($N = 243$) was randomly split into a training set (70%, $n = 170$) and a testing set (30%, $n = 73$). All model development and cutoff determination were conducted solely in the training set.

As an initial screening step, 15 inflammatory markers were assessed for overall prognostic performance using time-dependent AUCs and Harrell's C-index. Patients were dichotomized into high and low groups according to ROC-derived cut-off values for each inflammatory index ([Supplementary Figure 2](#)). POST_PIV, POST_SII, Δ PIV, and Δ SII consistently demonstrated the highest AUCs and C-index values ([Figure 1A](#)), indicating superior discriminative ability for overall survival.

To better contextualize these findings, we first performed univariate Cox regression analysis on clinical variables, identifying several factors significantly associated with overall survival, including Gender, Smoking History, cTNM stage, T stage, Histology, Lymph Node Metastasis, PD-L1 expression, and Preoperative Albumin ($P < 0.05$) ([Table 4](#)). These clinical predictors were then incorporated into multivariate models with each inflammation marker. As shown in [Figure 1B](#) and detailed in [Table 5](#), POST_PIV (HR = 7.87, $P < 0.001$), POST_SII (HR = 6.87, $P < 0.001$), Δ PIV (HR = 5.32, $P < 0.001$), and Δ SII (HR = 5.98, $P < 0.001$) remained independent predictors for poor survival in multivariate analysis after adjusting for relevant clinical confounders.

Time-dependent ROC analysis ([Figure 1C](#)) further confirmed their temporal predictive stability, with POST_SII yielding AUCs of 0.753, 0.796, and 0.828 at 1-, 3-, and 5-year, respectively. Standard ROC analysis ([Figure 1D](#)) further revealed these four indices with high overall discriminative ability. Using their ROC-derived optimal cutoffs derived from the training cohort (2004.23 for POST_SII, 1174.825 for POST_PIV, 1504.62 for Δ SII, and 1116.705 for Δ PIV), Kaplan-Meier curves stratified patients into high/low-risk groups, showing significantly shorter survival in high-risk groups (log-rank $P < 0.0001$; [Figure 1E](#)). Additionally, restricted cubic spline (RCS) analysis in univariable Cox models revealed significant non-linear associations for all inflammation-based indices with overall survival (all P for non-linearity < 0.05). These curves demonstrated that the risk of death did not increase in a strictly linear fashion but exhibited a threshold or plateau effect for certain markers, with sharp risk escalation beyond specific value ranges ([Supplementary Figure 3](#)). These findings highlight the prognostic superiority of dynamic and postoperative inflammatory markers, suggesting that systemic inflammation after surgery may more accurately reflect underlying disease aggression and long-term outcomes in NSCLC.

Prognostic Evaluation of Clinical and Inflammatory Variables

The four optimal inflammatory markers (POST_SII, POST_PIV, Δ SII, Δ PIV) and significant clinical variables identified from univariate Cox analysis ($P < 0.05$) were subjected to LASSO regression. Using the λ min criterion, 11 variables were retained ([Figure 2A](#) and [B](#)). To further refine the model, we further applied stepwise multivariate Cox regression based on these LASSO-selected variables, yielding a final model with five core predictors: Smoking History (HR = 2.65, 95% CI: 1.61–4.34), cTNM Stage (Stage II: HR = 2.95, 95% CI: 1.68–5.18; Stage III: HR = 2.78, 95% CI: 1.49–5.20), Preoperative Albumin (HR = 0.9, 95% CI: 0.84–0.96), POST_SII (HR = 3.02, 95% CI: 1.59–5.73), and POST_PIV (HR = 3.71, 95% CI: 1.66–8.27). Age and Gender were forcibly retained due to their known clinical relevance and potential impact on stratification in external populations, despite statistical non-significance (Age: HR = 1.018, $P = 0.19$; Gender [Male]: HR = 0.949, $P = 0.894$) ([Figure 2C](#)). All variables met the proportional hazards assumption (all $P > 0.05$) ([Supplementary Figure 4](#)).

A prognostic nomogram integrating these predictors was constructed in the training cohort ($N = 170$) ([Figure 3A](#)). The nomogram demonstrated strong predictive performance, with C-index of 0.85 and AUCs of 0.86, 0.89, and 0.94 at 1-, 3-, and 5-year, respectively ([Figure 3B](#)). Calibration curves showed strong agreement between predicted and observed survival probabilities at 1-, 3-, and 5-year ([Figure 3D](#)). Validation in the testing cohort ($n = 73$) maintained robust performance (C-index of 0.80 and AUCs of 0.74, 0.85, and 0.90 at 1-, 3-, and 5-year) ([Figure 3C](#) and [E](#)). Kaplan-Meier curves based on total nomogram points stratified patients into distinct risk groups with significantly different survival outcomes ([Figure 3F](#) and [G](#)).

Decision curve analysis (DCA) demonstrated a significantly superior net clinical benefit of the nomogram versus TNM and clinical variables-only models across threshold ranges of 0.05–0.5 in both the training and validation cohorts. ([Figure 4](#)). Although Age and Gender were not statistically significant, their removal led to subtle changes in DCA curves, especially in the validation cohort, indicating potential instability. Their inclusion may thus enhance the nomogram's robustness and generalizability. ([Supplementary Figure 5](#)).

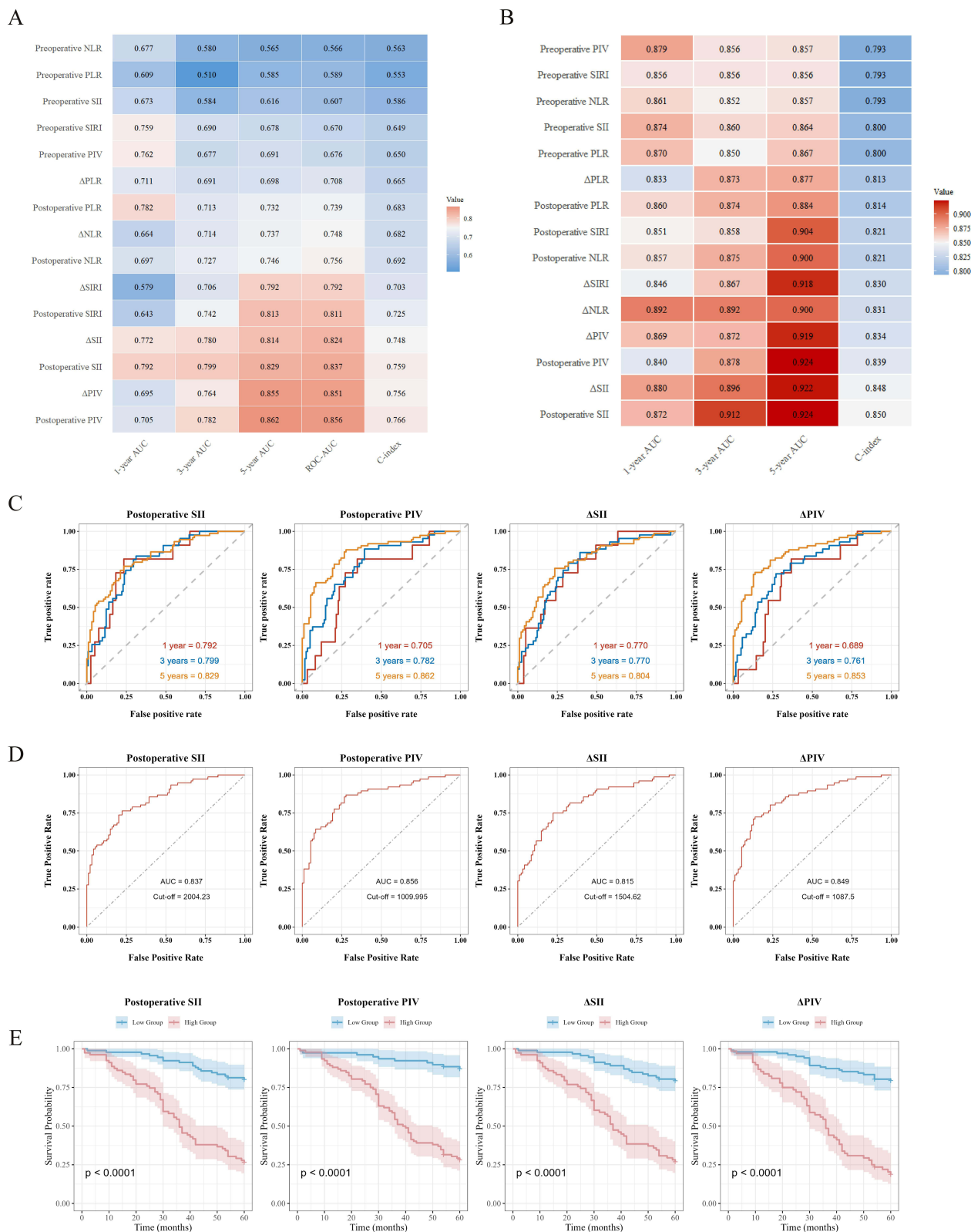


Figure 1 Prognostic evaluation of inflammation-based indices. **(A)** Heatmap showing AUCs and C-index of 15 inflammation markers for overall survival. **(B)** AUCs and C-index of Cox models incorporating each marker with significant clinical variables. **(C)** Time-dependent ROC curves of POST_SII, POST_PIV, ΔSII, and ΔPIV at 1-, 3-, and 5-year follow-up. **(D)** Standard ROC curves and cutoff values for the four selected markers. **(E)** Kaplan-Meier survival curves for high- and low-risk groups based on each marker's cutoff (log-rank $P < 0.0001$).

Table 4 Univariate Cox Regression for Clinical Characteristics

Characteristics	Level	HR (95% CI)	P value
Gender	Female	Reference	
	Male	2.82 (1.62–4.90)	<0.001
Age	Age	1.01 (0.98–1.03)	0.561
BMI(kg/m ²)	BMI	1.01 (0.95–1.07)	0.799
Smoking History	No	Reference	
	Yes	3.62 (2.28–5.76)	<0.001
Surgery Type	Wedge Resection	Reference	
	Lobectomy	1.29 (0.56–2.98)	0.557
	Thoracotomy	2.00 (0.72–5.49)	0.181
Clean Node Number	Clean_node_number	1.04 (0.94–1.16)	0.446
Tumor Location	Left	Reference	
	Right	0.93 (0.59–1.47)	0.76
Lobe Number	Multiple	Reference	
	Single	0.55 (0.26–1.15)	0.111
Histology	Adenocarcinoma	Reference	
	Non-Adenocarcinoma	1.78 (1.12–2.82)	0.014
cTNM Stage	Clinical I	Reference	
	Clinical II	4.30 (2.54–7.29)	<0.001
	Clinical III	6.07 (3.37–10.92)	<0.001
T_stage	T1	Reference	
	T2	2.07 (1.29–3.30)	0.002
	T3+	2.90 (1.13–7.46)	0.027
Lymph Node Metastasis	No Lymph Node Metastasis	Reference	
	Single-Station Metastasis	3.44 (2.02–5.85)	<0.001
	Multi-Station Metastasis	3.07 (1.54–6.11)	0.001
Pleural Invasion	No	Reference	
	Yes	1.41 (0.88–2.26)	0.157
Neural Invasion	No	Reference	
	Yes	2.61 (0.82–8.32)	0.105
Vascular Invasion	No	Reference	
	Yes	0.89 (0.22–3.63)	0.873
Preoperative Albumin(g/L)	PRE_ALB	0.91 (0.86–0.96)	0.001
Postoperative Albumin(g/L)	POST_ALB	0.95 (0.89–1.00)	0.071
PD-L1 expression(%)	PD-L1	1.01 (1.00–1.02)	0.003

Table 5 Inflammatory Index Univariate and Multivariate Cox Regression

Characteristics	Univariate Cox Regression		Multivariate Cox Regression	
	HR (95% CI)	P value	HR (95% CI)	P value
Preoperative PLR				
Low	Reference		Reference	
High	2.24 (1.42–3.54)	0.001	1.81 (1.07–3.07)	0.028
Preoperative NLR				
Low	Reference		Reference	
High	3.55 (1.3–9.71)	0.014	2.42 (0.83–7.01)	0.105
Preoperative SII				
Low	Reference		Reference	
High	2.02 (1.24–3.28)	0.004	1.66 (0.99–2.77)	0.054

(Continued)

Table 5 (Continued).

Characteristics	Univariate Cox Regression		Multivariate Cox Regression	
	HR (95% CI)	P value	HR (95% CI)	P value
Preoperative SIRI				
Low	Reference		Reference	
High	2.51 (1.6–3.95)	<0.001	1.62 (0.96–2.73)	0.071
Preoperative PIV				
Low	Reference		Reference	
High	2.56 (1.63–4.03)	<0.001	1.77 (1.05–3)	0.033
Postoperative PLR				
Low	Reference		Reference	
High	3.39 (2.15–5.33)	<0.001	2.86 (1.73–4.74)	<0.001
Postoperative NLR				
Low	Reference		Reference	
High	4.14 (2.62–6.53)	<0.001	3.86 (2.24–6.65)	<0.001
Postoperative SII				
Low	Reference		Reference	
High	6.09 (3.57–10.38)	<0.001	6.09 (3.41–10.88)	<0.001
Postoperative SIRI				
Low	Reference		Reference	
High	6 (3.48–10.34)	<0.001	5.09 (2.78–9.31)	<0.001
Postoperative PIV				
Low	Reference		Reference	
High	9.08 (4.65–17.74)	<0.001	7.87 (3.81–16.23)	<0.001
ΔPLR				
Low	Reference		Reference	
High	2.92 (1.76–4.83)	<0.001	2.6 (1.51–4.46)	<0.001
ΔNLR				
Low	Reference		Reference	
High	3.65 (2.24–5.93)	<0.001	4.29 (2.47–7.45)	<0.001
ΔSII				
Low	Reference		Reference	
High	5.67 (3.36–9.57)	<0.001	5.55 (3.14–9.83)	<0.001
ΔSIRI				
Low	Reference		Reference	
High	5.39 (3.06–9.53)	<0.001	5.25 (2.79–9.89)	<0.001
ΔPIV				
Low	Reference		Reference	
High	7.32 (4.35–12.3)	<0.001	5.76 (3.23–10.27)	<0.001

Notes: Univariate Cox Regression: unadjusted. Multivariate Cox regression was adjusted for Gender, Age, Smoking History, cTNM Stage, T Stage, Histology, Lymph Node Metastasis, PD-L1 expression, and Preoperative Albumin.

Abbreviations: PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value; Δ, postoperative value minus preoperative value.

To mitigate potential random selection bias and assess robustness, two complementary internal resampling procedures were conducted. In 5-fold cross-validation of the training cohort, refitting the final seven-variable Cox model in each fold yielded a C-index of 0.85 ± 0.03 and time-dependent AUCs of 0.78 ± 0.29 , 0.88 ± 0.04 , and 0.93 ± 0.06 at 1, 3, and 5 years, respectively ([Supplementary Table 1](#)). Across 100 repeated 70/30 random splits of the full cohort, discrimination remained consistent (mean C-index 0.80 ± 0.03 ; AUCs 0.76 ± 0.11 / 0.84 ± 0.04 / 0.89 ± 0.04 at 1/3/5 years), aligning with the single hold-out validation (validation C-index 0.80; AUCs 0.74 / 0.85 / 0.90) ([Supplementary Table 2](#)).

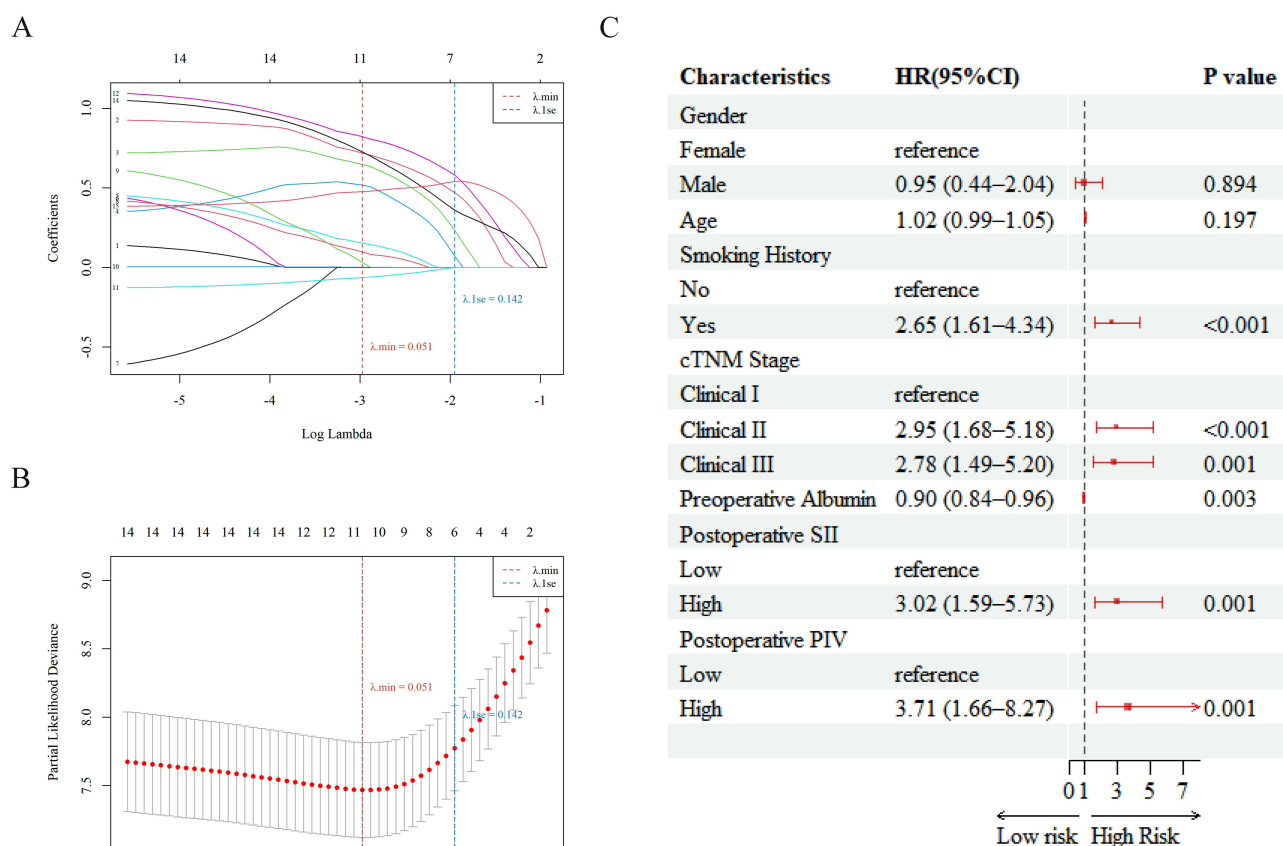


Figure 2 Selection and Confirmation of Prognostic Variables Using LASSO and Cox Regression. Feature selection and model refinement for prognostic variable identification. (A) LASSO coefficient profiles of the 12 variables with the penalty parameter (λ) selected via 10-fold cross-validation. (B) Partial likelihood deviance plotted against $\log(\lambda)$; six variables were retained at λ .lse. (C) Forest plot of the final multivariate Cox regression model. Gender and age were forcibly included due to clinical relevance, while five variables were statistically significant: smoking history, cTNM stage, preoperative albumin, postoperative SII, and postoperative PIV.

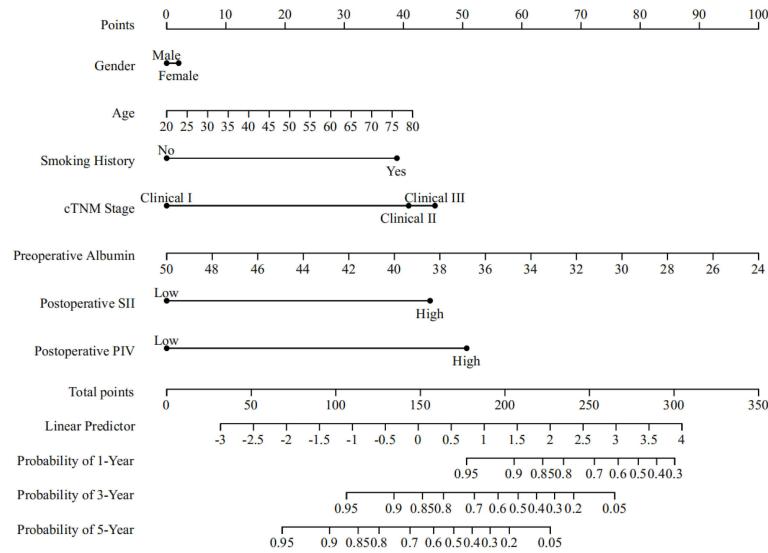
To further quantify the model’s added predictive value, we compared the nomogram with the TNM and clinical models using Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) (Table 6). In the training cohort, the nomogram demonstrated significantly higher NRI and IDI at all time points (all $P < 0.01$). In the validation set, although improvements were more modest, significant gains in both metrics were still observed at 3- and 5-years. Similar trends were observed in the full cohort analysis. These findings further underscore the superior prognostic capacity of the nomogram over conventional models.

Discussion

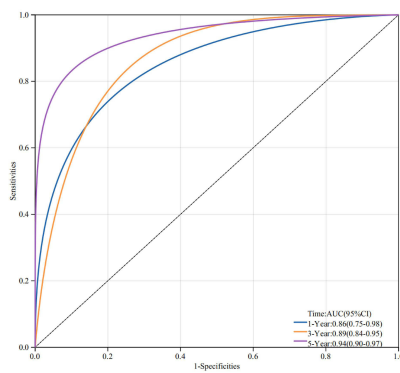
Inflammation and immune dysregulation have long been recognized as critical drivers of cancer initiation, progression, and metastasis.^{11,12} While tumor-associated inflammation exhibits paradoxical tumor-suppressive and -promoting effects, baseline inflammatory indices provide valuable insight into pre-existing immune status.¹³ Our study demonstrated that perioperative inflammatory dynamics, particularly POST_SII, POST_PIV, Δ SII and Δ PIV, provide superior prognostic stratification compared to preoperative baselines in postoperative NSCLC patients. These dynamic indicators outperformed preoperative baselines in predicting long-term survival with enhanced discrimination, improved classification capacity and consistent robustness.

In NSCLC, prognostic significance of systemic inflammation-based biomarkers, such as the NLR, PLR, SII, and PIV, have been elucidated.^{14–17} The high levels of postoperative systemic inflammation is a usual response to surgical stress, determined by the magnitude of injury.¹⁸ The association between baseline inflammatory indicators with cancer prognosis has highlighted the important role of patients’ intrinsic immune reserve in determining clinical outcomes.

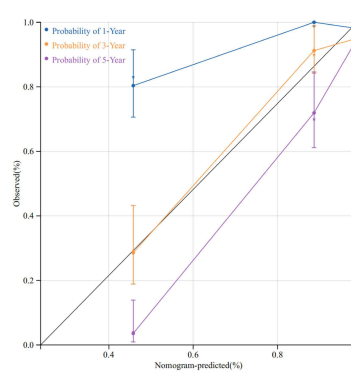
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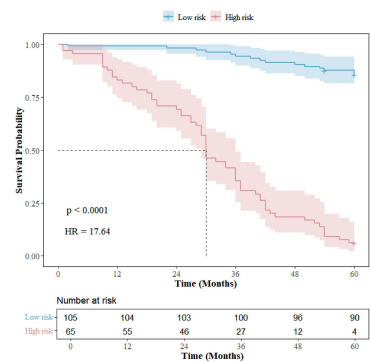
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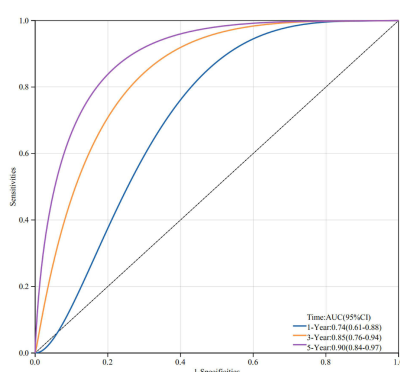
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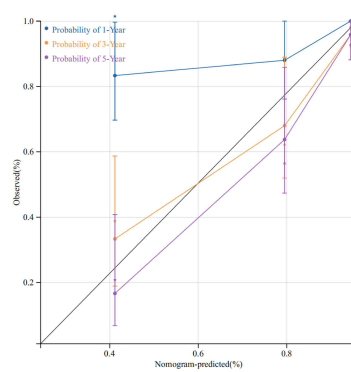
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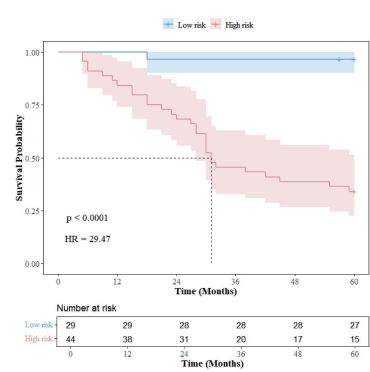


Figure 3 Construction and Validation of the Prognostic Nomogram. (A) Nomogram integrating seven variables (Gender, Age, Smoking History, cTNM stage, Preoperative Albumin, Postoperative SII, Postoperative PIV) for 1-, 3-, and 5-year survival prediction in the training cohort. (B and C) Time-dependent ROC curves for 1-, 3-, and 5-year in the training (B) and validation (C) cohorts. (D and E) Calibration plots for 1-, 3-, and 5-year survival prediction in the training (D) and validation (E) cohorts. (F and G) Kaplan–Meier survival curves stratified by total risk score in the training (F) and validation (G) cohorts.

Baseline inflammation indicators refer to inflammation-related biomarkers assessed before disease onset, prior to therapeutic intervention, or in a healthy state. The elevations of Δ SII and Δ PIV signifies failed immunological resolution, aligning with clinical observations where persistent postoperative inflammation and associated complications lead to a poor recovery, persistent disability or death.¹⁹

Surgical trauma provokes a coordinated systemic inflammatory response and a transient period of immune disequilibrium that can remodel the tumor microenvironment and attenuate antitumor surveillance in the early postoperative

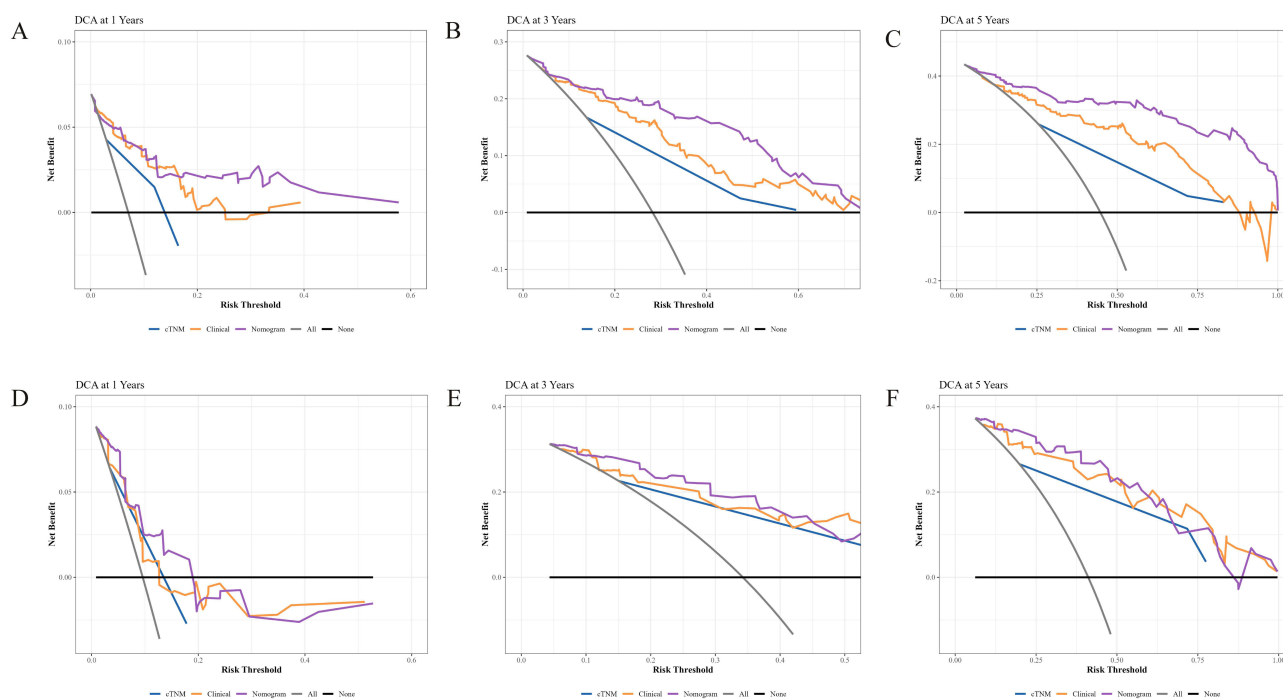


Figure 4 Decision Curve Analysis (DCA) for Evaluating Clinical Net Benefit of the Nomogram Model. (A–C) DCA curves for predicting 1-, 3-, and 5-year survival in the training cohort. (D–F) DCA curves for predicting 1-, 3-, and 5-year survival in the validation cohort. The nomogram model consistently showed superior net clinical benefit compared with TNM and clinical-only models across a wide range of threshold probabilities.

window. Mounting evidence suggests that surgical stress activates the neuroendocrine–immune axis, leading to catecholamine and glucocorticoid release that suppress cytotoxic T- and NK-cell activity while expanding myeloid-derived suppressor cells (MDSCs) and regulatory T cells.^{20,21} Concurrently, neutrophil extracellular traps (NETs) and platelet

Table 6 NRI and IDI of the Nomogram and Clinical Model in Survival Prediction Compared with TNM Stage

Model	IDI (95% CI)	P value	NRI (95% CI)	P value	Time		
Training group	Clinical	0.070 (0.010–0.210)	0.008	0.485 (0.140–0.650)	0.008	1-year	
		0.088 (0.019–0.194)	0.008	0.352 (0.126–0.520)	0.004	3-year	
		0.11 (0.037–0.224)	0.006	0.341 (0.179–0.510)	0.002	5-year	
	Nomogram	0.15 (0.060–0.320)	<0.001	0.444 (0.158–0.682)	0.006	1-year	
		0.228 (0.118–0.360)	0.002	0.500 (0.263–0.645)	0.002	3-year	
		0.308 (0.185–0.450)	<0.001	0.608 (0.410–0.725)	<0.001	5-year	
	Validation group	Clinical	0.027 (–0.021–0.238)	0.212	0.368 (–0.014–0.754)	0.058	1-year
			0.054 (–0.021–0.195)	0.122	0.348 (0.040–0.571)	0.022	3-year
			0.066 (–0.005–0.215)	0.064	0.371 (0.038–0.531)	0.02	5-year
Nomogram		0.057 (–0.013–0.427)	0.106	0.687 (0.013–0.789)	0.044	1-year	
		0.066 (–0.003–0.260)	0.058	0.388 (0.089–0.580)	0.016	3-year	
		0.095 (0.004–0.299)	0.042	0.404 (0.101–0.632)	0.016	5-year	
Full group		Clinical	0.024 (–0.003–0.088)	0.09	0.277 (–0.007–0.477)	0.054	1-year
			0.040 (0.004–0.109)	0.018	0.212 (0.038–0.375)	0.024	3-year
			0.062 (0.019–0.137)	0.004	0.257 (0.093–0.391)	0.002	5-year
	Nomogram	0.063 (0.025–0.151)	<0.001	0.306 (0.085–0.548)	0.012	1-year	
		0.163 (0.093–0.267)	<0.001	0.396 (0.261–0.561)	0.024	3-year	
		0.228 (0.152–0.333)	<0.001	0.524 (0.381–0.625)	0.002	5-year	

activation promote circulating tumor cell adhesion and metastatic niche formation, whereas elevated IL-6, IL-8, and TNF- α drive persistent STAT3 and PI3K/AKT/mTOR signaling that facilitates epithelial–mesenchymal transition (EMT) and immune evasion.^{22,23} Oxidative stress and metabolic reprogramming further amplify this immunosuppressive milieu by impairing lymphocyte proliferation and effector function.²³ Collectively, these cascades create a transient but biologically permissive environment in which residual tumor cells can survive, resist immune clearance, and disseminate. Neutrophil predominance, lymphocyte suppression, and platelet or monocyte activation, together with perioperative metabolic reprogramming and cytokine fluxes, provide a mechanistic basis for why postoperative composites such as POST_SII and POST_PIV, and their perioperative deltas, outperform static baselines.²⁴ These dynamics more faithfully reflect the shifting host–tumor balance immediately after resection, when micrometastatic progression and early recurrence risk may be determined.

While prior research has applied postoperative inflammation-based models in gastric and colorectal cancers,^{25,26} our work adds to the growing body of evidence supporting the prognostic value of postoperative inflammatory markers in NSCLC. Furthermore, restricted cubic spline (RCS) analyses revealed nonlinear associations between individual inflammatory indices and survival risk, though the overall risk trend remained consistent, reinforcing the robustness of our final multivariable model. Beyond assessing single markers, we developed a comprehensive nomogram that integrates immune–inflammatory responses, nutritional and physiologic status, and tumor burden.²⁷ By incorporating dynamic postoperative metrics that capture real-time host–tumor interactions, the nomogram advances risk stratification beyond static baselines. Clinically, it supports risk-adapted postoperative care: high-risk patients should undergo intensified surveillance with early MDT review and targeted perioperative optimization (nutrition rehabilitation and/or inflammation control), whereas low-risk patients can maintain standard follow-up intervals. Internal robustness was further supported by five-fold cross-validation in the training cohort and 100 repeated 70/30 random splits in the full cohort, which yielded concordant performance ([Supplementary Tables 1–2](#)). This multidimensional approach addresses limitations of existing models that neglect the impact of surgical injury.

Nonetheless, this study has certain limitations. It is based on a single-center retrospective cohort with a moderate sample size, which may introduce selection bias and limit generalizability. Center-specific perioperative pathways and laboratory platforms may also influence inflammatory indices and outcomes, contributing to spectrum and selection bias. Accordingly, we will undertake multicenter prospective validation and update the model as needed. Although postoperative inflammatory indices remained independently associated with survival after adjustment for available clinical covariates, other perioperative factors—such as anesthesia/analgesia strategies and postoperative complications—were not consistently standardized in the records and may contribute to residual confounding. We therefore consider these results hypothesis-generating and suitable for prospective confirmation. In addition, perioperative blood draws were performed within a 3–5-day window before and after surgery, which could introduce timing variability in the measured indices. Future protocols will fix sampling days to reduce temporal variability and evaluate short-term kinetics of SII/PIV. Internal robustness was supported by 5-fold cross-validation and 100 repeated 70/30 splits, but this does not substitute for external (including temporal) validation and formal calibration. Finally, inflammation-based indices are surrogate markers of immune status and do not directly delineate the molecular pathways linking inflammation to tumor progression and recurrence. Future studies will integrate tissue and circulating biomarkers with prospectively collected perioperative data to elucidate mechanisms and refine the model across histologic subtypes and treatment contexts.

Conclusion

POST_SII and POST_PIV were identified as the most robust inflammatory predictors of overall survival in resected NSCLC. A prognostic nomogram integrating postoperative inflammatory markers (POST_SII and POST_PIV) with clinical variables (smoking history, cTNM stage, preoperative albumin, age, and gender) demonstrated superior predictive performance compared with TNM and clinical models in resected NSCLC. This model provides a practical tool for individualized postoperative risk stratification and warrants external validation.

Data Sharing Statement

The raw clinical datasets used and/or analyzed during the current study are publicly available in the OMIX database under accession number OMIX011524. All code used for data processing and statistical analysis is accessible via GitHub at: <https://github.com/Yuki3885/inflammatory-Rdata>.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of The Second Xiangya Hospital of Central South University (approval No. Z0933-01). Written informed consent was obtained from all participants prior to enrollment. The research was conducted in accordance with the Declaration of Helsinki.

Author Contributions

Qian Yu contributed to conceptualization and methodology, performed data curation, formal analysis, and investigation, prepared visualization, drafted the original paper (writing – original draft), and contributed to writing – review and editing. Leliang Zheng assisted with data curation and formal analysis, contributed to investigation and visualization, and participated in writing – review and editing. Majid Iqbal contributed to validation and writing – review and editing. Juanjuan Xiang assisted with validation and project administration, and contributed to writing – review and editing. Jingqun Tang provided supervision, funding acquisition, and resources, and critically revised the paper (writing – review and editing), and served as guarantor of the work.

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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