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Research Article

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Original Article

Dynamic immune-inflammation-nutrition biomarkers and outcomes in advanced non-small cell lung cancer treated with immunotherapy

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Abstract

Purpose: While immune checkpoint inhibitors (ICIs) have improved survival in advanced non-small cell lung cancer (NSCLC), therapeutic benefits vary and current biomarkers are often costly or static. This study evaluated the associations of baseline and dynamic immune-inflammation-nutrition (IIN) biomarkers with clinical outcomes to develop a composite predictive score (INICS). **Materials and Methods:** We retrospectively analyzed 109 patients with driver-negative advanced NSCLC (68 receiving ICIs plus chemotherapy; 41 receiving platinum-based doublet chemotherapy). IIN biomarkers, including lymphocyte-to-monocyte ratio (LMR), prognostic nutritional index (PNI), and platelet-to-lymphocyte ratio (PLR), among others, were measured at baseline and week 6. Dynamic changes were defined as Δ (week 6 − baseline). The Immune-Inflammation-Nutrition Composite Score (INICS) was derived based on baseline LMR, PNI, and ΔPLR. **Results:** Baseline characteristics were comparable between groups except for pathological type. Overall survival (OS) was significantly longer in the ICI group ($P < 0.05$). In the ICI cohort, higher baseline LMR independently predicted better objective response ($P < 0.05$), while higher baseline PNI and albumin correlated with improved disease control ($P < 0.05$). Disease control was associated with significant decreases in PLR and systemic immune-inflammation index (SII) during treatment ($P < 0.05$). The INICS was independently associated with progression-free survival (PFS) (HR, 0.46; 95% CI, 0.26-0.81; $P = 0.008$), with a 12-month time-dependent AUC of 0.674. **Conclusion:** The INICS, integrating baseline IIN status and early dynamic inflammatory response, serves as a robust independent predictor of PFS in advanced NSCLC patients treated with ICIs, offering potential for clinical risk stratification.

Keywords: Carcinoma, Non-Small-Cell lung; immune checkpoint inhibitors; Biomarkers, Tumor; Nutritional Status; Progression-Free Survival; Prognosis

Introduction

Lung cancer continues to be the leading cause of malignancy-related incidence and mortality worldwide, with non-small cell lung cancer (NSCLC) representing approximately 80%–85% of cases[1, 2]. Due to the insidious onset of symptoms, the majority of patients are diagnosed with advanced disease, which is historically associated with a dismal prognosis[3, 4]. For patients with driver-negative advanced NSCLC, platinum-based chemotherapy has long remained the therapeutic cornerstone; however, its clinical efficacy has reached a plateau, with limited improvements in long-term survival[5, 6]. The therapeutic landscape of advanced NSCLC has been revolutionized by the emergence of immune checkpoint inhibitors (ICIs)[7]. Despite these advancements, clinical benefit remains remarkably heterogeneous, and a substantial proportion of patients fail to achieve a durable response[8, 9]. Although established biomarkers such as programmed death-ligand 1(PD-L1) expression, tumor mutational burden (TMB), and microsatellite instability (MSI) have been integrated into clinical practice, their predictive utility is often hampered by practical constraints[9-11]. Specifically, PD-L1 testing is plagued by spatial and temporal heterogeneity, while TMB assessment is limited by high costs, long turnaround times, and a lack of standardized thresholds[12, 13]. Furthermore, MSI-high status is exceptionally rare in the NSCLC population[14]. Thus, there is an urgent imperative to identify cost-effective, non-invasive, and readily accessible biomarkers to refine patient selection and optimize immunotherapy strategies[15].

Accumulating evidence indicates that the clinical course of malignancy is determined not only by tumor-intrinsic molecular profiles but also by the host’ s systemic environment, characterized by a complex interplay between immune surveillance, chronic inflammation, and nutritional status[16-18]. Peripheral blood-based indicators, such as the LMR and PNI, have

emerged as promising tools for reflecting this systemic milieu[19, 20]. However, most existing studies have relied on static, baseline assessments, which fail to capture the dynamic evolution of the host's immune-inflammation-nutrition (IIN) network during the course of treatment[20, 21]. Given that ICIs induce continuous physiological shifts in the immune microenvironment, longitudinal monitoring of these biomarkers may offer superior predictive value[22, 23].

Materials and Methods

1. Patients and Study Design

This was a single-center retrospective cohort study. We screened patients with advanced NSCLC who received treatment at the First Hospital of Shanxi Medical University between August 2022 and August 2025. A total of 109 patients were enrolled; among them, 68 received first-line ICIs combined with chemotherapy (the ICI cohort), while 41 received platinum-based doublet chemotherapy as a background reference (the chemotherapy cohort).

Eligible patients met the following inclusion criteria: (1) age ≥ 18 years; (2) histologically confirmed squamous or non-squamous NSCLC; (3) driver-mutation negative (defined as absence of alterations in *EGFR*, *ALK*, *ROS1*, *RET*, *BRAF V600E*, *MET* exon 14 skipping, *HER2*, *NTRK*, etc.); (4) TNM stage IIIB–IV with measurable lesions per RECIST v1.1; (5) ECOG performance status (PS) 0–1; and (6) completion of at least two treatment cycles with available complete hematological data at baseline and at weeks 3 and 6, along with comprehensive follow-up records.

Exclusion criteria included: (1) concurrent malignancies; (2) prior use of immunosuppressants (e.g., corticosteroids) within 2 months before enrollment; (3) active autoimmune diseases; (4) uncontrolled infections; or (5) prior local therapies, such as radiotherapy or ablation, during the study period. This study was conducted in accordance with

the Declaration of Helsinki and approved by the Medical Ethics Committee of the First Hospital of Shanxi Medical University (No. KYLL-2025-407).

2. Data Collection and Biomarker Definitions

Baseline clinicopathological data — including age, sex, body mass index (BMI), pathological type, and TNM stage—were retrospectively retrieved from electronic medical records. Peripheral blood parameters, comprising neutrophil, lymphocyte, monocyte, and platelet counts, as well as albumin and prealbumin levels, were collected at baseline and at weeks 3 and 6 of treatment.

The Immune-Inflammation-Nutrition (IIN) biomarkers were calculated as follows (all blood cell counts were expressed in $\times 10^9$/L):

Immune Indicator: Lymphocyte-to-monocyte ratio (LMR) = Lymphocyte / Monocyte.

Inflammatory Indicators: Neutrophil-to-lymphocyte ratio (NLR) = Neutrophil / Lymphocyte. Platelet-to-lymphocyte ratio (PLR) =Platelet / Lymphocyte. Systemic immune-inflammation index (SII) = (Platelet × Neutrophil) / Lymphocyte. Systemic inflammation response index (SIRI) = (Neutrophil × Monocyte) / Lymphocyte.

Nutritional Indicators: Prognostic nutritional index (PNI) = Albumin (g/L) + 5 × Lymphocyte count. BMI = Weight (kg) / Height² (m^2).

Dynamic changes in these biomarkers were defined as Δ = (Value at Week 6 − Baseline value).

3. Efficacy Assessment and Follow-up

Tumor response was evaluated every 6–8 weeks using computed tomography (CT) or magnetic resonance imaging (MRI) according to RECIST v1.1. Clinical outcomes were categorized as complete response (CR), partial response (PR), stable disease (SD), and

progressive disease (PD). The objective response rate (ORR) was defined as the proportion of patients achieving CR or PR, while the disease control rate (DCR) included those with CR, PR, or SD.

The primary endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval from treatment initiation to the first documentation of disease progression or death from any cause. OS was measured from treatment initiation to death from any cause. Patients who remained alive or progression-free at the last follow-up (August 31, 2025) were censored at the date of their last assessment.

4. Statistical Analysis

Statistical analyses were conducted using R (v4.3.0). Continuous and categorical variables were compared using appropriate parametric or non-parametric tests based on data distribution. Survival curves were estimated using the Kaplan-Meier method and compared via log-rank tests. Independent prognostic factors were identified using Cox proportional hazards models; for PFS, inverse probability of treatment weighting (IPTW) was applied to minimize selection bias, whereas only univariable Cox regression was performed for OS due to the limited number of events.

Baseline correlations were evaluated using Spearman's rank correlation. Multivariable logistic regression explored the associations between IIN biomarkers and treatment response. Notably, variance inflation factors (VIF $\approx$ 1.1) justified the concurrent inclusion of LMR and PNI. To address potential collinearity in DCR analysis, Firth's penalized logistic regression was utilized to adjust for clinicopathological covariates.

Linear mixed-effects models (LMM) were used to analyze longitudinal biomarker trajectories, with time, response group, and their interaction as fixed effects. The interaction term

reflected the difference in slopes between efficacy groups. A two-sided $P < 0.05$ was considered statistically significant.

5. Construction and Validation of the INICS

The Immune-Inflammation-Nutrition Composite Score (INICS) was developed based on baseline LMR, baseline PNI, and ΔPLR. Optimal cut-off values for LMR and PNI were determined by the maximum Youden index (sensitivity + specificity − 1) on ROC curves for PFS as the outcome. For these two indicators, values above the cut-off were assigned 1 point, and those below were assigned 0 points. For dynamic changes, ΔPLR was dichotomized: a decrease from baseline (ΔPLR < 0) was assigned 1 point, while an increase or no change (ΔPLR ≥ 0) was assigned 0 points. The total INICS (range 0–3) categorized patients into low- (0–1), intermediate- (2), and high-score (3) groups.

The association between the INICS and PFS was evaluated using Cox proportional hazards models, adjusting for TNM stage and ECOG PS. The predictive performance of the INICS for 12-month PFS was assessed using time-dependent ROC curves and the C-index. Model calibration was evaluated by comparing predicted versus observed 12-month PFS probabilities via calibration curves with Bootstrap resampling (1000 iterations). A calibration slope not significantly different from 1 ($P > 0.05$) indicated favorable model agreement. All statistical analyses were two-sided, with $P < 0.05$ considered significant.

Results

1. Baseline Characteristics

A total of 109 patients with driver-negative advanced NSCLC were retrospectively enrolled, consisting of 68 patients in the ICI cohort (first-line ICIs combined with chemotherapy) and 41

patients in the chemotherapy cohort (platinum-based doublet chemotherapy).

As summarized in **Table 1**, the baseline clinicopathological characteristics—including age, sex, TNM stage, smoking and drinking history, ECOG performance status (PS), and PD-L1 TPS expression—were well-balanced between the two cohorts (all $P > 0.05$). However, a significant difference was observed in pathological subtypes ($P = 0.018$); the ICI cohort had a higher proportion of squamous cell carcinoma (64.7% vs. 41.5%), whereas adenocarcinoma was more prevalent in the chemotherapy cohort (58.5% vs. 35.3%).

Table 1. Baseline characteristics of patients in the ICI and chemotherapy cohorts

Characteristics	Category	ICI cohort (n=68)	Chemotherapy cohort (n=41)	Statistics (χ^2/W)	*P*-value
Age (years)	Median (IQR)	68（63–71）	65（59–70）	1670.500	0.084
	< 65（%）	22（32.4）	19（46.3）	2.133	0.144
	≥ 65（%）	46（67.6）	22（53.7）		
Sex (%)				3.714	0.054
	Female	6 (8.8)	9 (22.0)		
	Male	62 (91.2)	32 (78.0)		
Histology (%)				5.607	0.018
	Adenocarcinoma	24 (35.3)	24 (58.5)		
	Squamous	44 (64.7)	17 (41.5)		
TNM Stage (%)				0.022	0.882
	Stage IIIB–IV	19 (27.9)	12 (29.3)		
	Stage IV	49 (72.1)	29 (70.7)		
Smoking (%)				0.756	0.385
	Never	21 (30.9)	16 (39.0)		
	Ever	47 (69.1)	25 (61.0)		
Drinking (%)				0.007	0.935
	Never	42 (61.8)	25 (61.0)		

	Ever	26 (38.2)	16 (39.0)		
ECOG PS (%)				0.074	0.786
	0	35 (51.5)	20 (48.8)		
	1	33 (48.5)	21 (51.2)		
PD-L1 TPS (%)				3.248	0.197
	< 1%	46 (67.6)	30 (73.2)		
	1–49%	7 (10.3)	7 (17.1)		
	≥ 50%	15 (22.1)	4 (9.8)		

Note: Categorical variables are presented as n (%). Continuous variables are presented as median (interquartile range [IQR]). Inter-group comparisons were performed using the χ^2 test or Wilcoxon rank-sum test (W-statistic). Bold P-values indicate statistical significance ($P < 0.05$). Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-L1 TPS, programmed death-ligand 1 tumor proportion score.

2. Clinical Efficacy and Survival Outcomes

To assess the survival benefits of first-line ICIs combined with chemotherapy in driver-negative advanced NSCLC, we compared the OS and PFS between the ICI and chemotherapy cohorts.

Kaplan-Meier analysis demonstrated a significantly superior OS in the ICI cohort compared with the chemotherapy cohort ($P < 0.05$, Fig. 1A). Univariable Cox regression analysis (Table 2) revealed that ICI treatment was associated with a markedly reduced risk of death (HR, 0.17; 95% CI, 0.05–0.58; $P = 0.005$). Additionally, a higher baseline LMR (HR, 0.55; CI, 0.31–0.98; $P = 0.044$) was significantly correlated with improved OS, whereas a higher SIRI (HR, 1.30; CI, 1.02–1.65; $P = 0.035$) was identified as a significant risk factor for mortality. Other baseline factors, including age, sex, TNM stage, histology, and PD-L1 expression, did not show significant prognostic value for OS (all $P > 0.05$). Due to the limited number of OS events (n=12),

multivariable analysis was not performed. However, the overall baseline characteristics were well balanced between the two groups (Section 2.1), and the only variable that differed significantly between groups, histological type, was not significantly associated with OS in the univariable analysis. These findings support the reliability of the observed survival benefit associated with ICIs.

No statistically significant difference in PFS was observed between the two cohorts ($P > 0.05$, Fig. 1B). In the univariable analysis, the HR for the ICI cohort was 0.66 (95% CI, 0.35–1.25; $P = 0.200$). Although patients with PD-L1 TPS ≥ 50% showed a trend toward reduced risk of progression (HR, 0.33; 95% CI, 0.10–1.09), this did not reach statistical significance ($P = 0.069$). After adjusting for treatment type, histology, and PD-L1 expression in a multivariable Cox model, the ICI cohort still showed no significant PFS benefit (HR, 0.71; 95% CI, 0.34–1.46; $P = 0.348$). Furthermore, the IPTW-adjusted sensitivity analysis yielded consistent results (HR, 0.68; 95% CI, 0.34–1.35; $P = 0.267$), confirming the absence of a significant PFS improvement (Table 3).

Table 2. Univariate Cox regression analysis of factors associated with OS and PFS.

Variables	OS HR	95% CI	*P*	PFS HR	95% CI	*P*
Age (years)	1.02	0.94–1.11	0.584	1.00	0.97–1.04	0.838
Gender (Male vs. Female)	1.57	0.20–12.30	0.669	1.00	0.39–2.54	0.992
Clinical Stage (IV vs. III)	2.65	0.33–21.10	0.358	1.70	0.78–3.70	0.181
Pathology (SCC vs. Adeno)	2.00	0.53–7.60	0.309	1.14	0.60–2.17	0.690
Treatment (ICI vs. Chemo)	0.17	0.05–0.58	**0.005**	0.66	0.35–1.25	0.200
PD‐L1 TPS（1–49% vs. <1%）	3.35	0.86–13.15	0.082	1.69	0.70–4.08	0.242
PD‐L1 TPS（≥50% vs. <1%）	0.25	0.03–2.15	0.208	0.33	0.10–1.09	0.069
ECOG PS (0–1 vs. 2)	3.22	0.69–15.18	0.138	1.24	0.66–2.32	0.506

Baseline NLR	1.04	0.85–1.26	0.722	1.05	0.95–1.15	0.340
Baseline LMR	0.55	0.31– 0.98	**0.044**	0.96	0.88–1.05	0.359
Baseline PNI	0.94	0.84–1.05	0.249	0.98	0.92–1.03	0.364
Baseline PLR	1.00	1.00–1.01	0.467	1.00	1.00–1.01	0.464
Baseline SII	1.00	1.00–1.00	0.136	1.00	1.00–1.00	0.416
Baseline SIRI	1.30	1.02–1.65	**0.035**	1.06	0.90–1.24	0.504
Baseline BMI (kg/m^2)	0.96	0.78–1.18	0.714	0.98	0.89–1.08	0.738
Baseline Albumin (g/L)	0.92	0.82–1.03	0.150	0.98	0.93–1.04	0.523
Baseline Pre-albumin (mg/L)	1.00	0.99–1.00	0.202	1.00	1.00–1.00	0.820

Note: Univariate analysis was performed using the Cox proportional hazards model.

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression-free survival; ICI, immune checkpoint inhibitor; Chemo, chemotherapy; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; TPS, tumor proportion score; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; BMI, body mass index.

Table 3. Multivariate Cox Regression and Sensitivity Analysis for PFS

Variables	HR (95% CI)	*P*
Multivariate Cox Model		
Treatment (ICI vs. Chemo)	0.71 (0.34–1.46)	0.348
Pathology (SCC vs. Adeno)	1.17 (0.56–2.47)	0.671
PD-L1 TPS (1–49% vs. <1%)	1.65 (0.66–4.08)	0.283
PD-L1 TPS (≥50% vs. <1%)	0.37 (0.11–1.27)	0.113
Sensitivity Analysis (IPTW)		
Treatment (ICI vs. Chemo)	0.68 (0.34–1.35)	0.267

Note: IPTW was used as a sensitivity analysis to adjust for potential baseline imbalances between treatment groups.

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; ICIs, immune checkpoint inhibitors; Chemo, chemotherapy; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; TPS, tumor proportion score; IPTW, inverse probability of treatment weighting.

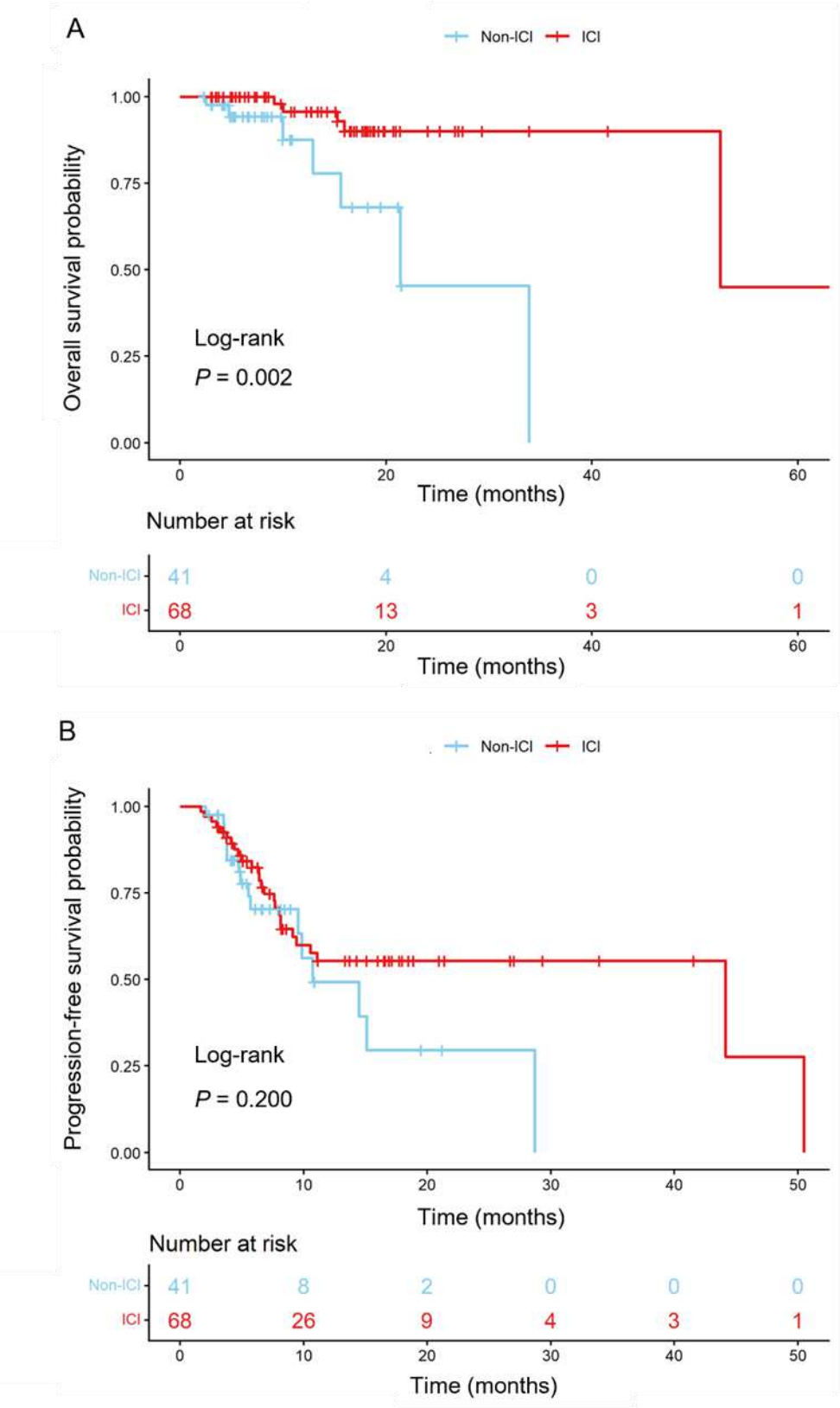


Figure 1. Survival outcomes in the ICI and Non-ICI groups. (A) Kaplan–Meier curves for overall survival (OS). (B) Kaplan–Meier curves for progression-free survival (PFS).

Note: The log-rank test was used to compare survival differences between the two groups.

Abbreviations: Detailed number-at-risk data are provided below each plot. ICI, immune

checkpoint inhibitor; NSCLC, non-small cell lung cancer.

3. Correlation Analysis of Baseline IIN Biomarkers in the ICI Cohort

To clarify the internal relationships among baseline biomarkers in the ICI cohort, a Spearman correlation analysis was conducted for immune (LMR), inflammatory (NLR, PLR, SII, and SIRI), and nutritional (BMI, PNI, albumin, and pre-albumin) indicators (Fig. 2).

A moderate-to-strong positive correlation was observed among the inflammatory biomarkers (r = 0.43–0.91, $P < 0.001$), suggesting that they collectively reflect the systemic inflammatory state and exhibit high multicollinearity. Strong associations were also found among nutritional indicators, particularly between PNI, albumin, and pre-albumin (r = 0.45–0.87, $P <$ 0.05). BMI showed weak correlations with PNI (r = 0.25, P = 0.038) and pre-albumin (r = 0.26, P = 0.031), while its correlation with albumin did not reach statistical significance (r = 0.24, P = 0.052). The immune biomarker LMR demonstrated a significant negative correlation with inflammatory markers (r = –0.47 to –0.79, $P < 0.001$), indicating that a lower LMR is associated with a higher inflammatory burden. The correlations between immune and nutritional biomarkers were generally weak ($|r| < 0.4$), with LMR showing a weak but significant positive correlation only with PNI (r = 0.38, P = 0.002). Overall, the correlations between inflammatory and nutritional clusters were also weak (maximum r = 0.47, $P < 0.001$). The complete correlation matrix, including all coefficients and P-values, is presented in Table S1.

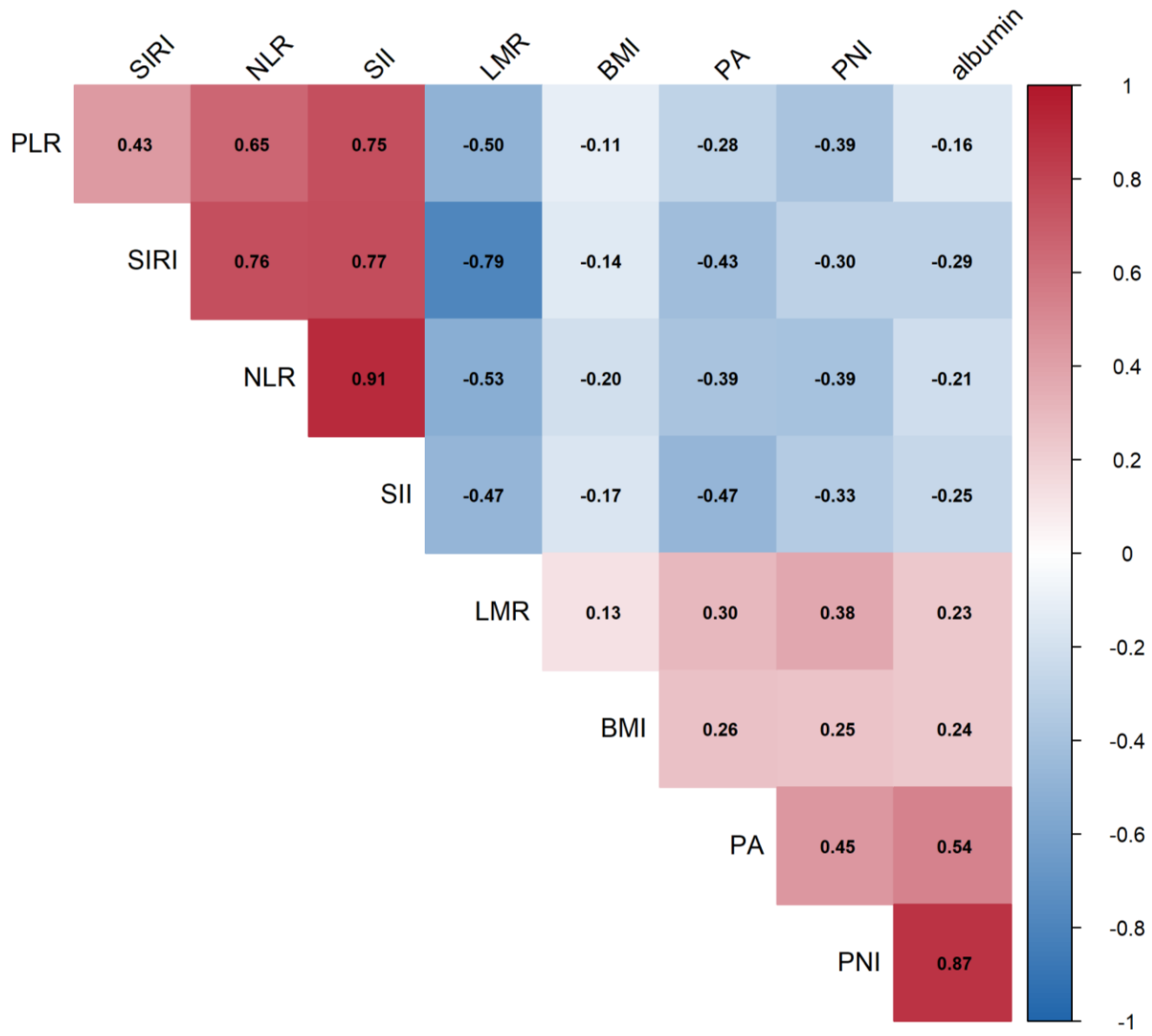


Figure 2. Spearman correlation heatmap of baseline IIN biomarkers in the ICI cohort.

Note: The color scale represents the Spearman correlation coefficient (r), with red indicating a positive correlation and blue indicating a negative correlation. The numbers within the cells denote the specific r values.

Abbreviations: ICI, immune checkpoint inhibitor; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; BMI, body mass index; PNI, prognostic nutritional index; PA, pre-albumin.

4. Association Between Baseline Biomarkers and Clinical Response in the ICI Cohort

In the ICI cohort (n=68), the objective response rate (ORR) was 51.5% and the disease control rate (DCR) was 89.7%. Logistic regression analysis was employed to evaluate the predictive value of baseline biomarkers for these clinical responses.

Univariable analysis (**Table 4**) showed that a higher baseline LMR was significantly associated with an increased likelihood of achieving an objective response (OR, 1.80; 95% CI, 1.23–2.91; $P = 0.007$). Baseline PNI also correlated positively with ORR (OR, 1.12; 95% CI, 1.02–1.24; $P = 0.025$). After adjusting for age as a potential confounder in the multivariable model (**Table 5**), LMR remained an independent predictor of ORR (OR, 1.56; 95% CI, 1.09–2.56; $P = 0.046$). In contrast, PNI and age did not exhibit independent predictive value ($P > 0.05$), suggesting that LMR is a more robust predictor of ORR in this population.

For DCR, univariable analysis indicated that higher baseline PNI (OR, 1.22; 95% CI, 1.06–1.46; $P = 0.010$) and albumin levels (OR, 1.24; 95% CI, 1.06–1.50; $P = 0.011$) were significantly associated with better disease control (**Table 4**). Given the high multicollinearity between PNI and albumin (as shown in Section 3.3), two separate multivariable Firth logistic regression models were constructed to adjust for age, histology, TNM stage, and ECOG PS (**Table 6**). Following adjustment, both PNI (OR, 1.33; 95% CI, 1.12–1.70; $P < 0.001$) and albumin (OR, 1.35; 95% CI, 1.13–1.75; $P < 0.001$) remained independently associated with DCR. These results suggest that superior baseline nutritional status is a critical determinant of disease control. Other biomarkers, including NLR, PLR, SII, SIRI, and BMI, showed no significant correlation with either ORR or DCR (all $P > 0.05$).

Table 4. Univariable Logistic regression analysis of factors associated with ORR and DCR.

Variables	ORR	*P* value	DCR	*P* value
	OR (95% CI)		OR (95% CI)	
LMR	1.80 (1.23–2.91)	**0.007**	1.13 (0.89–2.05)	0.573
PNI	1.12 (1.02–1.24)	**0.025**	1.22 (1.06–1.46)	**0.010**
Albumin	1.09 (0.99–1.21)	0.092	1.24 (1.06–1.50)	**0.011**
NLR	0.92 (0.75–1.09)	0.335	1.20 (0.87–1.97)	0.383
PLR	1.00 (0.99–1.00)	0.097	1.00 (0.99–1.02)	0.510
SII	1.00 (1.00–1.00)	0.155	1.00 (1.00–1.00)	0.288
SIRI	0.83 (0.61–1.09)	0.193	1.05 (0.70–1.85)	0.847
BMI	1.14 (0.98–1.34)	0.098	0.99 (0.79–1.27)	0.946
Pre-albumin	1.00 (0.99–1.01)	0.748	1.00 (0.98–1.01)	0.502

Abbreviations: OR, odds ratio; CI, confidence interval; ORR, objective response rate; DCR, disease control rate; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; BMI, body mass index.

Table 5. Multivariable Logistic regression analysis of factors associated with ORR.

Variables	ORR	*P* value
	OR (95% CI)	
LMR	**1.56 (1.09–2.56)**	**0.046**
PNI	1.10 (0.98–1.24)	0.116
Age	1.00 (0.93–1.09)	0.942

Abbreviations: OR, odds ratio; CI, confidence interval; ORR, objective response rate; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index.

Table 6. Multivariable Firth logistic regression analysis of factors associated with DCR.

Variables	Model 1 (including PNI) OR (95% CI)	*P* value	Model 2 (including Albumin) OR (95% CI)	*P* value
PNI	**1.33 (1.12–1.70)**	**<0.001**	–	–
Albumin	–	–	**1.35 (1.13–1.75)**	**<0.001**
Age	1.08 (0.96–1.23)	0.197	1.08 (0.95–1.22)	0.257
TNM Stage (IV vs. III)	2.71 (0.33–22.86)	0.339	2.93 (0.36–25.62)	0.300
ECOG PS (1 vs. 0)	0.69 (0.09–4.67)	0.698	0.47 (0.06–2.82)	0.407
Histology (SCC vs. AC)	2.72 (0.47–19.25)	0.261	2.26 (0.37–15.17)	0.364

Note: Bold P-values indicate statistical significance ($P < 0.05$). Firth logistic regression was performed to adjust for age, TNM stage, ECOG PS, and histology.

Abbreviations: DCR, disease control rate; OR, odds ratio; CI, confidence interval; PNI, prognostic nutritional index; ECOG PS, Eastern Cooperative Oncology Group performance status; SCC, squamous cell carcinoma; AC, adenocarcinoma.

5. Dynamic Changes of IIN Biomarkers and Their Association with Treatment Response

5.1. Comparison of Dynamic Trends Between ICI and Chemotherapy Cohorts

To elucidate the specific impact of immunotherapy on systemic biomarkers, we compared the longitudinal trends between the ICI and chemotherapy cohorts. Overall, NLR, PLR, SII, and LMR showed a downward trend during treatment, while PNI, albumin, and pre-albumin tended to increase. However, no significant differences were observed between the two cohorts for any biomarker (all interaction $P > 0.05$). This suggests that the dynamic modulation of IIN biomarkers is not unique to ICIs; conventional chemotherapy can also induce similar systemic improvements. Therefore, we further explored the association between these dynamics and clinical outcomes specifically within the ICI cohort.

5.2. Stratified Analysis of Biomarker Dynamics by Clinical Response in the ICI Cohort

Within the ICI cohort, LMM analysis was performed to evaluate the interaction between time and clinical response (ORR and DCR) (**Table 7**). While no significant differences in biomarker dynamics were found between ORR responders and non-responders ($P > 0.05$), a distinct pattern emerged when stratified by DCR. Patients achieving disease control exhibited significantly greater reductions in PLR (Estimate = –36.03; 95% CI: –68.79 to –3.28; $P = 0.033$) and SII (Estimate = –421.52; 95% CI: –783.89 to –59.16; $P = 0.024$) compared to those without disease control (Figs. 3A and 3B). No significant interactions were observed for LMR, NLR, SIRI, or nutritional indicators (all P > 0.05). These findings indicate that a dynamic decline in inflammatory burden (PLR and SII) is closely linked to stable disease control.

Table 7. Linear mixed model analysis of IIN biomarker dynamics stratified by clinical response in the ICI cohort.

Indicators	ORR Stratification (OR vs. Non-OR) Estimate (95% CI)	*P* value	DCR Stratification (DC vs. Non-DC) Estimate (95% CI)	*P* value
NLR	-0.16 (-0.97 to 0.66)	0.707	-0.98 (-2.31 to 0.35)	0.151
LMR	-0.65 (-1.42 to -0.13)	0.104	-0.58 (-1.86 to 0.71)	0.380
PLR	3.31 (-16.94 to 23.56)	0.749	**-36.03 (-68.79 to -3.28)**	**0.033**
PNI	-0.51 (-1.95 to 0.93)	0.491	-1.22 (-3.83 to 0.89)	0.224
SII	14.09 (-210.46 to 238.64)	0.902	**-421.52 (-783.89 to -59.16)**	**0.024**
Albumin	-0.56 (-1.77 to 0.64)	0.362	-1.64 (-3.61 to 0.33)	0.105
Pre-albumin	7.38 (-8.46 to 23.23)	0.363	1.49 (-26.61 to 29.59)	0.918

Note: Interaction *P*-values reflect the difference in dynamic trends over time between response groups.

Abbreviations: DC, disease control; ORR, objective response rate; DCR, disease control rate.

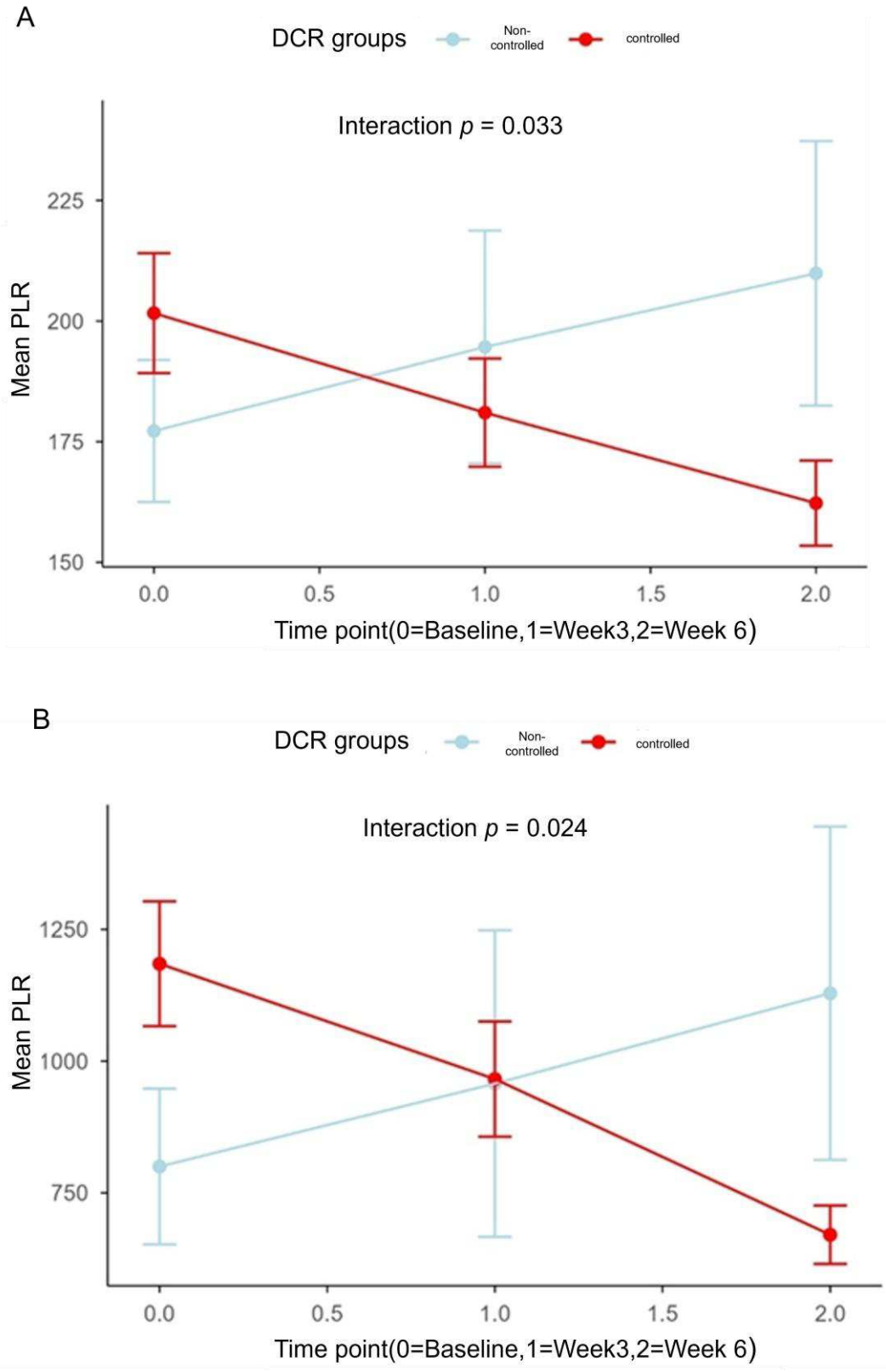


Figure 3. Dynamic changes in PLR and SII according to disease control status in the immunotherapy group. (A) Dynamic changes in PLR; (B) dynamic changes in SII.
Note: The interaction P values were derived from linear mixed-effects models.

5.3. Exploratory Analysis of Early Dynamic Changes and Survival Outcomes

We further investigated the relationship between early biomarker changes (from baseline to Week 6, denoted as Δ) and long-term survival. Patients were categorized into the "Decrease group" ($\Delta < 0$) and "Non-decrease group" ($\Delta \geq 0$). Kaplan-Meier analysis revealed that patients with an early decline in PLR (ΔPLR < 0) showed a trend toward improved OS compared to the non-decrease group, although the difference did not reach statistical significance (Fig. 4, P = 0.075). No significant associations were found between Δ values of other biomarkers and OS or PFS ($P > 0.10$). These exploratory results suggest that early mitigation of inflammatory load may portend survival benefit, a finding that warrants validation in larger cohorts.

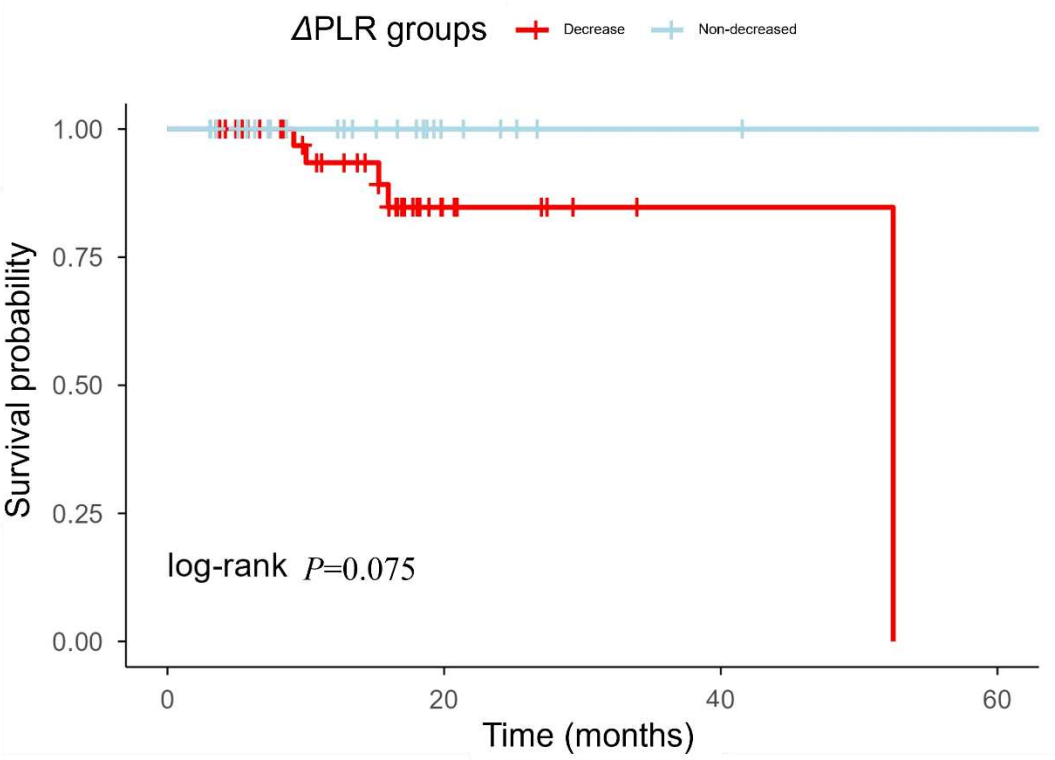


Figure 4. Kaplan–Meier curves for overall survival according to early changes in platelet-to-lymphocyte ratio (ΔPLR).
Note: The P value was calculated using the log-rank test.

6. Prognostic Performance of the Immune-Inflammation-Nutrition Composite Score

Based on the preceding findings, an Immune-Inflammation-Nutrition Composite Score (INICS) was constructed incorporating baseline LMR, baseline PNI, and ΔPLR. Each component was assigned 0 or 1 point according to the criteria described in the Methods, yielding a total score ranging from 0 to 3. Accordingly, patients were stratified into low-score (0–1), intermediate-score (2), and high-score (3) groups.

Kaplan–Meier analysis revealed distinct PFS among the three INICS strata, with higher scores associated with significantly longer PFS (log-rank $p = 0.008$; Fig. 5). When evaluated as a continuous variable, each 1-point increase in the INICS was associated with a lower risk of disease progression or death in univariable Cox regression (HR, 0.46; 95% CI, 0.26–0.81; $p = 0.008$). Relative to the low-score group, both the intermediate-score group (HR, 0.35; 95% CI, 0.14–0.86; $p = 0.021$) and the high-score group (HR, 0.25; 95% CI, 0.08–0.77; $p = 0.016$) exhibited significantly lower risks of disease progression or death. After adjustment for TNM stage and ECOG performance status, these associations remained significant for both the intermediate-score group (HR, 0.37; 95% CI, 0.15–0.93; $p = 0.035$) and the high-score group (HR, 0.26; 95% CI, 0.08–0.82; $p = 0.022$) (Table 8).

The INICS demonstrated modest discriminatory ability for 12-month PFS, with a time-dependent AUC of 0.674 (95% CI, 0.524–0.823; Fig. 6A). The multivariable Cox model incorporating the INICS yielded a C-index of 0.70. Calibration curves showed good agreement between predicted and observed 12-month PFS probabilities (Fig. 6B), with a mean bootstrap calibration slope of 1.14 (95% CI, 0.39–1.84; $p = 0.707$).

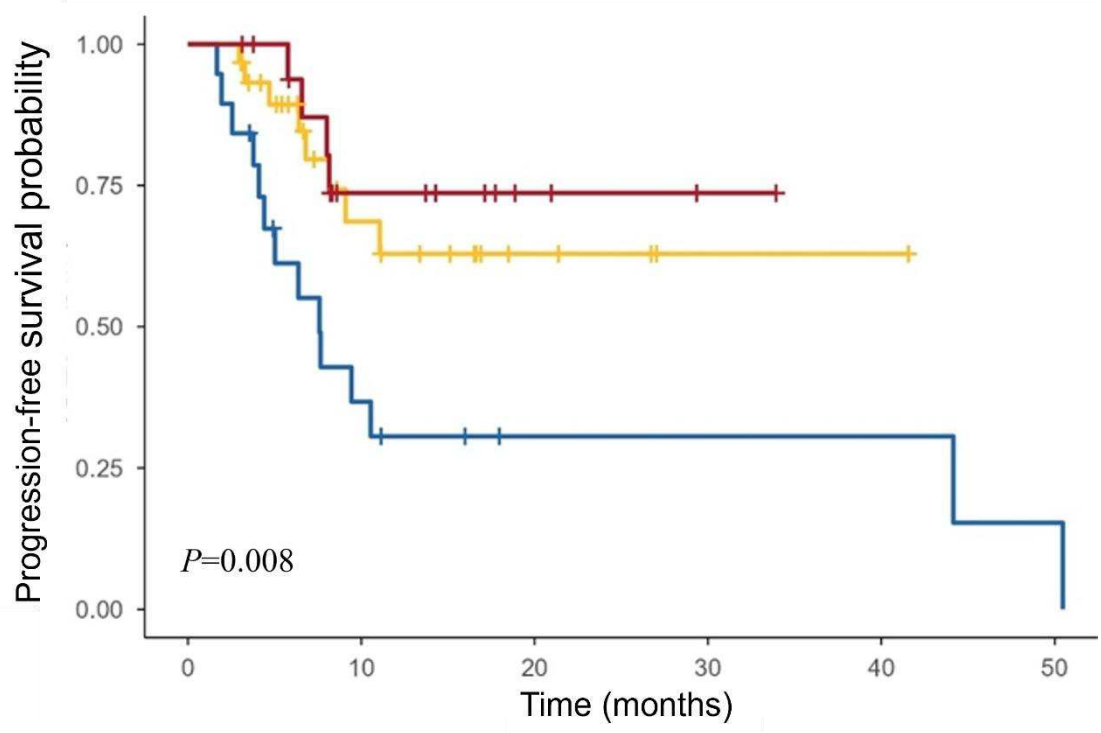


Figure 5A. Kaplan–Meier curves for progression-free survival according to INICS risk groups.

Note: Blue, low-score group (INICS 0–1); yellow, intermediate-score group (INICS 2); red, high-score group (INICS 3). The P value was calculated using the log-rank test.

Abbreviations: INICS, immune-inflammation-nutrition composite score; PFS, progression-free survival.

Table 8. Univariable and multivariable Cox regression analyses of the association between INICS score and PFS

INICS category	Univariable *HR* (95% CI)	*P* value	Multivariable *HR* (95% CI)	*P* value
Low (0~1 points)	1.00 (Reference)	-	1.00 (Reference)	-
Intermediate (2 points)	0.35 (0.14 ~ 0.86)	0.021	0.37 (0.15 ~ 0.93)	0.035
High (3 points)	0.25 (0.08 ~ 0.77)	0.016	0.26 (0.08 ~ 0.82)	0.022
INICS（continuous）	0.46 (0.26 ~ 0.81)	0.008	-	-

Note: Multivariable models were adjusted for TNM stage (stage IV vs stage III) and ECOG performance status (1 vs 0). In the continuous variable analysis, HR represents the hazard ratio per 1-point increase in INICS score. The INICS score was constructed based on the following cut-off values: baseline LMR ≥ 2.85, baseline PNI ≥ 40.27, and $\Delta PLR < 0$. One point was assigned for meeting each criterion, with total scores ranging from 0 to 3, stratifying patients into low (0–1 points), intermediate (2 points), and high (3 points) score groups.

Abbreviations: INICS, Immuno-Inflammation-Nutrition Composite Score; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; ECOG, Eastern Cooperative Oncology Group; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio.

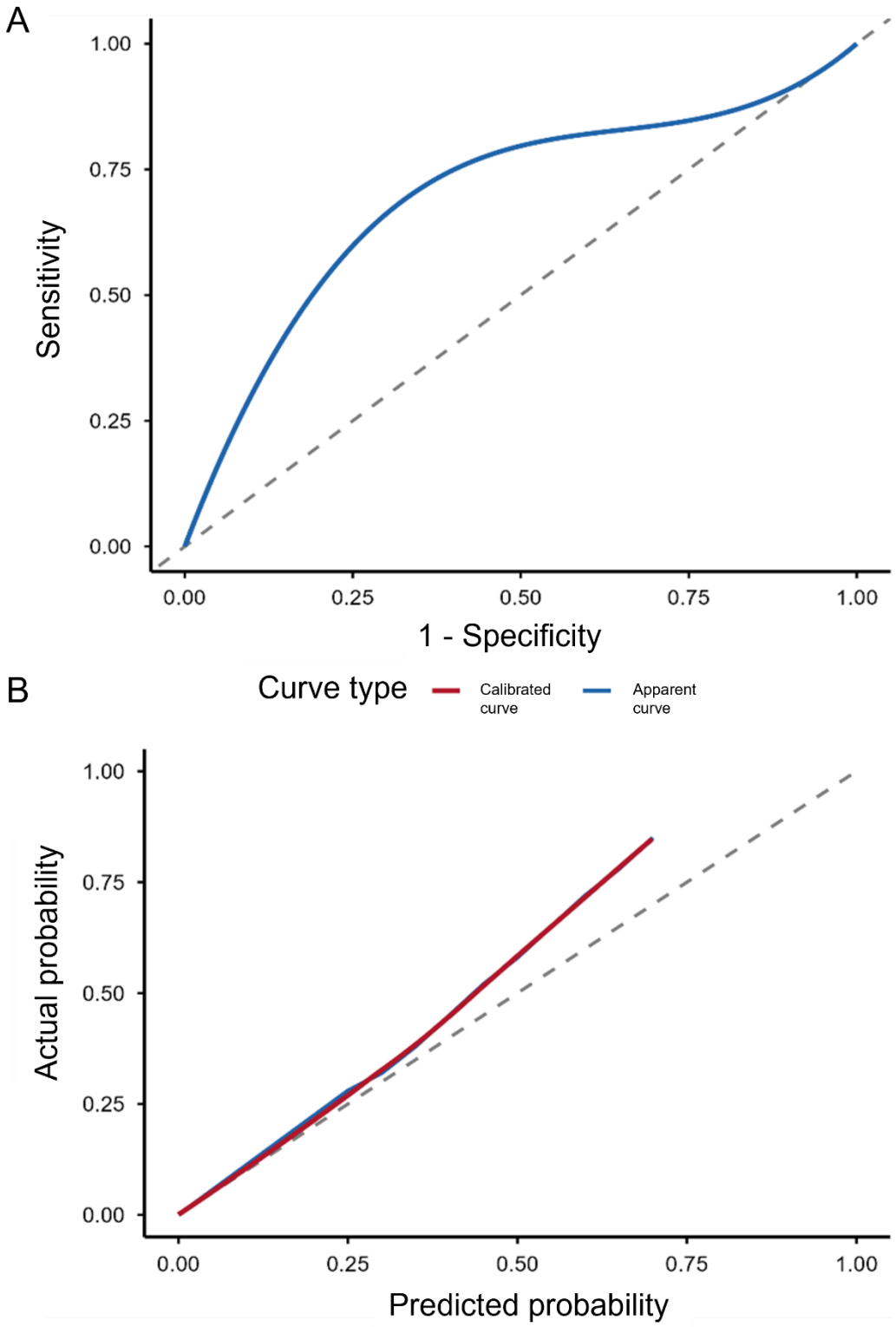


Figure 6. Predictive performance and calibration of the INICS for 12-month PFS. (A) Time-dependent ROC curve. (B) Calibration curve comparing predicted and actual probabilities.

Abbreviations: INICS, immune-inflammation-nutrition composite score; ROC, receiver operating characteristic; AUC, area under the curve; PFS, progression-free survival; CI, confidence interval.

Discussion

Systemic immune-inflammatory-nutritional factors closely interact with the tumor microenvironment and influence clinical outcomes in cancer patients[24, 25]. In this study, we evaluated peripheral blood biomarkers in patients with advanced NSCLC receiving first-line ICI-based chemoimmunotherapy and developed a novel prognostic tool, the Immune-Inflammation-Nutrition Composite Score (INICS). By integrating baseline LMR, baseline PNI, and early dynamic changes in PLR (*Δ*PLR), the INICS was independently associated with PFS (12-month AUC = 0.674; C-index = 0.70). Our findings suggest that combining static host reserves with early treatment-related inflammatory kinetics may provide complementary prognostic information for risk stratification.

1. Baseline Biomarkers and Clinical Efficacy

Pretreatment biomarkers reflected distinct dimensions of therapeutic response. Baseline LMR was independently associated with ORR after adjustment for PNI and age. Lymphocytes are major effector cells of antitumor immunity, whereas circulating monocytes can differentiate into immunosuppressive cells within the tumor microenvironment [26, 27]. Thus, a higher LMR may reflect a more favorable systemic immune profile and a greater likelihood of response to ICI-based therapy. This finding is consistent with previous studies showing that higher LMR was associated with better PFS or OS in patients with advanced or metastatic NSCLC receiving immunotherapy[28].

Although baseline PNI was significantly associated with ORR in univariable analysis, this association was no longer significant after adjustment for LMR and age. The VIF analysis showed no substantial collinearity between PNI and LMR (VIF ≈ 1.1), suggesting that this finding was unlikely to result from multicollinearity. Because PNI incorporates both serum

albumin and lymphocyte count, its association with ORR may partly overlap with the immune information captured by LMR. Our findings therefore suggest that LMR may provide greater prognostic information than PNI for predicting objective response in this setting, although this observation requires validation in larger cohorts.

In contrast, higher baseline PNI and serum albumin levels were associated with a higher DCR. PNI reflects both nutritional and immunological status[29, 30]. Previous studies have shown that higher pretreatment PNI is associated with better survival in advanced NSCLC patients receiving immunotherapy[31, 32], while albumin-based indices have also been associated with treatment outcomes[33]. Nutritional deficiency may impair immune function, including T-cell proliferation and cytokine production, and has been linked to T-cell exhaustion[34, 35]. These findings may partly explain why better pretreatment nutritional status was associated with greater disease control in our cohort.

Regarding PD-L1 expression, patients with TPS ≥50% showed a trend toward a lower risk of progression than those with TPS <1% (HR = 0.33, 95% CI: 0.10–1.09, P = 0.069). Although statistical significance was not reached, likely because of the limited sample size of the high PD-L1 subgroup, the observed effect direction was consistent with previous evidence supporting greater benefit from ICI-based chemoimmunotherapy among patients with high PD-L1 expression[36]. Larger studies are warranted to further clarify the predictive value of PD-L1 expression in this setting.

2. Biological Implications of Dynamic Biomarker Shifts

A notable finding was the different relationship between early dynamic biomarker changes and clinical endpoints. During treatment, dynamic changes in peripheral biomarkers did not significantly correlate with ORR. ORR measures rapid tumor burden reduction within 2–3

months, a process primarily governed by local microenvironmental characteristics, such as baseline TIL density and local PD-L1 status, rather than broad peripheral cell counts[37, 38]. Fan et al. similarly noted that early changes in peripheral markers failed to independently predict short-term ORR[39].

In contrast, early reductions in PLR and SII were significantly associated with achieving DCR. Elevated PLR and SII reflect sustained systemic inflammatory cascades that may contribute to cancer progression and immune evasion[40-42]. Decreases in these markers may reflect reduced systemic inflammatory activity during treatment. These results accord with findings in NSCLC and other solid malignancies [43, 44], supporting dynamic inflammatory markers as potentially useful indicators of mid- to long-term disease stabilization.

3. Performance and Potential Clinical Utility of the INICS Model

By combining baseline LMR, baseline PNI, and *Δ*PLR, the INICS captures both intrinsic host baseline status and early systemic inflammatory changes during treatment. Higher INICS values reflect a more favorable baseline immune and nutritional status together with a more favorable early inflammatory trajectory and are associated with prolonged PFS after adjustment for TNM stage and ECOG performance status.

Recent studies have developed the inflammation-immune-nutrition score (IINS) based on high-sensitivity C-reactive protein (hs-CRP), lymphocyte count, and serum albumin, and have demonstrated its prognostic value in several solid tumors [45-47]. Compared with the IINS, the INICS has several potential advantages. First, whereas the IINS primarily relies on static pretreatment parameters, the INICS incorporates an early dynamic biomarker, ΔPLR, thereby capturing changes in systemic inflammatory status during the initial phase of treatment. This dynamic component may provide additional prognostic information beyond baseline

characteristics by reflecting early treatment-related biological changes.

Second, all components of the INICS are derived from routinely available clinical laboratory parameters, including complete blood count measures and serum albumin, without requiring specialized assays such as hs-CRP. This may improve the accessibility and feasibility of the INICS in routine clinical practice. Third, previous studies of the IINS in NSCLC have primarily focused on patients receiving curative-intent treatment, whereas the INICS was specifically developed in patients with advanced NSCLC receiving first-line ICI-based chemoimmunotherapy. Overall, the INICS may serve as a potential tool for individualized prognostic assessment in patients with advanced NSCLC receiving first-line ICI-based chemoimmunotherapy.

Nevertheless, the prognostic performance of the INICS should be interpreted cautiously. The 12-month time-dependent AUC of 0.674 indicates moderate discriminatory ability, while the C-index of 0.70 suggests potentially useful but not definitive prognostic discrimination. Moreover, the INICS was developed and evaluated within the same cohort, and therefore optimism and overfitting cannot be completely excluded. Prospective multicenter studies with independent external validation are warranted to determine whether the INICS provides reproducible and incremental prognostic value beyond established clinical factors before its routine clinical application can be considered.

4. Limitations

Several limitations should be considered when interpreting our results. First, the single-center retrospective design and modest cohort size introduce potential selection bias; despite IPTW sensitivity analyses, residual confounding across histological subtypes cannot be fully ruled out. Second, limited overall survival (OS) events restricted the ability to perform detailed

long-term survival analyses. Third, because the INICS was developed and evaluated within the same cohort, optimism and overfitting cannot be entirely excluded. Therefore, prospective multicenter studies with independent external validation are needed to confirm these findings and determine whether the INICS can provide robust prognostic value before it can be considered for routine clinical use.

Conclusion

In patients with advanced NSCLC receiving first-line ICI-based chemoimmunotherapy, higher baseline LMR was associated with a higher ORR, whereas higher baseline PNI and serum albumin levels were associated with a higher DCR. Dynamic changes in peripheral biomarkers were not significantly associated with objective response, while reductions in PLR and SII were associated with disease control.

The INICS, integrating baseline LMR, baseline PNI, and ΔPLR, was independently associated with PFS, with higher scores indicating a lower risk of disease progression. By incorporating immune, inflammatory, and nutritional dimensions, the INICS may provide complementary prognostic information for risk stratification. Further prospective multicenter studies with external validation are warranted to confirm its clinical utility.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the First Hospital of Shanxi Medical University (No. KYLL-2025-407). The requirement for informed consent was waived by the ethics committee owing to the retrospective nature of the study and the use of de-identified data obtained from existing

medical records.

Consent to Publish

Not applicable. This study does not contain any individual person's data in any form (including individual details, images or videos) that would require consent for publication.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request..

Clinical Trial Registration

Not applicable. This was a retrospective observational cohort study and does not meet the definition of a clinical trial requiring registration.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Contributions

Conceived and designed the analysis: Chang W, Jia J.

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Contributed data or analysis tools: Chang W, Liang Y, Li Y.

Performed the analysis: Chang W, Li Y.

Wrote the paper: Chang W, Liang Y.

Supervised the study, provided critical intellectual input, critically revised the manuscript, and approved the final version of the manuscript: Jia J.

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