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Original Article

Peripheral blood neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index values as prognostic predictors for non-small cell lung carcinoma

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Abstract: Objective: To evaluate whether systemic inflammatory biomarkers - neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) - have prognostic value in patients with non-small cell lung carcinoma (NSCLC). Methods: In this retrospective study, NLR, PLR, and SII levels were examined in 183 NSCLC cases. Correlations between these biomarkers and 3-year overall survival (OS) and progression-free survival (PFS) were assessed. Receiver operating characteristic (ROC) curves were used to evaluate predictive performance. Point-biserial correlation was applied to explore associations between each biomarker and 3-year OS/PFS, followed by multivariate analyses to identify independent prognostic factors. Results: The 3-year OS and PFS were 74.86% and 65.03%, respectively. Survivors and patients without progression had significantly lower NLR, PLR, and SII values than non-survivors and those with progression. ROC curve analysis showed moderate predictive accuracy for individual biomarkers (area under the curve [AUC]: 0.714-0.808 for OS; 0.635-0.754 for PFS), whereas their combination substantially enhanced prognostic discrimination (AUC=0.906 for OS; AUC=0.812 for PFS) ($P<0.001$). Further investigation demonstrated an inverse correlation between NLR, PLR, SII and 3-year OS/PFS ($P<0.01$). Multivariate analysis identified high NLR (≥3.57, OR=9.923), PLR (≥216.00, OR=9.978), and SII (≥969.50, OR=4.913) were independently associated with worse survival outcomes ($P<0.05$). Conclusion: NLR, PLR, and SII are valuable predictors of survival in NSCLC. Integrating these biomarkers further improves prognostic accuracy.

Keywords: Peripheral blood, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, non-small cell lung carcinoma, prognostic prediction, clinical value

Introduction

With an estimated incidence of 85% among lung cancer cases, non-small cell lung carcinoma (NSCLC) is one of the most prevalent malignancies and a major contributor to cancer-associated mortality [1]. It is characterized by high incidence and mortality rates, with well-established risk factors including tobacco use, genetic susceptibility, radiation exposure, and pre-existing pulmonary conditions [2]. The pathogenesis of NSCLC is complex and heterogeneous, involving genomic instability, dysregulation of cell cycle control, oncogenic mutations, tumor suppressor gene inactivation, and impaired DNA repair mechanisms [3]. Despite substantial therapeutic advances, the 5-year relative survival rate remains discouragingly low, at around 23%, underscoring the urgent need for reliable prognostic tools [4].

Hematologic indices derived from routine blood tests, particularly composite inflammatory indices including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have

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emerged as valuable biomarkers reflecting tumorigenesis and disease progression. These readily accessible indicators demonstrate substantial clinical utility across multiple domains, including early diagnosis, assessment of treatment response, and prognostic evaluation, offering important guidance for clinical decision-making in oncology [5-7]. Notably, Han et al. [8] reported elevated NLR and PLR as independent predictors of adverse outcomes following sleeve lobectomy in NSCLC, demonstrating their cost-effective prognostic value for survival and recurrence in centrally located tumors. Similarly, Wang et al. [9] observed significant correlations between NLR/PLR and clinical outcomes in surgically treated lung cancer patients, with lower values indicating better survival. The SII has also shown promising prognostic capability, correlating with advanced pathologic stage in NSCLC [10]. Furthermore, evidence suggests SII is a robust predictor of survival outcomes in lung cancer patients undergoing trimodality therapy, where reduced SII levels correlate significantly with improved disease-free survival (DFS), overall survival (OS), and recurrence-free status [11].

Our study innovatively validated the prognostic value of peripheral blood NLR, PLR, and SII in NSCLC. We retrospectively analyzed 183 NSCLC patients (stages I-IV), assessing the association of these inflammatory markers with survival outcomes (OS and PFS) and disease progression status. The predictive performance of NLR, PLR, and SII for OS and PFS was comprehensively evaluated using statistical analyses, and significant prognostic factors were identified through univariate and multivariate analyses. Our findings suggest that these hematologic indices may serve as effective prognostic biomarkers for NSCLC, supporting clinical decision-making and facilitating individualized treatment strategies.

This research features several novel contributions: (1) It evaluates peripheral blood indices as predictor of clinical outcomes in NSCLC cases, highlighting their clinical relevance and potential to reduce medical expenses; (2) The combined application of NLR, PLR, SII yields superior prognostic accuracy, particularly concerning 3-year OS; (3) It pinpoints key prognostic factors, offering a practical tool for risk stratification to aid in prognostic prediction and support clinical decision-making.

Materials and methods

Case selection

Approval for this retrospective study was obtained from the Ethics Committee of the First Affiliated Hospital of Huzhou University (Ethics No.: 2023KYLL014). Patient information was retrieved from the hospital's medical records database, and all data were collected in a de-identified format. Between February 2020 and February 2022, a total of 183 patients diagnosed with NSCLC at the First Affiliated Hospital of Huzhou University were enrolled.

Inclusion criteria: Histologically or cytologically confirmed NSCLC [12]; presence of at least one measurable lesion evaluable by imaging, with repeatable assessments; disease staging based on the 9th edition of the Union for International Cancer Control (UICC) TNM classification for lung cancer [13]; treatment-naïve status at enrollment; availability of complete clinical records; willingness to participate in a 3-year follow-up.

Exclusion criteria: Diagnosis of multiple primary malignancies; concurrent autoimmune-related diseases; severe cardiac, pulmonary, or renal insufficiency; history of bleeding disorders or blood transfusion; receipt of neoadjuvant chemotherapy, radiotherapy, or targeted therapy before evaluation of marker status; death within 30 days postoperatively.

Figure 1 illustrates the patient selection flowchart.

Data extraction

Blood test data (neutrophils, lymphocytes, platelets, etc.) and survival outcomes (OS, PFS) were obtained from medical records. For blood tests, fasting venous blood (3 mL) was collected from all patients prior to treatment initiation after a 12-hour overnight fast. Complete blood count values, including platelet count (PLT), absolute neutrophil count (ANC), and lymphocyte count (LY), were analyzed using an automated hematology analyzer (Shanghai Jumu Medical Devices Co., Ltd., b3513). Inflammatory indices were calculated as follows: NLR = ANC ÷ LY; PLR = PLT ÷ LY; SII = (PLT × ANC) ÷ LY. OS was defined as the interval between surgery and death from any cause. PFS was calculated

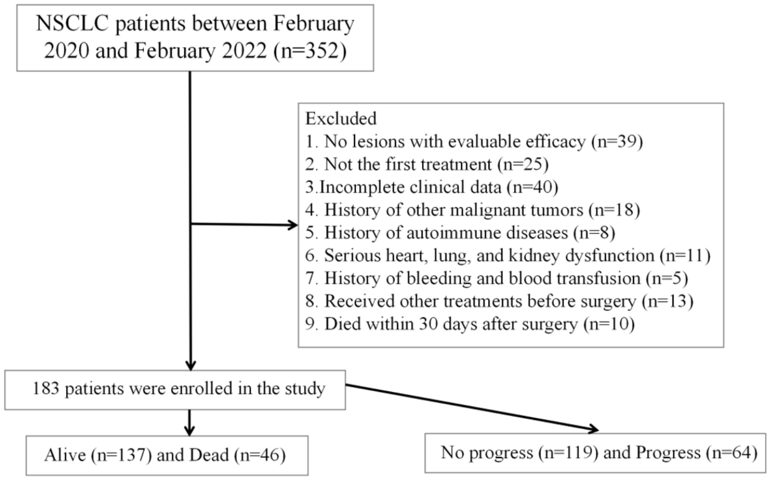

Figure 1. Flow chart of patient selection. NSCLC, non-small cell lung carcinoma.

from diagnosis to either imaging-confirmed disease progression or the final follow-up. In this study, the primary analyses focused on NLR, PLR, SII, and OS, with PFS being a secondary focus.

Statistical methods

Data analyses were conducted with SPSS software (v20.0). Continuous variables were reported as mean ± standard error of the mean (SEM), with group comparisons made using independent-sample t-tests. Categorical data were represented as percentages (%) and analyzed using chi-square tests. Receiver operating characteristic (ROC) curves were applied to evaluate the ability of NLR, PLR, and SII to predict OS and PFS. Kaplan-Meier survival curves were generated, and between-group differences were assessed using the log-rank test. Associations between NLR, PLR, SII and 3-year OS/PFS were assessed using point-biserial correlation analysis. Furthermore, prognostic factors were further explored through univariate and multivariate regression analyses. Statistical significance was established at $P<0.05$.

Results

Analysis of peripheral blood NLR, PLR, and SII in survivors and non-survivors over the 3-year OS period

All enrolled patients completed the 3-year follow-up, with 137 survivors, yielding a 3-year OS rate of 74.86%. Non-survivors exhibited markedly elevated peripheral blood NLR, PLR, and SII levels compared to survivors ($P<0.001$). These differences are illustrated in **Figure 2**.

ROC analysis of NLR, PLR, and SII for OS prediction

ROC analysis was performed to evaluate the prognostic value of NLR, PLR, and SII for predicting OS. The AUC values were 0.714 for NLR, 0.808 for PLR, and 0.752 for SII. Importantly, the combined model outperformed individual markers, achieving an AUC of 0.906. Among individual indices, NLR showed the highest specificity (97.08%) and accuracy (83.06%), whereas the combined model achieved optimal sensitivity (84.78%). Importantly, the integrated prediction model maintained balanced performance, with specificity, sensitivity, and accuracy all exceeding 80%. Detailed results are presented in **Figure 3** and **Table 1**.

Association of NLR, PLR, and SII with 3-year OS in NSCLC patients

Kaplan-Meier survival analysis revealed a significant inverse association between NLR, PLR, and SII levels and 3-year OS in NSCLC patients (all $P<0.05$). Elevated values of these inflammatory markers were associated with reduced survival, as illustrated in **Figure 4**.

Peripheral blood NLR, PLR, and SII in progressive vs. non-progressive NSCLC patients

Among the 183 patients with NSCLC, the 3-year PFS rate was 65.03%. Notably, patients with disease progression demonstrated significantly higher NLR, PLR, and SII levels compared to those remaining progression-free ($P<0.001$, **Figure 5**).

ROC analysis of NLR, PLR, and SII in PFS prediction

ROC curve analysis demonstrated that the AUC values for NLR, PLR, and SII in predicting PFS

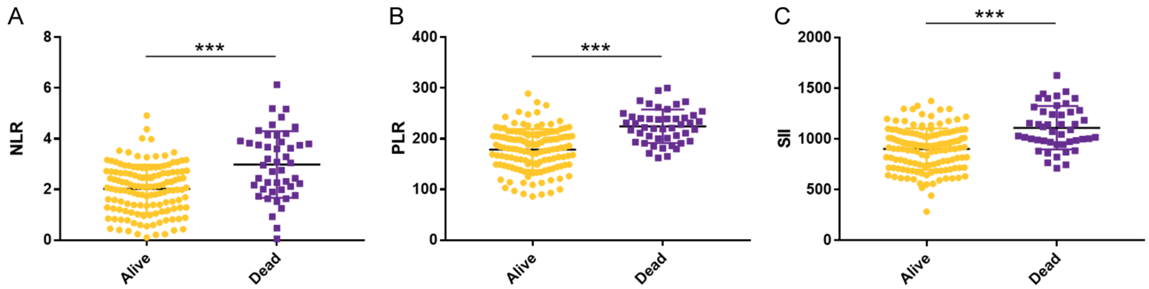

Figure 2. Comparison of NLR (A), PLR (B), and SII (C) values between survivors and non-survivors over the 3-year OS assessment period. Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; OS, overall survival; ***P<0.001.

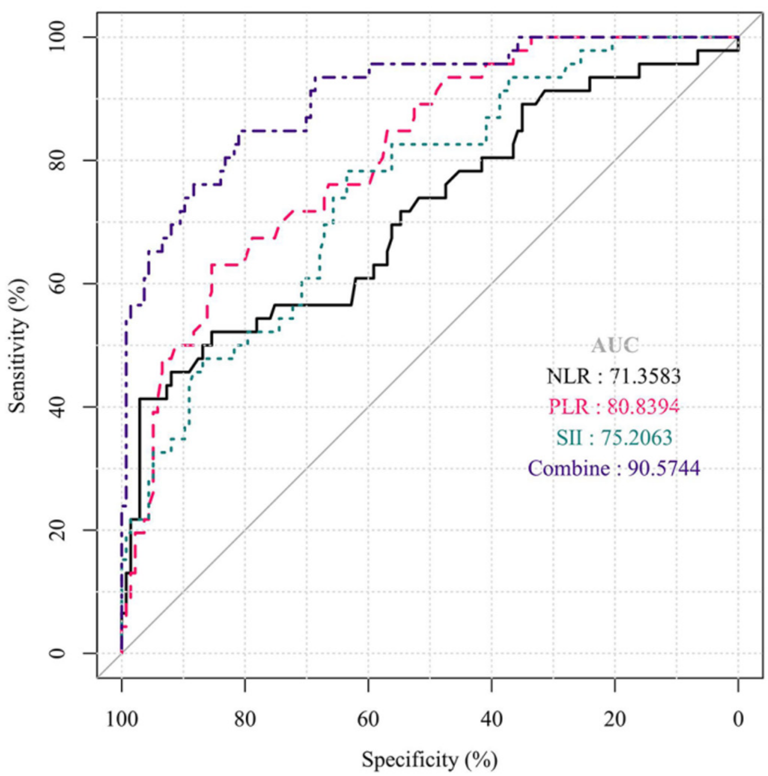

Figure 3. ROC curves for NLR, PLR, SII, and their combination in predicting OS of NSCLC patients. Note: ROC, receiver operating characteristic; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Association of NLR, PLR, and SII with 3-year PFS in NSCLC patients

Kaplan-Meier analysis indicated a significant inverse associations between NLR, PLR, and SII levels and 3-year PFS in NSCLC patients (P<0.05, **Figure 7**). Elevated values of these inflammatory indices were associated with poorer PFS.

Correlation of NLR, PLR and SII with 3-year OS/PFS

Point-biserial correlation analysis indicated inverse correlations between all three inflammatory biomarkers and clinical outcomes. For 3-year OS, the correlation coefficients were -0.369 for NLR, -0.459 for PLR, and -0.404 for SII (all P<0.001). For 3-year PFS, the corresponding coefficients were -0.208 (P=0.005), -0.402 (P<0.001), and -0.346 (P<0.001) (**Table 3**).

were 0.635, 0.754, and 0.714, respectively. The combined model exhibited superior predictive performance, with an AUC of 0.812. Notably, the integrated biomarker panel achieved the highest specificity (84.03%) and overall accuracy (78.14%), whereas PLR and SII displayed the greatest sensitivity (73.44%). Detailed results are shown in **Figure 6** and **Table 2**.

Univariate analysis of NSCLC survival outcomes

Univariate analysis identified several factors significantly correlated with NSCLC prognoses, including age, Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, NLR, PLR, and SII (P<0.05, **Table 4**).

Table 1. Performance metrics of NLR, PLR, and SII in predicting OS of NSCLC patients based on ROC curve analysis

Indicator	AUC	95% CI	*P* value	Cutoff	Specificity	Sensitivity	Accuracy
NLR	0.714	0.621-0.806	<0.001	3.57	97.08%	41.30%	83.06%
PLR	0.808	0.740-0.877	<0.001	216.00	85.40%	63.04%	79.78%
SII	0.752	0.673-0.831	<0.001	969.50	63.50%	78.26%	67.21%
Combined	0.906	0.856-0.956	<0.001	0.21	81.02%	84.78%	81.97%

Note: NSCLC, non-small cell lung cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; OS, overall survival; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

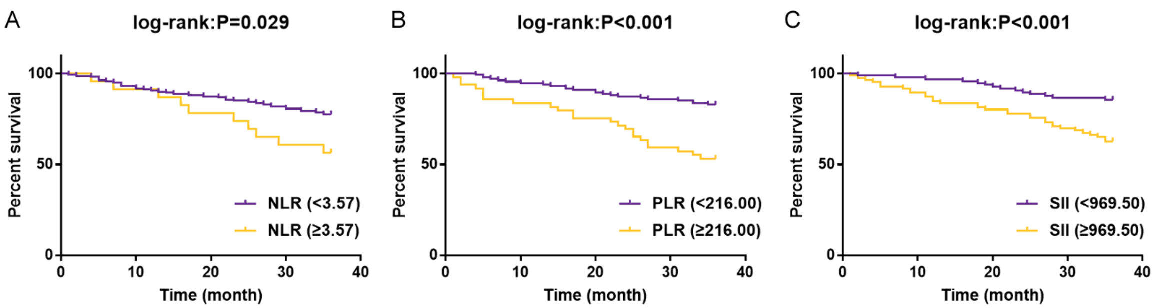

Figure 4. Kaplan-Meier survival analysis of NLR (A), PLR (B), and SII (C) in relation to 3-year OS. Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; OS, overall survival.

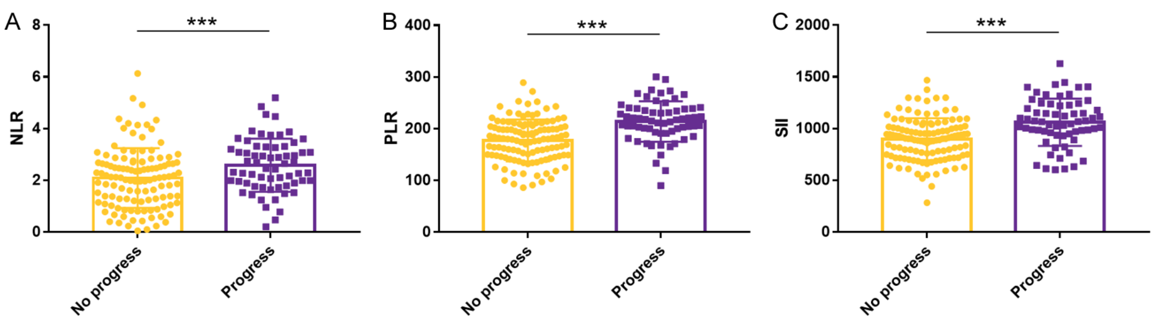

Figure 5. Comparison of NLR (A), PLR (B), and SII (C) between NSCLC patients with and without disease progression over a 3-year PFS evaluation period. Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; PFS, progression-free survival; *** P<0.001.

Multivariate analysis of NSCLC survival outcomes

Multivariate regression analysis identified NLR (OR: 9.923, P<0.001), PLR (OR: 9.978, P<0.001), and SII (OR: 4.913, P=0.001) as independent predictors of NSCLC outcomes (**Table 5**).

Discussion

This retrospective study enrolled 183 NSCLC patients, revealing 3-year OS and PFS rates of 74.86% and 65.03%, respectively. These findings align with previous reports by Ji et al. [14], supporting the reliability of our results. The study focused on systemic inflammatory markers (NLR, PLR, and SII), given their established associations with tumor progression and immune microenvironment modulation. These hematologic markers, known for their clinical utility due to easy accessibility and economic advantages [15, 16], provide valuable insight into the inflammatory state of NSCLC patients. Notably, our data demonstrated that disease

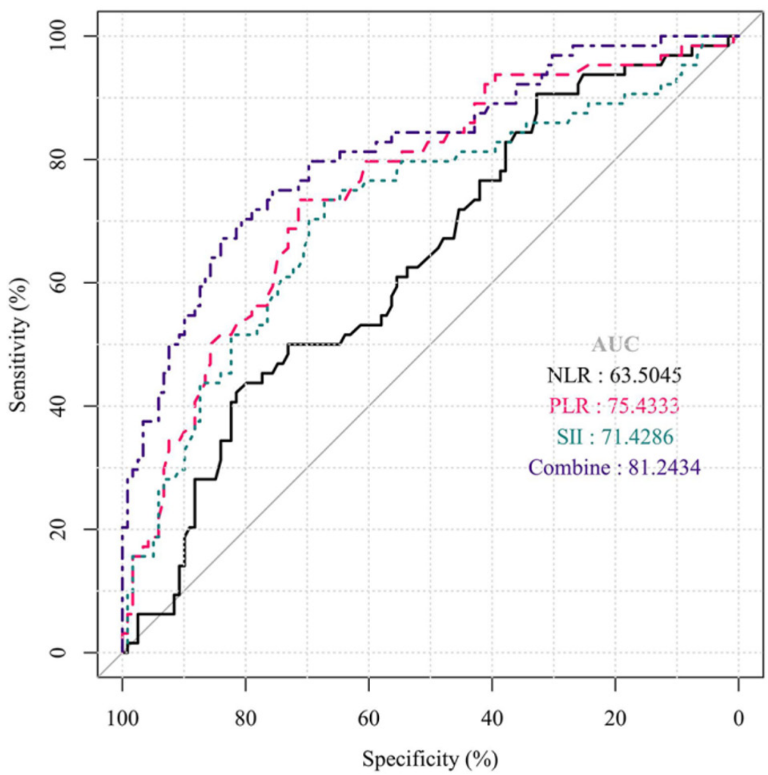

Figure 6. ROC curves for NLR, PLR, SII, and their combination in predicting PFS in NSCLC patients. Note: ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; PFS, progression-free survival.

progression or mortality were frequently associated with elevated NLR, PLR, and SII values. This observation underscores the close relationship between systemic inflammatory responses and adverse clinical outcomes in NSCLC patients and suggests that these biomarkers may serve as practical prognostic tools for ongoing clinical monitoring and management.

ROC curve analysis was conducted to evaluate the prognostic performance of NLR, PLR, and SII in NSCLC patients. For OS prediction, the AUCs were 0.714 for NLR, 0.808 for PLR, and 0.752 for SII, whereas the combined model significantly improved predictive accuracy, reaching an AUC of 0.906. In predicting PFS, the corresponding AUCs were 0.635 for NLR, 0.754 for PLR, and 0.714 for SII, with the integrated model enhancing accuracy to an AUC of 0.812. These results indicate that while all three indices demonstrated strong predictive capacity for OS, they exhibited only moderate performance for PFS. Notably, their combined use significantly enhanced prognostic accuracy for both clinical outcomes. Meanwhile, the incorporation of multidimensional inflammatory biomarkers may thus enable more precise risk stratification in NSCLC. The enhanced clinical utility of combining these markers likely arises from their complementary roles: NLR reflects inflammatory/immune equilibrium, PLR reflects platelet-lymphocyte interactions related to coagulation and immunity, and SII provides a comprehensive assessment of systemic inflammation [17-19]. Comparative analysis with previous research highlights variability in predictive performance. Liu et al. [20] reported lower AUC values for NLR in stage III-IV NSCLC (0.660 for OS, 0.651 for PFS) compared to our findings. Similarly, Zhang et al. [21] observed modest predictive capacity for NLR (AUC=0.623) and SII (AUC=0.539) in assessing response to immune checkpoint inhibitor (ICI) therapy in advanced NSCLC. Supporting our conclusions, Liu et al. [22] identified SII, NLR, and PLR as reliable prognostic indicators in metastatic NSCLC, with all three markers showing robust associations with both PFS and OS.

In addition, survival analysis revealed a clear connection between elevated NLR, PLR, and SII and reduced 3-year OS and PFS in NSCLC patients. These findings align with the study by Diem et al. [23], which reported that increased NLR and PLR before treatment were associated with poorer OS and PFS in metastatic NSCLC patients undergoing nivolumab therapy. However, Zhou et al. [24] presented partially discordant results, showing that while high SII levels significantly predicted worse OS in SCLC patients, no such association was observed for PFS. Findings from correlation analyses indicated that NLR, PLR, and SII were inversely associated with 3-year OS/PFS in NSCLC, suggesting a close tie between these

Table 2. Performance metrics of NLR, PLR, and SII in predicting PFS of NSCLC patients based on ROC curve analysis

Indicator	AUC	95% CI	*P* value	Cutoff	Specificity	Sensitivity	Accuracy
NLR	0.635	0.552-0.718	<0.001	2.88	81.51%	42.19%	67.76%
PLR	0.754	0.681-0.828	<0.001	199.50	71.43%	73.44%	72.13%
SII	0.714	0.633-0.796	<0.001	969.50	67.23%	73.44%	69.40%
Combined	0.812	0.746-0.879	<0.001	0.44	84.03%	67.19%	78.14%

Note: NSCLC, non-small cell lung cancer; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; PFS, progression-free survival; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

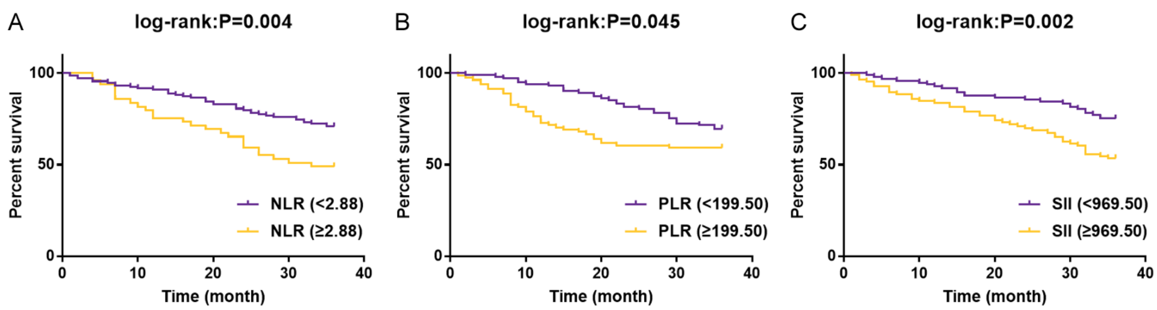

Figure 7. Kaplan-Meier survival curves of NLR (A), PLR (B), and SII (C) in relation to 3-year PFS. Note: PFS, progression-free survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Table 3. Point-biserial correlation of NLR, PLR, and SII with 3-year OS/PFS in NSCLC patients

Indicator	r_{pb}	P
NLR and 3-year OS	-0.369	<0.001
PLR and 3-year OS	-0.459	<0.001
SII and 3-year OS	-0.404	<0.001
NLR and 3-year PFS	-0.208	0.005
PLR and 3-year PFS	-0.402	<0.001
SII and 3-year PFS	-0.346	<0.001

Note: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; OS, overall survival; PFS, progression-free survival; NSCLC, non-small cell lung carcinoma.

three measures and the clinical outcomes in NSCLC.

Both univariate and multivariate analyses identified these inflammatory markers as independent prognostic indicators for NSCLC prognosis, implying that their elevation may reliably predicts unfavorable survival outcomes. Supporting evidence comes from Lei et al. [25], who identified an SII/albumin ratio exceeding 17.79 independently predicted poor prognosis following immunotherapy in NSCLC patients receiving ICIs and opioids.

Notably, previous literature has established several favorable prognostic factors for NSCLC, including good performance status, non-smoking history, early disease stage, female sex, and squamous cell carcinoma subtype [26]. Cancer progression is closely associated with systemic inflammation and can induce alterations in the tumor microenvironment by enhancing angiogenesis and metastasis, ultimately compromising patient outcomes. Neutrophils support this process by releasing vascular endothelial growth factor (VEGF) and other growth-promoting cytokines during tumor proliferation [27]. Conversely, lymphocytes exert cytotoxic effects and play a critical role in tumor immune surveillance [28]. Platelets, on the other hand, may shield tumor cells from immune system attacks, thereby facilitating their survival. Moreover, platelet activity has been linked to enhanced tumor growth and metastatic spread by disrupting endothelial cell function [29]. These findings provide insight into why elevated NLR, PLR, and SII levels are strongly correlated with unfavorable outcomes in NSCLC patients.

Table 4. Univariate analysis of survival outcomes in NSCLC patients

Indicator	Survivors (n=137)	Non-survivors (n=46)	χ^2	P
Age (years)			5.356	0.021
<65 (n=110)	89 (64.96)	21 (45.65)		
≥65 (n=73)	48 (35.04)	25 (54.35)		
Gender			1.955	0.162
Male (n=119)	93 (67.88)	26 (56.52)		
Female (n=64)	44 (32.12)	20 (43.48)		
Pathological type			0.147	0.701
Squamous-cell carcinoma (n=91)	67 (48.91)	24 (52.17)		
Adenocarcinoma (n=92)	70 (51.09)	22 (47.83)		
ECOG (score)			4.864	0.027
0-1 points (n=141)	111 (81.02)	30 (65.22)		
2-3 points (n=42)	26 (18.98)	16 (34.78)		
Clinical staging			2.005	0.157
I-II (n=100)	79 (57.66)	21 (45.65)		
III-IV (n=83)	58 (42.34)	25 (54.35)		
Differentiated degree			2.109	0.146
High differentiation (n=71)	49 (35.77)	22 (47.83)		
Moderate to low differentiation (n=112)	88 (64.23)	24 (52.17)		
Smoking history			5.356	0.021
None (n=110)	89 (64.96)	21 (45.65)		
Yes (n=73)	48 (35.04)	25 (54.35)		
Alcohol abuse history			2.449	0.118
None (n=117)	92 (67.15)	25 (54.35)		
Yes (n=66)	45 (32.85)	21 (45.65)		
NLR			22.457	<0.001
<3.57 (n=160)	129 (94.16)	31 (67.39)		
≥3.57 (n=23)	8 (5.84)	15 (32.61)		
PLR			41.222	<0.001
<216.00 (n=134)	117 (85.40)	17 (36.96)		
≥216.00 (n=49)	20 (14.60)	29 (63.04)		
SII			10.262	0.001
<969.50 (n=97)	82 (59.85)	15 (32.61)		
≥969.50 (n=86)	55 (40.15)	31 (67.39)		

Note: NSCLC, non-small cell lung carcinoma; ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Several limitations of this study warrant future improvement. First, the single-center design limits sample representativeness, highlighting the need for multi-center investigations to enhance the generalizability of the findings. Second, the biological mechanisms linking peripheral blood NLR, PLR, and SII to NSCLC development and progression remain insufficiently explored. Further experimental studies would help clarify their underlying mechanisms and broaden current knowledge. Lastly, the economic feasibility of incorporating NLR, PLR, and SII into routine prognostic assessment remains unassessed; cost-effectiveness analyses could support their broader clinical application.

In summary, peripheral blood NLR, PLR, and SII values were markedly increased in NSCLC patients experiencing disease progression or death. Elevated values of these three biomarkers were consistently correlated with reduced 3-year OS and PFS. Notably, the combined evaluation of NLR, PLR, and SII exhibited superior

Table 5. Multivariate analysis of survival outcomes in NSCLC patients

Indicator	β	SE	Wald	P	OR	95% CI
Age (years; <65=0, ≥65=1)	0.724	0.447	2.627	0.105	2.063	0.859-4.950
ECOG (score; 0-1 points =0, 2-3 points =1)	0.549	0.514	1.143	0.285	1.732	0.633-4.743
Smoking history (No =0, yes =1)	0.795	0.450	3.125	0.077	2.215	0.917-5.348
NLR (<3.57=0, ≥3.57=1)	2.295	0.642	12.758	<0.001	9.923	2.817-34.958
PLR (<216.00=0, ≥216.00=1)	2.300	0.472	23.747	<0.001	9.978	3.956-25.169
SII (<969.50=0, ≥969.50=1)	1.592	0.477	11.144	0.001	4.913	1.930-12.511

Note: NSCLC, non-small cell lung carcinoma; ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

predictive performance for both 3-year OS and PFS outcomes, establishing this as an independent predictor of NSCLC outcome. These results suggest that these readily accessible hematologic markers could serve as cost-effective and non-invasive tools for prognostic assessment in NSCLC.

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Disclosure of conflict of interest

None.

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