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Original Article

Hematological parameters as predictors of immune-related adverse events: risk factor analysis in non-small cell lung cancer patients undergoing immunotherapy

Yong Jia[1], Rong Wang[2], Junlong Shen[1], Yingying Wang[3]

[1]Department of Thoracic Surgery, Baoji Central Hospital, No. 8 Jiangtan Road, Weibin District, Baoji 721000, Shaanxi, China; [2]Department of Oncology Hematology, Baoji Traditional Chinese Medicine Hospital, No. 2 Baozhong Road, Jintai District, Baoji 721000, Shaanxi, China; [3]Tumor Ward 2, Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, No. 2, Deputy Weiyang West Road, Xianyang 712000, Shaanxi, China

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Abstract: Objective: To evaluate the predictive value of hematological biomarkers in assessing the risk of immune-related adverse events (irAEs) in non-small cell lung cancer (NSCLC) patients undergoing immunotherapy and to identify potential risk factors for personalized treatment optimization. Methods: Clinical data of 274 NSCLC patients who received immunotherapy between April 2018 and January 2021 were retrospectively analyzed. Patients were divided into irAEs and non-irAEs groups based on the occurrence of irAEs. Peripheral blood indices within one week before treatment initiation were assessed and compared, including absolute neutrophil count (ANC), lymphocyte count (LYM), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), albumin-to-alkaline phosphatase ratio (AAPR), and albumin-to-fibrinogen ratio (AFR). Kaplan-Meier analysis compared overall survival (OS) and progression-free survival (PFS), while logistic regression identified independent risk factors for irAEs. Receiver operating characteristic (ROC) curve analysis evaluated predictive performance. Results: Among the 274 patients, 116 (42.2%) developed irAEs. Compared to the non-irAEs group, the irAEs group exhibited significantly higher ANC, NLR, PLR, and SII, along with lower LYM, AAPR, and AFR as well as lower OS and PFS rates (all $P < 0.05$). Logistic regression showed that all hematological indicators were independent risk factors for irAEs ($P < 0.05$). ROC analysis showed an AUC of 0.722 for NLR and 0.829 for the combined model. Conclusion: Pretreatment assessment of ANC, LYM, NLR, PLR, SII, AAPR, and AFR provides valuable predictive utility for irAEs risk in NSCLC patients undergoing immunotherapy. Integrating these biomarkers into clinical practice may enhance risk stratification and guide personalized treatment strategies to improve safety and therapeutic outcomes.

Keywords: Hematological indicators, non-small cell lung cancer, immunotherapy, immune-related adverse events, risk factors

Introduction

Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases, remaining a leading cause of cancer-related mortality worldwide. The introduction of immune checkpoint inhibitors (ICIs), particularly PD-1/PD-L1 and CTLA-4 inhibitors, has revolutionized NSCLC treatment by harnessing the host immune system to target tumor cells, significantly improving overall survival (OS) and progression-free survival (PFS) in advanced-stage disease [1, 2].

Despite these advancements, immune-related adverse events (irAEs) pose a major clinical challenge, often limiting treatment efficacy and compromising patient quality of life. These toxicities, stemming from dysregulated immune activation, can affect multiple organ systems including the lungs, liver, thyroid, skin, and gastrointestinal tract, with potentially life-threatening consequences in severe cases [3, 4]. The underlying pathophysiology of irAEs remains incompletely elucidated but is thought to involve loss of immune tolerance, wherein activated T cells inadvertently attack healthy tissues along-

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side malignant cells [5]. Emerging evidence suggests that inflammatory cascades, influenced by baseline immune status, genetic predisposition, and patient-specific factors, play a pivotal role in irAEs development [6]. Given their unpredictable nature and variable severity, early identification of high-risk patients is crucial for optimizing therapeutic outcomes.

Recent research has highlighted the potential of hematological biomarkers as accessible and cost-effective indicators of systemic inflammation and immune dysregulation, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) [7, 8]. Demonstrated prognostic value in predicting irAEs, reflecting the dynamic interplay between pro-inflammatory and immunosuppressive pathways during immunotherapy [9, 10]. However, a comprehensive evaluation of their predictive utility, particularly in combination with other emerging markers like the albumin-to-alkaline phosphatase ratio (AAPR) and albumin-to-fibrinogen ratio (AFR), remains underexplored.

Therefore, this study aims to evaluate the clinical utility of these hematological indices in predicting the risk of irAEs in NSCLC patients undergoing ICIs treatment. Additionally, we aim to identify associated risk factors for irAEs to provide clinicians with theoretical guidance in identifying high-risk patients and optimizing treatment strategies.

Materials and methods

Sample size calculation

The sample size for this study was determined based on the incidence of irAEs reported by Gao et al. [11] (16.7%). Using the formula for cross-sectional study rates: $N = Z^2 \times [P \times (1\text{-}P)]/E^2$ where $Z = 1.96$ for a 95% confidence level, $P = 0.167$ (expected incidence), and $E = 0.05$ (allowable error), the required sample size was calculated to be at least 214 patients to meet statistical power requirements.

Case selection

This study included 274 NSCLC patients who received immunotherapy at our hospital from April 2018 to January 2021. The study was approved by the Baoji Central Hospital Ethics Committee.

Inclusion criteria: Histologically or molecularly confirmed NSCLC diagnosis; Stage IV disease according to the 8th edition TNM classification [12]; Received ≥ 2 cycles of ICI therapy (monotherapy or combination with chemotherapy/anti-angiogenic agents); Completed ≥ 30 months of follow-up with at least one clinical evaluation during treatment; Availability of complete baseline and post-treatment hematological profiles; Presence of irAEs at grade 1-2.

Exclusion criteria: Severe underlying conditions (e.g., severe cardiac or renal dysfunction) prior to or during immunotherapy; Pre-existing autoimmune disorders or immunodeficiency conditions; Non-ICI-based immunotherapy regimens; Insufficient clinical data or loss to follow-up; Concurrent use of immunomodulatory drugs/supplements affecting outcomes; Other factors affecting survival or prognosis during follow-up.

Data collection

Data were obtained from the hospital's Information System (HIS) and Electronic Medical Record (EMR) system. Collected data included:

Basic information: Age, gender, BMI, underlying conditions (e.g., hypertension, diabetes), smoking history, pathological type, ECOG performance status (PS), immunotherapy regimen, and the number of immunotherapy lines.

Tumor characteristics: Tumor metastasis, baseline tumor burden (size and number), and treatment regimen (immunotherapy, combination, or monotherapy).

Laboratory data: Blood test results within 1 week before the first immunotherapy dose, including neutrophil count (ANC), lymphocyte count (LYM), NLR, PLR, SII, prognostic nutritional index (AAPR), and albumin-to-platelet ratio (AFR).

Assessment and grouping of irAEs

irAEs were defined and assessed using the Common Terminology Criteria for Adverse Events (CTCAE), 5th edition [13]. Patients were divided into two groups: those with irAEs (irAEs group) and those without (non-irAEs group). The types of irAEs included pneumonia, thyroid dysfunction, liver dysfunction, gastrointestinal reactions, skin toxicity, and others. The occur-

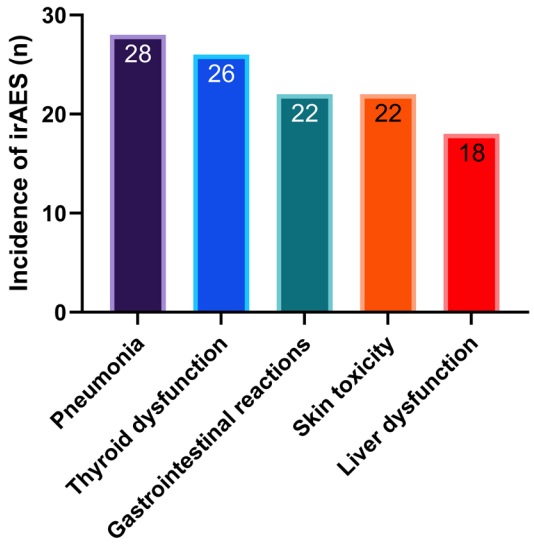

Figure 1. Distribution of irAEs types.

rence of irAEs was monitored within 1 week to 6 months after treatment.

Grade 1: Asymptomatic or mildly symptomatic, detected by clinical or laboratory examination, requiring no special treatment.

Grade 2: Symptoms present but tolerable, requiring local or non-invasive treatment (e.g., topical steroids, antidiarrheal drugs), potentially affecting instrumental activities of daily living.

Statistical methods

Data were analyzed using SPSS 26.0 software. Continuous variables were expressed as means ± standard deviations ($\bar{x} \pm s$) and comparisons used independent sample t-tests. Categorical variables were expressed as frequencies and percentages (n, %) and compared using the Chi-square test or Fisher's exact test. Correlations were analyzed with Pearson's test. Multivariate logistic regression was performed to identify independent risk factors for irAEs in NSCLC patients receiving ICIs. Kaplan-Meier survival curves were used for OS and PFS analysis and survival differences were assessed using the Log-rank test. ROC curve analysis was adopted to analyze the predictive value of hematological indices for irAE risk. Statistical significance was set at $P < 0.05$.

Results

General information and basic clinical characteristics

A total of 274 patients with NSCLC were enrolled in this study. The average age of the patients was 62.5±7.4 years, with 189 males and 85 females. The mean BMI was 22.6±3.2 kg/m^2. Among the patients, 183 had a history of smoking. Regarding underlying comorbidities, 78 patients had hypertension, 39 had diabetes mellitus, 33 had coronary heart disease, 24 had COPD, and 14 had other conditions. In terms of the pathological subtypes, 196 patients were diagnosed with adenocarcinoma, and 78 patients had squamous cell carcinoma. The treatment history indicated that 138 patients received first-line treatment, 104 received second-line treatment, and 32 received third-line treatment. The ECOG performance status was 0-1 in 212 patients, while 62 patients had a PS score of ≥ 2. There were bone metastasis in 120 patients, lung metastasis in 96 patients, liver metastasis in 68 patients, and brain metastasis in 32 patients.

Distribution of irAEs types

Out of the 274 NSCLC patients treated with ICIs, 116 patients (42.2%) developed irAEs. The most common irAE was pneumonia, which occurred in 28 patients (24.1%), followed by thyroid dysfunction in 26 patients (22.4%), gastrointestinal reactions in 22 patients (19.0%), skin toxicity in 22 patients (19.0%), and liver dysfunction in 18 patients (15.5%) (**Figure 1**).

Comparison of clinical factors between the irAEs group and non-irAEs group

When comparing clinical factors between the irAEs group and the non-irAEs group, there were no significant differences observed for age (P = 0.065), gender (P = 0.594), BMI (P = 0.595), smoking history (P = 0.335), ECOG PS score (P = 0.609), or underlying comorbidities. Specifically, no significant differences were observed for hypertension (P = 0.853), diabetes mellitus (P = 0.212), coronary heart disease (P = 0.505), COPD (P = 0.648), chronic renal insufficiency (P = 0.826), or other comorbid conditions (P = 0.578). Additionally, there were no significant differences in the patholo-

Table 1. Comparison of clinical factors between the irAEs group and non-irAEs group

Factor		irAEs Group (n = 116)	Non-irAEs Group (n = 158)	t/x^2	*P*
Age (years)		61.90±6.17	63.44±7.55	-1.853	0.065
Gender (Male/Female)		78/38	111/47	0.284	0.594
BMI (kg/m^2)		23.06±2.88	22.87±3.14	0.532	0.595
Smoking History (yes/no)		81/35	102/56	0.928	0.335
ECOG PS score (0-1/≥ 2)		88/28	124/34	0.262	0.609
Basic Diseases (n)	Hypertension	32 (27.6%)	42 (26.6%)	0.034	0.853
	Diabetes	14 (12.1%)	12 (7.6%)	1.559	0.212
	Coronary heart disease	11 (9.5%)	19 (%)	0.444	0.505
	COPD	20 (%)	24 (15.2%)	0.209	0.648
	Chronic renal insufficiency	8 (6.9%)	12 (7.6%)	0.048	0.826
	Other	11 (%)	12 (7.6%)	0.310	0.578
Pathological type (n)	Adenocarcinoma	84 (72.4%)	112 (70.9%)	0.077	0.782
	Squamous cell carcinoma	32 (27.6%)	46 (29.1%)		
Immunotherapy lines (n)	First line	58 (50.0%)	80 (50.6%)	0.465	0.793
	Second line	46 (39.7%)	58 (36.7%)		
	Third line	12 (10.3%)	20 (12.7%)		
Combination Therapy (single agent/combination)		54/62	72/86	0.026	0.872
Baseline tumor metastasis (yes/no)		94/22	118/40	1.541	0.215

Note: BMI: body mass index, COPD: Chronic obstructive pulmonary disease.

Table 2. Comparison of hematological index changes between the irAEs group and non-irAEs group

Group	irAEs Group (n = 116)	Non-irAEs Group (n = 158)	*t*	*P*
ANC	4.61±1.43	4.17±1.16	2.716	0.007
LYM	1.66±0.47	1.80±0.60	-2.095	0.037
NLR	3.21±0.81	2.58±0.63	6.931	< 0.001
PLR	178.03±43.84	160.67±41.28	3.32	0.001
SII	609.83±107.93	549.07±82.47	5.072	< 0.001
AAPR	0.40±0.07	0.43±0.09	-3.711	< 0.001
AFR	0.95±0.16	1.02±0.19	-3.192	0.002

Note: ANC: Absolute Neutrophil Count, LYM: Lymphocyte Count, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, AAPR: Albumin to Alkaline Phosphatase Ratio, AFR: Albumin to Fibrinogen Ratio.

gical types (P = 0.782), lines of immunotherapy (first-line: P = 0.793, second-line: P = 0.597, third-line: P = 0.302), use of combination therapy (P = 0.872), or tumor metastasis (P = 0.215; **Table 1**).

Comparison of hematological parameters between the irAEs group and non-irAEs group

The ANC was significantly higher in the irAEs group (P = 0.007), while LYM levels were significantly lower (P = 0.037). Additionally, NLR, PLR, and SII levels were significantly higher in the irAEs group (all P < 0.001). On the other hand, AAPR and AFR levels were significantly lower in the irAEs group (both P < 0.01; **Table 2**).

Prognostic impact of irAEs in NSCLC patients undergoing ICI therapy

Survival outcomes were analyzed in 274 NSCLC patients, with a follow-up duration of 30 months post-ICI initiation. The mean OS and the PFS in the irAEs group were significantly shorter than those in the non-irAEs group (both P < 0.05). Further analysis revealed that there were no significant association between irAE severity grades and OS (P = 0.202; **Table 3** and **Figure 2**).

Association between irAE severity and hematological parameters

Correlation analysis demonstrated no significant associations between irAE severity grades

Table 3. Comparison of survival duration between the irAEs and non-irAEs groups

Group	Deaths	Survivors	Mean OS (months)	Mean PFS (months)
irAEs group (n = 116)	14	102	17.48±4.98	9.80±4.60
Non-irAEs group (n = 158)	18	140	21.25±4.18	13.20±3.90
t/x^2	0.030		-6.610	-6.605
P	0.863		0.000	0.000

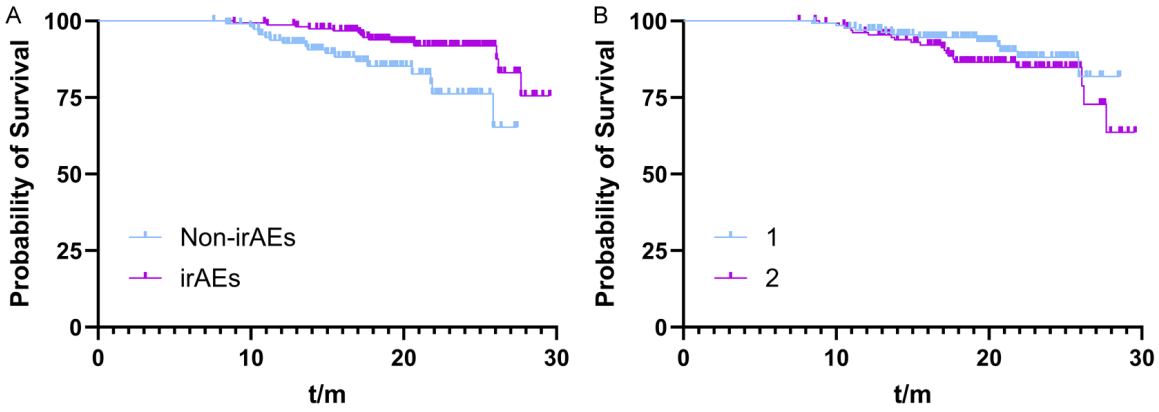

Figure 2. Kaplan-Meier survival analysis of OS k-m curves between. A. irae and non-irae groups. B. k-m curves for patients with different irae grades. Note: OS: Overall Survival.

and any of the evaluated hematological parameters, including ANC, LYM, NLR, PLR, SII, AAPR, or AFR (all P > 0.05; **Figure 3**).

Independent risk factors for irAE development

Multivariate logistic regression analysis identified several hematological parameters as independent predictors of irAEs (**Figure 4**). The results showed that elevated ANC, NLR, PLR and SII, along with reduced LYM, AAPR and AFR were significant independent risk factors for the development of irAEs (P < 0.05).

Predictive value of hematological indicators for the occurrence of irAEs

ROC curve analysis demonstrated differential predictive capacity among the evaluated parameters. NLR showed the strongest individual predictive value (AUC 0.722, 95% CI 0.660-0.784). Moreover, a composite model incorporating NLR, PLR, SII, AAPR, and AFR exhibited superior predictive performance (AUC 0.829, 95% CI 0.781-0.878; P < 0.05 vs NLR alone). This suggests that the combined model of these hematological indicators has substantial predictive value for the occurrence of irAEs in NSCLC patients receiving ICIs treatment (**Table 4** and **Figure 5**).

Discussion

ICIs have revolutionized cancer therapy, demonstrating remarkable efficacy across multiple malignancies including NSCLC, melanoma, and renal cell carcinoma (RCC) through immune system potentiation [14, 15]. However, this therapeutic breakthrough comes with a paradoxical challenge, irAEs, resulting from systemic immune hyperactivation. These toxicities frequently involve the skin (rash, pruritis), gastrointestinal tract (colitis), hepatic system (hepatitis), and endocrine organs (thyroiditis, hypophysitis), creating a complex risk-benefit calculus in clinical practice [16].

Our study advances this field by showing that ANC, NLR, PLR, and SII are significantly elevated in the irAE group compared to the non-irAE group, while LYM, AAPR, and AFR are reduced in NSCLC patients undergoing ICI therapy. These findings align with prior research linking hematological markers to immune and inflammatory states [17, 18]. The neutrophil-dominated inflammatory signature (elevated ANC/NLR) suggests a crucial role for innate immune activation in irAE pathogenesis [19]. Neutrophils, key mediators of acute inflammation, release cytokines like IL-6 and TNF-α, amplifying systemic immune responses and potentially driv-

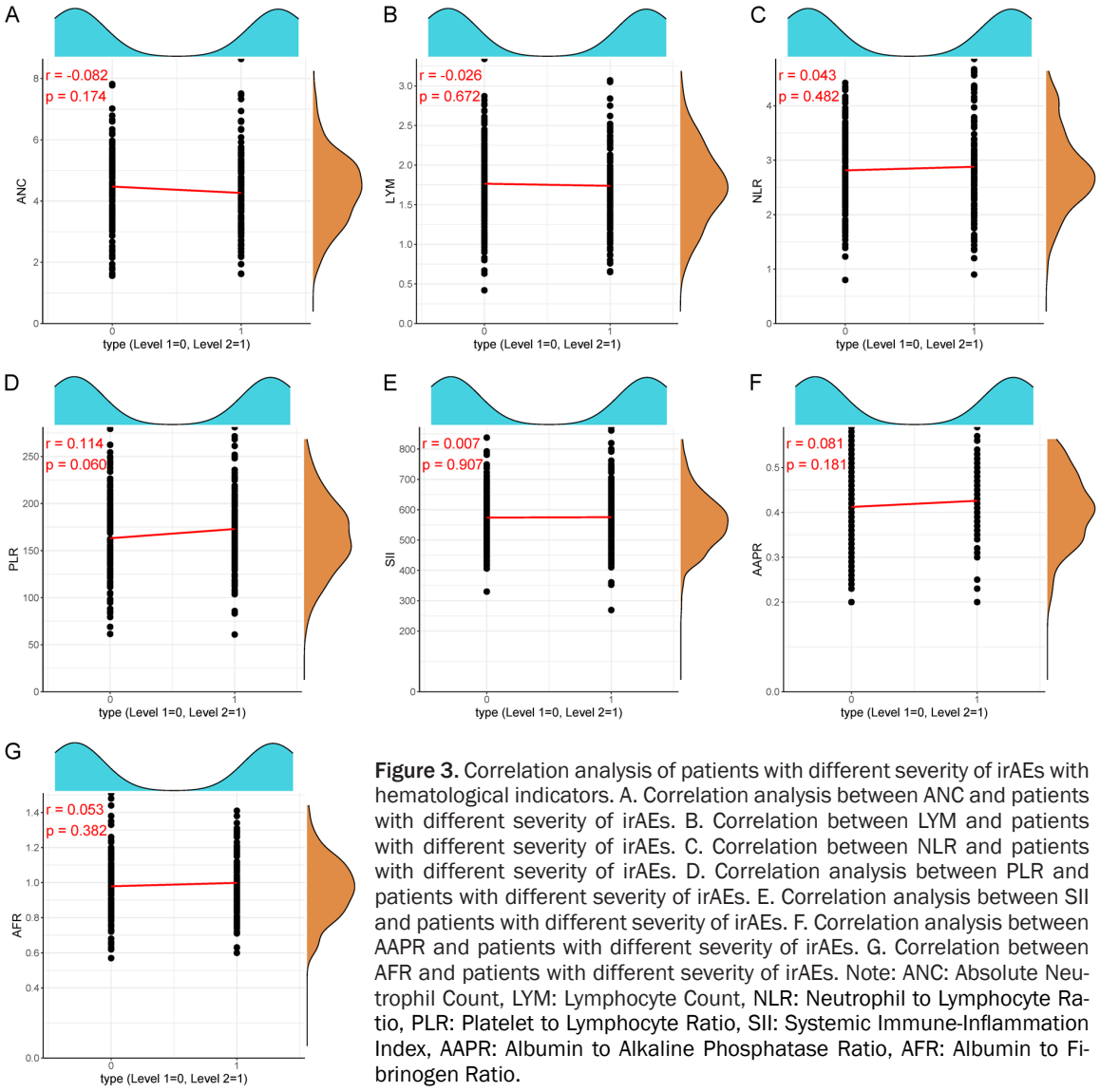

Figure 3. Correlation analysis of patients with different severity of irAEs with hematological indicators. A. Correlation analysis between ANC and patients with different severity of irAEs. B. Correlation between LYM and patients with different severity of irAEs. C. Correlation between NLR and patients with different severity of irAEs. D. Correlation analysis between PLR and patients with different severity of irAEs. E. Correlation analysis between SII and patients with different severity of irAEs. F. Correlation analysis between AAPR and patients with different severity of irAEs. G. Correlation between AFR and patients with different severity of irAEs. Note: ANC: Absolute Neutrophil Count, LYM: Lymphocyte Count, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, AAPR: Albumin to Alkaline Phosphatase Ratio, AFR: Albumin to Fibrinogen Ratio.

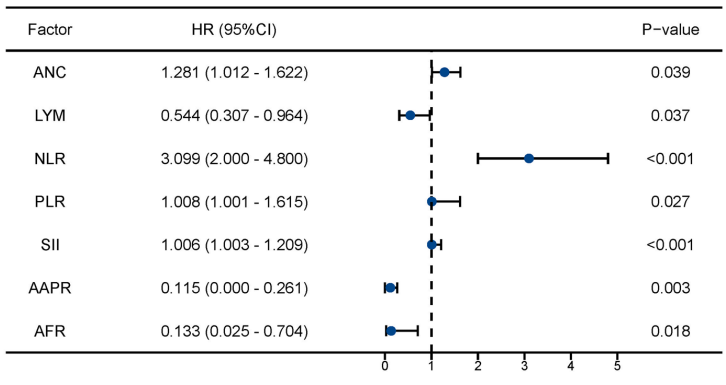

Figure 4. Forest plot of logistic regression analysis for each indicator. Note: ANC: Absolute Neutrophil Count, LYM: Lymphocyte Count, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, AAPR: Albumin to Alkaline Phosphatase Ratio, AFR: Albumin to Fibrinogen Ratio.

ing tissue damage in irAEs [20]. NLR, by capturing the neutrophil-lymphocyte imbalance, highlights both inflammation and immune suppression, as reduced LYM counts suggest diminished anti-tumor immunity [21]. Mechanistically, this could stem from lymphocyte exhaustion or apoptosis amid chronic inflammation, tipping the immune balance toward toxicity. Therefore, a high NLR may indicate excessive T-cell activation - intended to combat tumors - spilling over into autoimmunity, a plausible trigger for irAEs in ICI-treated NSCLC.

Table 4. Predictive value of hematological indicators for the occurrence of irAEs in NSCLC patients receiving ICIs treatment

Detection indicators	AUC	*S.E.*	95% CI	Specificity	Sensitivity	*P*
ANC	0.607	0.036	0.536-0.678	0.509	0.612	0.002
LYM	0.584	0.034	0.516-0.651	0.505	0.522	0.018
NLR	0.722	0.032	0.660-0.784	0.718	0.729	0.000
PLR	0.625	0.034	0.557-0.692	0.601	0.667	0.000
SII	0.662	0.034	0.595-0.729	0.645	0.678	0.000
AAPR	0.645	0.033	0.579-0.710	0.632	0.634	0.000
AFR	0.606	0.034	0.539-0.673	0.598	0.617	0.003
Joint	0.829	0.025	0.781-0.878	0.807	0.875	0.000

Note: ANC: Absolute Neutrophil Count, LYM: Lymphocyte Count, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, AAPR: Albumin to Alkaline Phosphatase Ratio, AFR: Albumin to Fibrinogen Ratio.

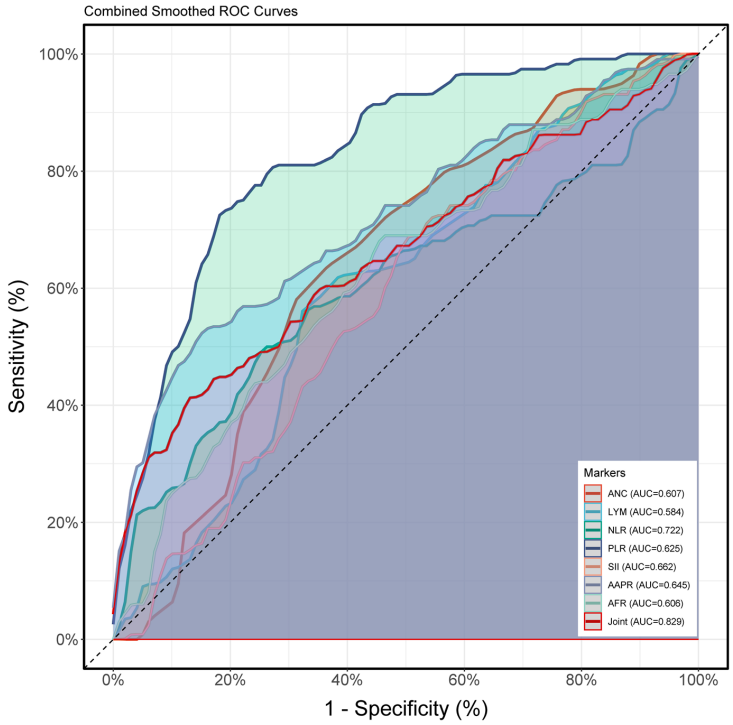

Figure 5. ROC curve for predicting the occurrence of irAEs in NSCLC patients receiving ICIs treatment. Note: ANC: Absolute Neutrophil Count, LYM: Lymphocyte Count, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, SII: Systemic Immune-Inflammation Index, AAPR: Albumin to Alkaline Phosphatase Ratio, AFR: Albumin to Fibrinogen Ratio.

PLR, integrating platelet and lymphocyte dynamics, further illuminates the inflammatory landscape [22]. Platelets, beyond their clotting role, secrete VEGF and PDGF, promoting angiogenesis and immune cell infiltration in the tumor microenvironment [23]. An elevated PLR in our irAE group suggests that platelet-driven inflammation synergizes with ICI-induced immune activation, heightening irAE risk. This is particularly relevant in NSCLC, where the tumor microenvironment features dense immune cell interactions that ICIs disrupt. The mechanistic link may involve platelet microparticles or thromboxane, enhancing local inflammation and exacerbating immune-mediated adverse events.

SII, combining ANC, PLR, and LYM, offers a broader snapshot of immune dysregulation [24]. Its elevation in the irAE group points to a hyperactive immune state, where neutrophils and platelets dominate over lymphocytes [25]. This could involve NETs, which intensify inflammation and tissue injury, or platelet-neutrophil aggregates that amplify immune responses, creating a feedback loop predisposing patients to irAEs [26]. Conversely, lower LYM counts in the irAE group suggest impaired adaptive immunity, critical for immune homeostasis during ICI therapy. This lymphocyte depletion might reflect T-cell exhaustion driven by sustained inflammation or checkpoint inhibitor overstimulation, further elevating irAE susceptibility.

Lower AAPR and AFR in the irAE group highlight the pivotal role of nutritional and immune status in ICI outcomes [27]. Albumin, a core com-

ponent of both ratios, serves as a barometer of nutritional health and immune competence, while elevated alkaline phosphatase and fibrinogen signal heightened inflammation and coagulation activity [28]. Reduced AAPR and AFR likely indicate a catabolic state induced by chronic inflammation, depleting anti-inflammatory proteins such as albumin-bound antioxidants that normally mitigate irAEs. High fibrinogen, which lowers AFR, may exacerbate this by fostering a pro-inflammatory and pro-thrombotic environment, potentially through fibrin deposition in affected tissues, worsening immune-mediated damage. Mechanistically, low albumin could impair the transport of immunosuppressive molecules, allowing unchecked immune activation, while elevated fibrinogen might enhance neutrophil recruitment via integrin signaling, amplifying irAE severity. These markers thus bridge systemic health and immune function, suggesting that malnutrition or immune suppression disrupts the delicate regulation of ICI-induced immune responses, increasing irAE risk. In NSCLC, where cachexia and chronic inflammation are prevalent, baseline malnutrition and immune dysfunction may prime patients for excessive immune activation upon ICI initiation. This imbalance could shift the therapeutic equilibrium from controlled antitumor immunity to unchecked autoinflammation, heightening irAE susceptibility.

Logistic regression confirmed ANC, LYM, NLR, PLR, SII, AAPR, and AFR as independent predictors of irAEs in NSCLC patients on immunotherapy. Detectable a week before ICI initiation, these markers provide an early warning system, enabling clinicians to identify high-risk patients and implement preventive strategies, such as anti-inflammatory agents (e.g., corticosteroids) or intensified monitoring. This predictive window is crucial, as it allows preemptive action before irAEs manifest clinically, potentially reducing their incidence and severity. Kaplan-Meier analysis revealed lower OS and PFS in the irAE group compared to the non-irAE group, contrasting with reports linking irAEs to improved outcomes in certain cancers [29]. Our data suggests decreased survival, likely due to severe immune overactivation overwhelming therapeutic benefits, leading to systemic toxicity that compromises patient resilience [30]. This paradox reflects the dual-edged nature of ICI therapy: while immune activation drives anti-tumor effects, excessive responses can trigger debilitating irAEs, negating survival gains. For instance, severe irAEs like pneumonitis or hepatitis could directly impair vital organ function, accelerating disease progression or treatment discontinuation. This underscores the clinical challenge of optimizing ICI efficacy while minimizing toxicity, necessitating tailored management guided by these hematological predictors, such as dose titration or adjunctive immunosuppression.

ROC analysis showed that combining multiple markers outperformed NLR alone in predicting irAEs. This multi-marker model captures the interplay of inflammation (NLR, PLR, SII), immune suppression (LYM), and nutritional status (AAPR, AFR), offering a robust risk assessment tool. Clinically, routine blood tests could leverage this approach to flag high-risk patients for early interventions - e.g., dose adjustments or supportive care, to enhancing irAE prevention and management.

Our study's retrospective nature introduces potential selection bias, and its single-center design may limit generalizability due to regional variability. Without multicenter validation, the findings' broader applicability remains uncertain. Additionally, while we established associations between hematological markers and irAEs, the underlying mechanisms - e.g., specific cytokine pathways, T-cell subsets, or NETosis - require deeper exploration. Future prospective, multicenter studies should validate these results and dissect these pathways to refine personalized ICI strategies.

Conclusion

In summary, ANC, NLR, PLR, SII, AAPR, and AFR serve as valuable predictors of irAEs in NSCLC patients on ICI therapy. Their combined assessment enhances early risk stratification, informing personalized treatment plans to reduce irAE incidence and improve safety.

Disclosure of conflict of interest

None.

Address correspondence to: Yingying Wang, Tumor Ward 2, Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, No. 2, Deputy Weiyang West Road, Xianyang 712000, Shaanxi, China. E-mail: listars555@163.com

References

[1] Lazzari C, Spagnolo CC, Ciappina G, Di Pietro M, Squeri A, Passalacqua MI, Marchesi S, Gregorc V and Santarpia M. Immunotherapy in Early-Stage Non-Small Cell Lung Cancer (NSCLC): current evidence and perspectives. Curr Oncol 2023; 30: 3684-3696.

[2] Li W and Yu H. Separating or combining immune checkpoint inhibitors (ICIs) and radiotherapy in the treatment of NSCLC brain metastases. J Cancer Res Clin Oncol 2020; 146: 137-152.

[3] Shankar B, Zhang J, Naqash AR, Forde PM, Feliciano JL, Marrone KA, Ettinger DS, Hann CL, Brahmer JR, Ricciuti B, Owen D, Toi Y, Walker P, Otterson GA, Patel SH, Sugawara S and Naidoo J. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol 2020; 6: 1952-1956.

[4] Ghanbar MI and Suresh K. Pulmonary toxicity of immune checkpoint immunotherapy. J Clin Invest 2024; 134: e170503.

[5] Nuñez NG, Berner F, Friebel E, Unger S, Wyss N, Gomez JM, Purde MT, Niederer R, Porsch M, Lichtensteiger C, Kramer R, Erdmann M, Schmitt C, Heinzerling L, Abdou MT, Karbach J, Schadendorf D, Zimmer L, Ugurel S, Klümper N, Hölzel M, Power L, Kreutmair S, Capone M, Madonna G, Cevhertas L, Heider A, Amaral T, Hasan Ali O, Bomze D, Dimitriou F, Diem S, Ascierto PA, Dummer R, Jäger E, Driessen C, Levesque MP, van de Veen W, Joerger M, Früh M, Becher B and Flatz L. Immune signatures predict development of autoimmune toxicity in patients with cancer treated with immune checkpoint inhibitors. Med 2023; 4: 113-129, e117.

[6] Barron CC, Stefanova I, Cha Y, Elsolh K, Zereshkian A, Gaafour N and McWhirter E. Chronic immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors: a systematic review. J Immunother Cancer 2023; 11: e006500.

[7] Kuwano A, Yada M, Tanaka K, Koga Y, Nagasawa S, Masumoto A and Motomura K. Neutrophil-to-lymphocyte ratio predicts immune-related adverse events in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab. Cancer Diagn Progn 2024; 4: 34-41.

[8] Zhang W, Tan Y, Li Y and Liu J. Neutrophil to lymphocyte ratio as a predictor for immune-related adverse events in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Front Immunol 2023; 14: 1234142.

[9] Locci F and Parker JE. Plant NLR immunity activation and execution: a biochemical perspective. Open Biol 2024; 14: 230387.

[10] Lee PY, Oen KQX, Lim GRS, Hartono JL, Muthiah M, Huang DQ, Teo FSW, Li AY, Mak A, Chandran NS, Tan CL, Yang P, Tai ES, Ng KWP, Vijayan J, Chan YC, Tan LL, Lee MB, Chua HR, Hong WZ, Yap ES, Lim DK, Yuen YS, Chan YH, Aminkeng F, Wong ASC, Huang Y and Tay SH. Neutrophil-to-lymphocyte ratio predicts development of immune-related adverse events and outcomes from immune checkpoint blockade: a case-control study. Cancers (Basel) 2021; 13: 1308.

[11] Gao W, Liu Q, Zhou Y, Yang M and Yu Y. The predictive model construction for immune-related adverse events in non-small cell lung cancer patients receiving immunotherapy. Technol Cancer Res Treat 2023; 22: 15330338231206705.

[12] Koul R, Rathod S, Dubey A, Bashir B and Chowdhury A. Comparison of 7th and 8th editions of the UICC/AJCC TNM staging for non-small cell lung cancer in a non-metastatic North American cohort undergoing primary radiation treatment. Lung Cancer 2018; 123: 116-120.

[13] Freites-Martinez A, Santana N, Arias-Santiago S and Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr (Engl Ed) 2021; 112: 90-92.

[14] Vaddepally R, Doddamani R, Sodavarapu S, Madam NR, Katkar R, Kutadi AP, Mathew N, Garje R and Chandra AB. Review of Immune-Related Adverse Events (irAEs) in Non-Small-Cell Lung Cancer (NSCLC)-their incidence, management, multiorgan irAEs, and rechallenge. Biomedicines 2022; 10: 790.

[15] Chen M, Ma P, Zhang Y, Wang D, Yu Z, Fu Y, Zhao X, Wang M, Zhuang G and Jing Y. Divergent tumor and immune cell reprogramming underlying immunotherapy response and immune-related adverse events in lung squamous cell carcinoma. J Immunother Cancer 2023; 11: e007305.

[16] Li N, Hou X, Huang S, Tai R, Lei L, Li S, Abuliz A, Wang G and Yang S. Biomarkers related to immune checkpoint inhibitors therapy. Biomed Pharmacother 2022; 147: 112470.

[17] Mitri F, Machiraju D, Naoum C and Hassel JC. Early serum markers for immune checkpoint inhibitor induced hypophysitis in melanoma patients. Cancers (Basel) 2024; 16: 1340.

[18] Matsukane R, Watanabe H, Minami H, Hata K, Suetsugu K, Tsuji T, Masuda S, Okamoto I, Nakagawa T, Ito T, Eto M, Mori M, Nakanishi Y and Egashira N. Continuous monitoring of neu-

trophils to lymphocytes ratio for estimating the onset, severity, and subsequent prognosis of immune related adverse events. Sci Rep 2021; 11: 1324.

[19] Mesti T, Grašič Kuhar C and Ocvirk J. Biomarkers for outcome in metastatic melanoma in first line treatment with immune checkpoint inhibitors. Biomedicines 2023; 11: 749.

[20] Liu W, Liu Y, Ma F, Sun B, Wang Y, Luo J, Liu M and Luo Z. Peripheral blood markers associated with immune-related adverse effects in patients who had advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Manag Res 2021; 13: 765-771.

[21] Sahoo BR. Structure of fish Toll-like receptors (TLR) and NOD-like receptors (NLR). Int J Biol Macromol 2020; 161: 1602-1617.

[22] Lu HR, Zhu PF, Deng YY, Chen ZL and Yang L. Predictive value of NLR and PLR for immune-related adverse events: a systematic review and meta-analysis. Clin Transl Oncol 2024; 26: 1106-1116.

[23] Manne A, Mulekar MS, Escobar DE, Alsayed A, Sharma G, Prodduturvar P, Khushman M, Howard JH, Gilbert R and Alkharabsheh O. Clinical and hematological predictors of high-grade immune-related adverse events associated with immune checkpoint inhibitors. J Clin Med Res 2021; 13: 268-275.

[24] Ekinci F, Balcik OY, Demir B, Gursoy P, Ozveren A and Erdogan AP. Systemic immune inflammation index as a key marker of survival and immune-related adverse events in immune checkpoint inhibitor therapy. J Coll Physicians Surg Pak 2022; 32: 996-1003.

[25] Maloney S, Pavlakis N, Itchins M, Arena J, Mittal A, Hudson A, Colvin E, Sahni S, Diakos C, Chan D, Gill AJ, Samra J and Clarke SJ. The prognostic and predictive role of the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Lymphocyte-to-Monocyte Ratio (LMR) as biomarkers in resected pancreatic cancer. J Clin Med 2023; 12: 1989.

[26] Dionese M, Bimbatti D, Pierantoni F, Lai E, Erbetta E, Cavasin N, Jubran S, Basso U and Maruzzo M. Systemic inflammation indexes and risk of immune-related adverse events in patients with metastatic urothelial carcinoma treated with immunotherapy. Anticancer Res 2024; 44: 4379-4386.

[27] Zhang Y, Jin J, Tang M, Li P, Zhou LN, Du YP and Chen MB. Prognostic nutritional index predicts outcome of PD-L1 negative and MSS advanced cancer treated with PD-1 inhibitors. Biomed Res Int 2022; 2022: 6743126.

[28] Yang M, Lin SQ, Liu XY, Tang M, Hu CL, Wang ZW, Zhang Q, Zhang X, Song MM, Ruan GT, Zhang XW, Liu T, Xie HL, Zhang HY, Liu CA, Zhang KP, Li QQ, Li XR, Ge YZ, Liu YY, Chen Y, Zheng X and Shi HP. Association between C-reactive protein-albumin-lymphocyte (CALLY) index and overall survival in patients with colorectal cancer: from the investigation on nutrition status and clinical outcome of common cancers study. Front Immunol 2023; 14: 1131496.

[29] Wang J, Ma Y, Lin H, Wang J and Cao B. Predictive biomarkers for immune-related adverse events in cancer patients treated with immune-checkpoint inhibitors. BMC Immunol 2024; 25: 8.

[30] Ksienski D, Wai ES, Alex D, Croteau NS, Freeman AT, Chan A, Patterson T, Clarkson M, Fiorino L, Poonja Z, Fenton D, Irons S and Lesperance M. Prognostic significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for advanced non-small cell lung cancer patients with high PD-L1 tumor expression receiving pembrolizumab. Transl Lung Cancer Res 2021; 10: 355-367.