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The association of immune-inflammation indices at multiple time points with treatment response and survival in advanced non-small cell lung cancer patients receiving immune checkpoint inhibitors

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Abstract

Background Immune and inflammation participate in the progression of non-small cell lung cancer (NSCLC) and some immune-inflammation indexes may serve as prognostic biomarkers in NSCLC patients. This study aimed to investigate the association between immune-inflammation indices at multiple time points and prognosis in advanced NSCLC patients treated with immune checkpoint inhibitors (ICIs).

Methods This retrospective study included 102 advanced NSCLC patients treated with ICIs and collected their blood indices within 7 days before treatment (T1), before the 3rd treatment cycle (T2), and before the 5th treatment cycle (T3) to calculate neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), pan-immune-inflammatory value (PIV), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), and lung immune prognostic index (LIPI).

Results dNLR ($P=0.006$), SII ($P=0.005$), PIV ($P=0.010$), and LIPI ($P=0.001$) reduced, while PNI increased ($P=0.009$) from T1 to T3; NLR was not different among T1, T2, and T3 ($P=0.282$). A lower NLR ($P=0.011$) and higher PNI ($P=0.026$) at T3, and lower LIPI at T2 ($P=0.023$) were related to better disease control rate, but these immune-inflammation indices were not linked with objective response rate at any timepoint. Multivariate Cox regression analysis showed that high NLR at T1 was independently related to worse PFS (hazard ratio: 4.187, $P=0.008$), while high PNI at T3 was independently associated with better PFS (hazard ratio: 0.454, $P=0.021$).

Conclusion NLR before and after treatment, as well as PNI and LIPI after treatment may serve as potential biomarkers for treatment response or survival in advanced NSCLC patients receiving ICIs.

Keywords Advanced non-small cell lung cancer, Immune checkpoint inhibitors, Immune-inflammation indices, Treatment response, Progression-free survival

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Introduction

Lung cancer is the most commonly diagnosed cancer worldwide in 2022, among which almost 85% of cases are non-small cell lung cancer (NSCLC) [1, 2]. Unfortunately, most NSCLC patients are first diagnosed with advanced disease and ineligible for surgery resection [3]. Recently, advances in immune checkpoint inhibitors (ICIs) have changed the treatment paradigm of advanced NSCLC [4, 5]. However, the prognosis of advanced NSCLC patients treated with ICIs is heterogeneous and poor due to the early metastasis, with a median progression-free survival (PFS) ranging from 5.4 months to 15.3 months [6–10]. This variability underscores the need for finding some prognostic biomarkers for advanced NSCLC patients who receive ICIs to improve their management. Until now, programmed cell death ligand 1 (PD-L1) expression and tumor mutation burden are considered as potential biomarkers for treatment response to ICIs, but their predictive ability is controversial [11, 12]. Therefore, it is crucial to investigate alternative biomarkers for predicting treatment outcomes of advanced NSCLC patients receiving ICIs.

Immune and inflammation have a substantial influence on tumor growth, immune evasion, and metastasis in cancer patients [13, 14]. Recently, some immune-inflammation indices, such as neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), pan-immune-inflammatory value (PIV), systemic immune-inflammation index (SII), lung immune prognostic index (LIPI), and prognostic nutritional index (PNI), are reported to show an association with the prognosis of advanced NSCLC patients treated with ICIs [15–19]. In detail, the NLR, dNLR, and SII represent the neutrophil count, lymphocyte count, white blood cell count, and platelet count; meanwhile, the PIV integrates these peripheral blood parameters, which is regarded as the objective indicator of the complex immune and inflammatory status. Several studies indicated that NLR, dNLR, PIV, SII scores, and LIPI scores were dynamic before and after treatment, with a relationship to worse outcomes in advanced NSCLC patients who received ICIs [15–19]. In addition, some studies also revealed that the change in PNI scores after treatment was associated with better prognosis in advanced NSCLC patients receiving ICIs [15, 18]. However, the previous studies did not assess these immune-inflammation indices at multiple time points and the prognostic value of immune-inflammation indices at different time points still remains unclear in advanced NSCLC patients treated with ICIs.

This study assessed NLR, dNLR, PIV, SII, PNI, and PILI at different time points, aiming to investigate the association of these immune-inflammation indices at multipoint with treatment response and survival in advanced NSCLC patients treated with ICIs.

Materials and methods

Patients

In this retrospective study, 102 advanced NSCLC patients who were treated with ICIs in Hebei General Hospital between January 2017 and January 2023 were included. The inclusion criteria were: (1) diagnosed as NSCLC by pathology method; (2) age more than 18 years old; (3) with III or IV stages of tumor-node-metastasis (TNM); (4) received ICIs as treatment; (5) had available peripheral blood indices data that could be used to calculate immune-inflammation indices. The following criteria were applied for exclusion: (1) with other malignant diseases; (2) completed with infection or systemic immune diseases; (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score > 2. The study was approved by the Ethics Committee. Informed consent was gained from each patient or their families.

Data collection

Clinical characteristics of patients were collected. The peripheral blood indices at T1 (within 7 days before treatment), T2 (within 7 days before the 3rd treatment cycle), and T3 (within 7 days before the 5th treatment cycle) were also collected, which included white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (Lym), monocyte count (MONO), platelet count (PLT), lactate dehydrogenase (LDH), and albumin (ALB). Besides, treatment response information and follow-up information were screened. Additionally, immune-related adverse events (irAEs) were retrieved.

Immune-inflammation indices

Based on the collected peripheral blood indices, the NLR, dNLR, SII, PIV, PNI, and LIPI were calculated. The corresponding formulas referred to the previous studies [20–22]. In this study, NLR, dNLR, SII, PIV, PNI, and LIPI were defined as immune-inflammation indices [21]. The formulas of these immune-inflammation indices were as follows: (1) NLR = NEUT (10^9/L) / Lym (10^9/L); (2) dNLR = NEUT (10^9/L) / (WBC (10^9/L) - NEUT (10^9/L)); (3) SII = PLT (10^9/L) * NEUT (10^9/L) / Lym (10^9/L); (4) PIV = NEUT (10^9/L) * PLT (10^9/L) * MONO (10^9/L) / Lym (10^9/L); (5) PNI = ALB (g/L) + 5 * Lym (10^9/L). Besides, LIPI was a categorized variable characterized into 3 groups: (1) 0, dNLR ≤ 3 and LDH ≤ ULN (245 U/L); (2) 1, either dNLR>3 or LDH > ULN; (3) 2, dNLR>3 and LDH > ULN. To further explore their associations with PFS, they were cut into high and low levels by their median values, except for LIPI. The detailed cut-off values for categorizing the immune-inflammation indices were shown in Supplementary Table 1.

Follow-up

Follow-up was performed by telephone or in the clinic, and the endpoint of follow-up was disease progression, death, or the date of censoring. Accumulating PFS rate was calculated, which was based on the disease progression status and duration from the initiation of treatment to the endpoint of follow-up.

Statistics

SPSS ver.26.0 was used to analyze data. The peripheral blood indices and immune-inflammation indices belong to the non-normal distribution determined by the Kolmogorov-Smirnov method. The Friedman test was used to analyze the changes in peripheral blood indices and immune-inflammation indices over time. Wilcoxon rank-sum test was utilized to compare immune-inflammation indices between groups. Kaplan-Meier curve was performed to show the accumulating PFS rate. Univariate and multivariate Cox regression analyses were applied to find the relationships between immune-inflammation indices and PFS, with the proportional hazards assumption assessed using Schoenfeld residuals. A $P<0.05$ indicated significance.

Table 1 Clinical characteristics of advanced NSCLC patients

Characteristics	Patients ($N=102$)
Age (years), mean ± SD	61.6 ± 10.1
Age stratification, n (%)	
< 55 years	24 (23.5)
55 ~ 64 years	34 (33.3)
65 ~ 74 years	38 (37.3)
≥ 75 years	6 (5.9)
Sex, n (%)	
Female	20 (19.6)
Male	82 (80.4)
Smoking, n (%)	
Never	41 (40.2)
Former	19 (18.6)
Current	42 (41.2)
ECOG PS score, n (%)	
0	6 (5.9)
1	63 (61.8)
2	33 (32.4)
Pathological type, n (%)	
Adenocarcinoma	61 (59.8)
Squamous cell carcinoma	37 (36.3)
Large cell carcinoma	4 (3.9)
TNM stage, n (%)	
III	33 (32.4)
IV	69 (67.6)
PD-L1 expression, n (%)	
Low	24 (23.5)
High	16 (15.7)
Unknown	62 (60.8)
Driver gene mutation, n (%)	
No	79 (77.5)
Yes	23 (22.5)
EGFR mutation, n (%)	12 (11.8)
KRAS mutation, n (%)	6 (5.9)
TP53 mutation, n (%)	4 (3.9)
Met mutation, n (%)	2 (2.0)
ERBB2 mutation, n (%)	1 (1.0)
ROS1 mutation, n (%)	1 (1.0)
STK11 mutation, n (%)	1 (1.0)

NSCLC, non-small cell lung cancer; SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis; PD-L1, programmed cell death ligand 1

Results

Baseline characteristics

The mean age of patients was 61.6 ± 10.1 years. There were 20 (19.6%) female and 82 (80.4%) male patients. Regarding the TNM stage, 33 (32.4%) patients were at stage III and 69 (67.6%) patients were at stage IV. Twenty-four (23.5%) and 16 (15.7%) patients had low and high PD-L1 expression, while 62 (60.8%) patients were unknown for this issue. Twenty-three (22.5%) patients harbored driver gene mutation and the remaining 79 (77.5%) patients did not. The detailed baseline characteristics are listed in Table 1.

Peripheral blood indices and immune-inflammation indices at T1, T2, and T3

WBC ($P=0.003$), NEUT ($P=0.016$), MONO ($P=0.041$), PLT ($P=0.002$), and ALB ($P<0.001$) were different among T1, T2, and T3; but Lym ($P=0.617$) and LDH ($P=0.660$) did not vary among these assessment points (Supplementary Fig. 1A-F).

No difference was observed among NLR at T1, T2, and T3 ($P=0.282$, Fig. 1A). In contrast, dNLR ($P=0.006$, Fig. 1B), SII ($P=0.005$, Fig. 1C), and PIV ($P=0.010$, Fig. 1D) were decreased from T1 to T3. Whereas PNI was increased from T1 to T3 ($P=0.009$, Fig. 1E). Percentages of patients with different LIPI varied at T1, T2, and T3. Specifically, LIPI tended to reduce from T1 to T3 ($P=0.001$, Fig. 1F).

The association of immune-inflammation indices at T1, T2, and T3 with the response

The treatment information was shown in Supplementary Table 2. It was observed that the ICI drug type and the combination chemotherapy regimens did not correlate with the objective response rate (ORR) or disease control rate (DCR) (Supplementary Table 3). The complete response, partial response, stable disease, and progressive disease rates were 2.0%, 23.5%, 53.9%, and 20.6%, accordingly. The ORR and DCR were 25.5% and 79.4%, respectively (Table 2).

In patients who had an objective response, SII was decreased ($P=0.008$) while PNI was elevated ($P=0.005$)

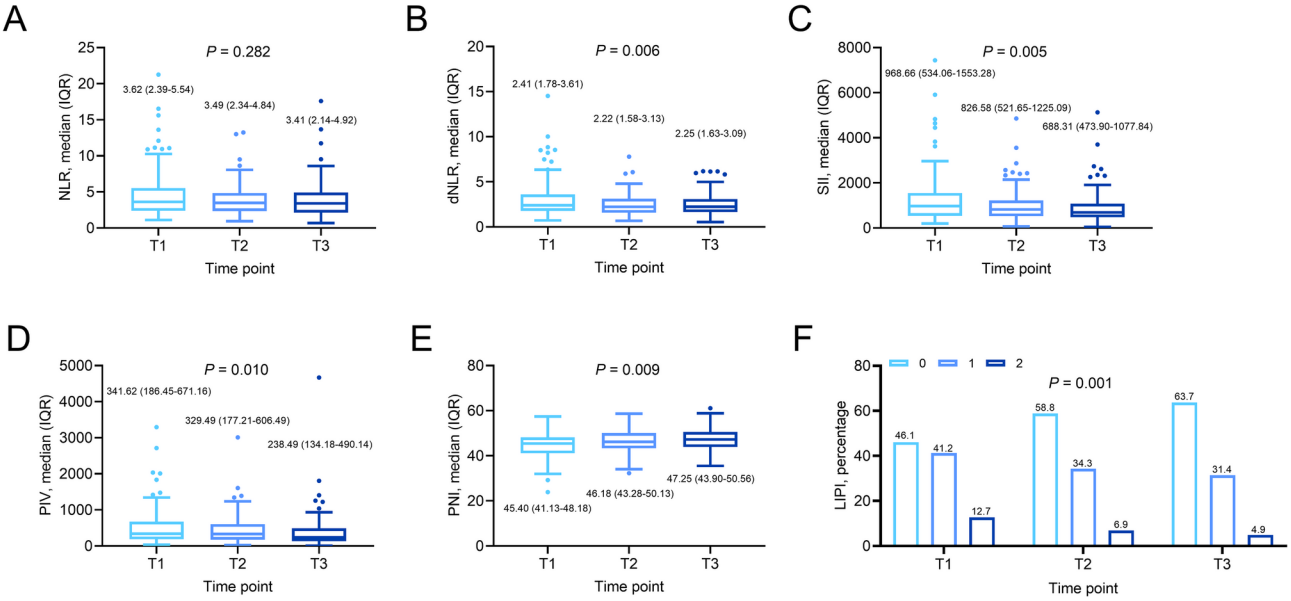

Fig. 1 Longitudinal changes in immune-inflammation indices in advanced NSCLS patients treated with ICIs. Comparison of NLR (**A**), dNLR (**B**), SII (**C**), PIV (**D**), PNI (**E**), and LIPI (**F**) at T1, T2, and T3

Table 2 Treatment response

Items	Patients (*N* = 102)
Best response, n (%)	
CR	2 (2.0)
PR	24 (23.5)
SD	55 (53.9)
PD	21 (20.6)
ORR, n (%)	26 (25.5)
DCR, n (%)	81 (79.4)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate

from T1 to T3. In patients who did not achieve objective response, PIV ($P = 0.010$) and percentages of patients with LIPI of 0, 1, and 2 ($P = 0.007$) were different among T1, T2, and T3. However, no difference was observed in immune-inflammation indices at T1, T2, or T3 between patients reaching or not reaching objective response (all $P > 0.05$).

In patients who achieved disease control, dNLR ($P = 0.006$), SII ($P = 0.001$), PIV ($P = 0.011$), and LIPI ($P = 0.003$) were reduced, while PNI ($P = 0.025$) was increased from T1 to T3. Whereas in patients who did not have disease control, immune-inflammation indices were not changed among T1, T2, and T3 (all $P > 0.05$). Additionally, NLR at T3 ($P = 0.011$) and LIPI at T2 ($P = 0.023$) was decreased, while PNI at T3 was elevated ($P = 0.026$) in patients with disease control compared to those without (Table 3).

The association of immune-inflammation indices at T1, T2, and T3 with PFS

The median (95% confidence interval (CI)) PFS was 13.8 (10.3–17.3) months. The 6-, 12-, 18-, and 24-month accumulating PFS rates were 76.8%, 56.0%, 38.8%, and 33.9%, respectively (Fig. 2).

Through univariate Cox regression analysis, NLR at T1 (high versus (vs.) low) ($P = 0.010$), LIPI at T1 (2 vs. 0) ($P = 0.046$), NLR at T3 (high vs. low) ($P = 0.019$), dNLR at T3 (high vs. low) ($P = 0.020$), SII at T3 (high vs. low) ($P = 0.044$), PIV at T3 (high vs. low) ($P = 0.045$), and LIPI at T3 (1 vs. 0) ($P = 0.038$) were associated with worse PFS. In addition, PNI at T2 (high vs. low) ($P = 0.027$) and at T3 (high vs. low) ($P = 0.004$) were linked with better PFS.

The Schoenfeld residuals were used to validate the proportional hazards assumption, which was shown in Supplementary Fig. 2. It was shown that the P-values of the Schoenfeld residual test for all variables were greater than 0.05, with no significant deviations observed, suggesting that the model met the proportional hazards hypothesis. Furthermore, the multicollinearity test indicated that these inflammatory indices did not show multicollinearity among them (Supplementary Table 4).

Multivariate Cox regression analysis showed that NLR at T1 (high vs. low) was independently related to worse PFS (hazard ratio: 4.187, $P = 0.008$), while PNI at T3 (high vs. low) was independently associated with better PFS (hazard ratio: 0.454, $P = 0.021$) (Table 4).

After adjusting the treatment lines, ICI drugs, and combination chemotherapy regimens in Model 1, and adjusting treatment lines, ICI drugs, combination chemotherapy regimens, age, sex, smoking, ECOG PS score,

Table 3 Correlation of immune-inflammation indices with ORR and DCR

Indices	ORR		*P* value	DCR		*P* value
	Not achieved	Achieved		Not achieved	Achieved	
NLR, median (IQR)						
T1	3.63 (2.38–5.57)	3.57 (2.83–5.31)	0.896	4.96 (2.55–8.49)	3.51 (2.38–5.34)	0.140
T2	3.43 (2.32–4.96)	3.52 (2.43–4.24)	0.800	3.91 (2.28–6.20)	3.42 (2.40–4.54)	0.343
T3	3.65 (2.40–5.08)	2.69 (1.80–4.29)	0.127	4.33 (2.96–6.02)	3.28 (2.05–4.40)	0.011
P value#	0.525	0.135		0.467	0.144	
dNLR, median (IQR)						
T1	2.43 (1.72–3.78)	2.39 (1.82–3.26)	0.824	3.31 (1.73–4.12)	2.39 (1.79–3.40)	0.192
T2	2.21 (1.53–3.40)	2.25 (1.65–2.60)	0.830	2.33 (1.32–3.76)	2.21 (1.64–2.93)	0.823
T3	2.42 (1.67–3.20)	1.79 (1.40–2.69)	0.153	2.63 (1.83–3.65)	2.15 (1.60–2.91)	0.064
P value#	0.076	0.054		0.264	0.006	
SII, median (IQR)						
T1	830.07 (490.86-1618.04)	1033.97 (624.51-1385.75)	0.623	1076.96 (578.09-2141.24)	879.40 (508.53-1520.41)	0.288
T2	937.19 (484.99-1328.45)	758.92 (538.46-1120.10)	0.565	881.19 (411.11-1663.56)	811.42 (535.58-1173.18)	0.731
T3	768.73 (524.56-1083.52)	512.28 (353.97-982.78)	0.075	919.54 (581.09-1459.81)	640.38 (439.77-996.43)	0.054
P value#	0.137	0.008		0.717	0.001	
PIV, median (IQR)						
T1	296.06 (169.00-606.68)	390.53 (224.02-913.27)	0.153	341.72 (196.09-675.63)	341.52 (170.45-677.36)	0.658
T2	357.62 (176.10-654.66)	290.00 (185.84-484.36)	0.425	324.53 (179.05-791.59)	334.45 (173.24-574.94)	0.490
T3	254.04 (155.99-491.46)	186.85 (100.00-451.14)	0.214	360.13 (224.03-594.55)	219.73 (130.36-460.32)	0.083
P value#	0.010	0.056		0.717	0.011	
PNI, median (IQR)						
T1	45.38 (41.36–48.59)	45.80 (40.85–47.74)	0.667	42.90 (39.38–49.10)	45.95 (42.35–48.03)	0.108
T2	46.18 (43.22–50.24)	46.55 (43.29–48.99)	0.942	44.90 (40.23–50.73)	46.25 (43.70-49.83)	0.339
T3	47.10 (43.90-49.53)	48.55 (43.90-52.08)	0.218	44.25 (39.85–48.50)	47.65 (44.25–50.80)	0.026
P value#	0.238	0.005		0.264	0.025	
LIPI, n (%)						
T1			0.755			0.132
0	35 (46.1)	12 (46.2)		8 (38.1)	39 (48.1)	
1	30 (39.5)	12 (46.2)		7 (33.3)	35 (43.2)	
2	11 (14.5)	2 (7.7)		6 (28.6)	7 (8.6)	
T2			0.089			0.023
0	41 (53.9)	19 (73.1)		8 (38.1)	52 (64.2)	
1	29 (38.2)	6 (23.1)		10 (47.6)	25 (30.9)	
2	6 (7.9)	1 (3.8)		3 (14.3)	4 (4.9)	
T3			0.262			0.190
0	46 (60.5)	19 (73.1)		11 (52.4)	54 (66.7)	
1	26 (34.2)	6 (23.1)		8 (38.1)	24 (29.6)	
2	4 (5.3)	1 (3.8)		2 (9.5)	3 (3.7)	
P value#	0.007	0.063		0.190	0.003	

ORR, objective response rate; DCR, disease control rate; NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range; T1, within 7 days before treatment; T2, within 7 days before the 3rd treatment cycle; T3, within 7 days before the 5th treatment cycle; dNLR, derived neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune-inflammatory value; PNI, prognostic nutritional index; LIPI, lung immune prognostic index

The superscript '#' indicated that the *P* value was determined by comparison within a group

pathological type, TNM stage, and driver gene mutation in Model 2, the multivariate Cox's regression analysis was carried out. It was shown that the key findings of the multivariate Cox's regression analysis on the PFS remained unchanged (Supplementary Table 5).

Records of IrAEs

The irAEs are listed in Table 5. The most common irAEs were liver injury and thyroid dysfunction, with incidences of both 32.4%. Meanwhile, other reported irAEs included interstitial inflammation (23.5%), rash (14.7%), and cardiotoxicity (13.7%).

Discussion

Dynamic immune-inflammation indices during immunotherapy in cancer patients have been reported by several studies [23, 24]. Similarly, this study found that dNLR, SII, PIV, and LIPI were decreased, while PNI was increased

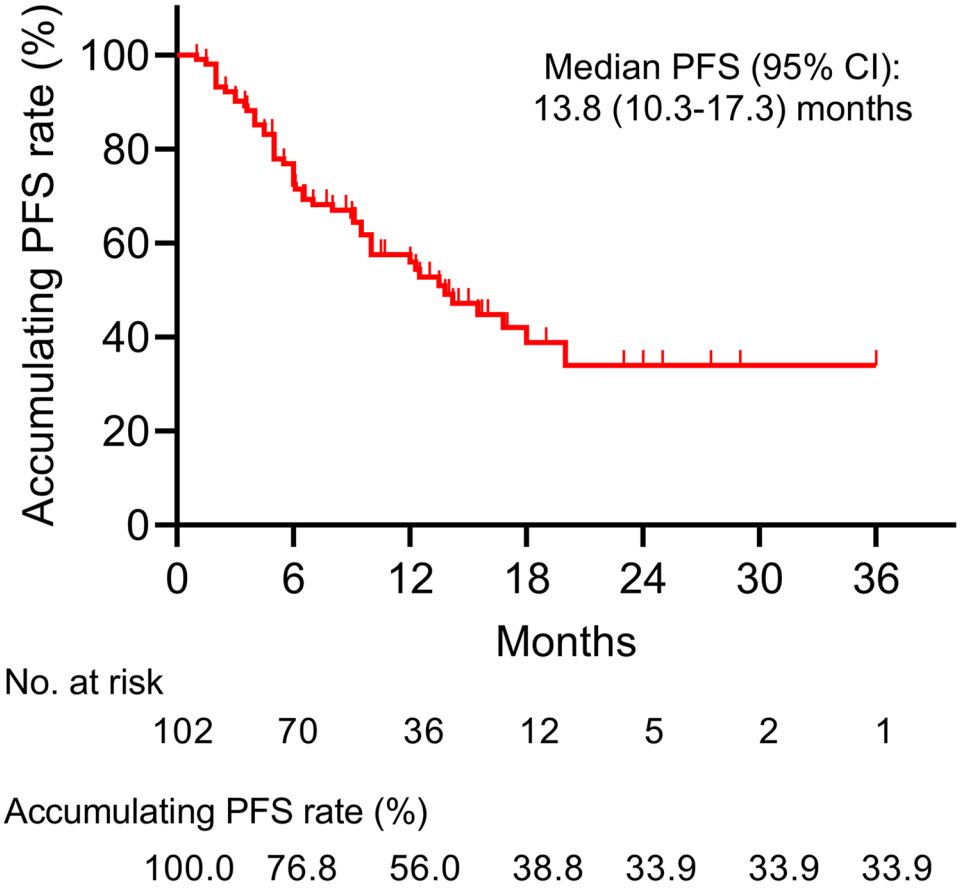

Fig. 2 Kaplan-Meier curve of PFS in advanced NSCLC patients treated with ICIs

during ICI treatment in advanced NSCLC patients, suggesting that the immune function was improved and inflammatory status was alleviated in these patients. The possible reasons could be: (1) ICIs restore functions of adaptive immune systems [25]. (2) ICIs reduce tumor burden and the latter is related to inflammation [14]. Thus, immune-inflammation indices were changed from T1 to T3 in advanced NSCLC patients treated with ICIs.

In this study, the ORR was 25.5% and DCR was 79.4% in advanced NSCLC patients treated with ICIs, which were consistent with previous studies (ORR: 17.1-29.5%, DCR: 72.1-82.3%) [26–28]. According to several studies, advanced NSCLC patients who received ICIs and had a better treatment response showed decreased NLR after treatment [29–31]. Similarly, this study found that a lower NLR level at T3 was related to elevated DCR in advanced NSCLC patients treated with ICIs. Additionally, this study showed that a higher PNI level at T3 and a lower LIPI level at T2 were also associated with elevated DCR in advanced NSCLC patients treated with ICIs. The possible explanation could be: a lower level of NLR and LIPI as well as a higher PNI level indicated a lower inflammation level and improved immune function, which reshaped T cell repertoire and promoted anti-tumor response to therapy [32, 33]. These findings suggested that a lower NLR and LIPI score, and higher PNI level after treatment might serve as predictive biomarkers of response to ICIs in advanced NSCLC patients.

The median (95% CI) PFS in this study was 13.8 (10.3–17.3) months in advanced NSCLC patients treated with ICIs, which was in the range of that in previous studies (median PFS: 4.6–24.7 months) [26–28]. The association between dynamic changes in immune-inflammation indices and PFS in advanced NSCLC patients receiving ICIs has been reported in several previous studies [18, 29, 31, 34]. However, the previous study only focused on the linkage of variations of immune-inflammation indices, such as a decrease of NLR at 6 weeks or 12 weeks after treatment and an increase of PNI at 6 weeks after treatment, with PFS in these patients [18, 29, 34]. In contrast, this study assessed immune-inflammation indices at different time points, which simplified the analysis process and was more economic. In the current study, the multivariate Cox regression analysis revealed that high NLR at T1 and low PNI at T3 were independently associated with worse PFS in advanced NSCLC patients treated with ICIs, suggesting that these immune-inflammation indices might have a potential to serve as prognostic biomarkers

Table 4 Association between immune-inflammation indices and PFS

Factors	*P* value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Upper			Lower	Upper
Univariate Cox regression analysis					**Multivariate Cox regression analysis**			
T1								
NLR (high vs. low)	0.010	2.138	1.198	3.816	0.008	4.187	1.465	11.961
dNLR (high vs. low)	0.081	1.657	0.940	2.922	0.688	1.240	0.434	3.547
SII (high vs. low)	0.573	1.176	0.670	2.063	0.230	0.442	0.116	1.678
PIV (high vs. low)	0.940	1.022	0.583	1.790	0.698	0.818	0.297	2.254
PNI (high vs. low)	0.305	0.744	0.422	1.310	0.343	0.746	0.408	1.366
LIPI								
0 (reference)	(-)	1.000	(-)	(-)	(-)	1.000	(-)	(-)
1 vs. 0	0.954	0.982	0.524	1.840	0.183	0.594	0.276	1.279
2 vs. 0	0.046	2.216	1.016	4.837	0.693	1.219	0.457	3.249
T2								
NLR (high vs. low)	0.234	1.409	0.801	2.479	0.767	1.161	0.431	3.124
dNLR (high vs. low)	0.542	1.191	0.679	2.090	0.517	0.713	0.257	1.981
SII (high vs. low)	0.552	1.186	0.676	2.081	0.615	1.303	0.464	3.660
PIV (high vs. low)	0.918	1.030	0.586	1.810	0.328	0.647	0.271	1.548
PNI (high vs. low)	0.027	0.526	0.297	0.931	0.081	0.578	0.312	1.071
LIPI								
0 (reference)	(-)	1.000	(-)	(-)	(-)	1.000	(-)	(-)
1 vs. 0	0.056	1.774	0.985	3.195	0.115	1.784	0.869	3.661
2 vs. 0	0.232	1.913	0.661	5.542	0.259	2.022	0.596	6.865
T3								
NLR (high vs. low)	0.019	2.005	1.123	3.581	0.594	1.405	0.402	4.907
dNLR (high vs. low)	0.020	1.983	1.112	3.538	0.782	1.183	0.359	3.900
SII (high vs. low)	0.044	1.799	1.016	3.187	0.291	0.537	0.169	1.704
PIV (high vs. low)	0.045	1.796	1.013	3.186	0.370	1.412	0.664	3.002
PNI (high vs. low)	0.004	0.427	0.238	0.765	0.021	0.454	0.232	0.890
LIPI								
0 (reference)	(-)	1.000	(-)	(-)	(-)	1.000	(-)	(-)
1 vs. 0	0.038	1.871	1.037	3.376	0.174	1.581	0.816	3.062
2 vs. 0	0.189	2.240	0.672	7.469	0.311	1.950	0.536	7.098

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; T1, within 7 days before treatment; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; PIV, pan-immune-inflammatory value; PNI, prognostic nutritional index; LIPI, lung immune prognostic index; T2, within 7 days before the 3rd treatment cycle; T3, within 7 days before the 5th treatment cycle

NLR, dNLR, SII, PIV, and PNI were cut into high and low levels by their median values

Table 5 irAEs

irAEs, *n* (%)	Patients (*N* = 102)
Liver injury	33 (32.4)
Thyroid dysfunction	33 (32.4)
Interstitial inflammation	24 (23.5)
Rash	15 (14.7)
Cardiotoxicity	14 (13.7)

irAEs, immune-related adverse events

for these patients. Moreover, monitoring immune-inflammation indices at multiple time points could assist clinicians in the risk stratification of advanced NSCLC patients treated with ICIs.

Previously, studies have reported that systemic inflammation, immune dysregulation, tumor microenvironment (TME) variation, such as T cell exhaustion, might play a critical role during the development of lung cancer, which could be the roadmap for future research [35]. Some biomarkers, such as the nucleolar and spindle-associated protein 1 (PLIN3), plays an important role in tumor immune microenvironment, which have shown its ability to predict the prognostic outcomes in various cancers [36]. In our study, we found that these inflammtory indices might reflect the prognosis of lung cancer patients, and the potential explanation might be that: The prognostic value of these inflammtory indices for PD-1 inhibitor efficacy in lung cancer patients may stem from their ability to reflect systemic inflammation, immune dysregulation, and TME; for instance, elevated NLR and dNLR indicate a pro-inflammatory state dominated by neutrophils, which suppress cytotoxic T-cell activity through mechanisms such as arginase secretion and ROS production. Neutrophils also promote

immunosuppressive cell populations like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), further impairing antitumor immunity [37]. Conversely, lymphocytopenia (low lymphocyte counts) correlates with reduced adaptive immune function, limiting PD-1 inhibitor efficacy [38].

In addition to activating effector T cells, ICIs can induce substantial autoimmune responses, which increase the risks of irAE, with an incidence of 15-90% [39]. In this study, irAE included liver injury (32.4%), thyroid dysfunction (32.4%), interstitial inflammation (23.5%), rash (14.7%), and cardiotoxicity (13.7%) in advanced NSCLC patients treated with ICIs, which was consistent with previous studies [39, 40]. These results indicated that the tolerance of ICIs was acceptable in advanced NSCLC patients.

Some limitations were unavoidable in the current study. First, the sample size was relatively small in this study, which weakened statistical power. Therefore, studies with a larger sample size are warranted for validation. Second, this study collected data on T1, T2, and T3 of advanced NSCLC patients treated with ICIs. Hence, the predictive ability of immune-inflammation indices on other time points for treatment response and survival outcomes in advanced NSCLC patients treated with ICIs requires more exploration. Third, this study only collected advanced NSCLC patients treated with ICIs, thereby, our results might not be applicable to patients receiving other treatments, such as chemotherapy and target therapy. Fourth, the use of inflammatory markers in T3 (cycle 5) to predict the ORR, DCR, and PFS of all patients lacked clinical value due to that some patients with PD were already included in the recent efficacy assessment. Fifth, the external validation or cross-validation should be carried out in further study.

Conclusions

In conclusion, immune-inflammation indices are changed during ICI treatment in advanced NSCLC patients. Notably, post-treatment NLR, PNI, and LIPI reflect increased DCR, meanwhile, pre-treatment NLR and post-treatment PNI are independent factors for PFS in these patients. These findings support that longitudinal immune-inflammation indices may serve as prognostic biomarkers to improve the management of advanced NSCLC patients treated with ICIs.

Supplementary Information

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Supplementary Material 1 Fig. 1: Longitudinal changes in peripheral blood indices in advanced NSCLS patients treated with ICIs. Comparison of WBC (**A**), NEUT (**B**), Lym (**C**), MONO (**D**), PLT (**E**), LDH (**F**), and ALB (**G**) at T1, T2, and T3.

Supplementary Material 2 Fig. 2: The Schoenfeld residuals test for all variables included in the multivariate Cox's regression analysis.

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

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Author contributions
Conceptualization and study design: Yaqing Li, Zhigang Cai. Acquisition of data: Yaqing Li, Jianping Xu. Data analysis: Yaqing Li, Jianping Xu, Lijuan Zhang, Zhigang Cai. Data interpretation: Jianping Xu, Lijuan Zhang. Writing-original draft: All authors. Writing-review & editing: All authors.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee. Informed consent was gained from each patient or their families.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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