Peripheral Blood Biomarkers Provide Prediction of Survival and Immune-Related Pneumonitis in Stage III/IV Non-Small Cell Lung Cancer Treated with Immune Checkpoint Inhibitors

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Abstract

Background: Immune checkpoint inhibitors (ICIs) have been considered as a standard therapy for non-small cell lung cancer (NSCLC). This study aimed to explore associations between peripheral blood biomarkers with survival and immune-related pneumonitis (IRP) in patients with stage III/IV NSCLC treated with ICIs, and establish a novel risk stratification to predict outcomes.

Methods: This study enrolled 95 patients with stage III/IV NSCLC receiving ICIs. Univariate and multivariate cox regression analyses were used to determine prognostic factors affecting overall survival (OS) and progression-free survival (PFS). Logistic regression analysis was applied to explore the correlation between peripheral blood markers and IRP.

Results: Multivariate Cox analysis revealed that pretreatment absolute lymphocyte count (ALC) (HR: 0.113, 95%CI: 0.113–0.863, $P=0.025$), and post-treatment systemic inflammation response index (SIRI) (HR: 4.199, 95%CI: 1.058–16.662, $P=0.041$) were independent prognostic factors for OS. Similarly, pretreatment ALC (HR: 0.333, 95%CI: 0.129–0.857, $P=0.023$) and post-treatment SIRI (HR: 3.160, 95%CI: 1.046–9.551, $P=0.041$) were also independent predictors of PFS. Based on these biomarkers, patients were classified into 3 categories: low-risk group: $ALC >1.5$ and $SIRI \leq 1.69$ ($n=28$); medium-risk group: $ALC >1.5$ or $SIRI \leq 1.69$ ($n=35$); high-risk group $ALC \leq 1.5$ and $SIRI >1.69$ ($n=32$). The 1-year OS rate were 69.2%, 63.6%, 27.1%, respectively ($P=0.001$) and 1-year PFS rate were 51.8%, 44.8%, 21.1%, respectively ($P=0.007$). Furthermore, we found patients with post-treatment $NLR >3$ were associated with a significantly higher risk for occurring IRP than that $NLR \leq 3$ (HR: 2.917, 95%CI: 1.037–8.206, $P=0.043$), and the time to IRP onset in post-treatment $NLR >3$ group was significantly shorter than that in $NLR \leq 3$ ($P=0.018$).

Conclusions: Pretreatment ALC and post-treatment SIRI appeared to be biomarkers of outcome in stage III/IV NSCLC patients treated with ICIs. Furthermore, post-treatment $NLR >3$ was more likely to develop IRP.

1. Background

Lung cancer is one of the most prevalent cancers globally and the incidence increases 26% annually. Non-small cell lung cancer (NSCLC), which is comprised of approximately 85% of all lung cancer patients. [1] And almost 75% of the patients are diagnosed at stage III/IV NSCLC with the poor prognosis.[2]

Recently, immune-checkpoint inhibitors (ICIs), anti-PD-1 (programmed cell death-1) and anti-PD-L1 (programmed cell death-Ligand 1) have demonstrated to improve long-term survival and considered as a novel standard treatment for advance non-small-cell lung cancer (NSCLC).[3–8] However, it was only approximately 20% patients who had positively response to ICIs, and a minority of patients who could not benefit from ICIs.[9] Furthermore, the use of ICIs also commonly emerged immune-related adverse effects (irAEs),[10] one particular irAE is the development of immune-related pneumonitis (IRP), which is a rare but potentially fatal.[11–14] Therefore, it is important to select eligible patients who may benefit the ICIs therapy and identify factors associated with the onset of IRP.

Inflammatory response and immune surveillance have been deemed crucial signatures regarding cancer development and treatment outcomes.[15] A variety of evidence indicated that peripheral blood inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), prognostic nutritional index (PNI), systemic inflammation index (SII), and systemic inflammation response index (SIRI) could facilitate the prediction of treatment outcomes for various solid carcinomas, including melanoma, prostate cancer, colorectal cancer, esophageal squamous cell carcinoma, and NSCLC.[16–20] These inflammatory biomarkers are easy to obtain in clinical practice and directly reflect the condition of the immune system, and may potentially impact on the response to ICIs.[20, 21]

However, in currently, there were few reported studies on the predictive value of peripheral blood biomarkers for NSCLC treated with ICIs. Therefore, we performed a retrospective analysis to investigate the usefulness of inflammatory biomarkers including ANC, ALC, AMC, LMR, NLR, PLR, PNI, SII, and SIRI as predictors of outcomes and the development of IRP in stage III/IV NSCLC treated with ICIs therapy.

2. Patients And Methods

2.1 Patients

We enrolled 95 patients with stage III/IV NSCLC who had treated with PD-1/PD-L1 inhibitors at Fujian Medical University Cancer Hospital between January 2017 and December 2020. The inclusion criteria were: (1) pathologically diagnosed with NSCLC; (2) clinical stage was III/IV; (3) KPS > 70; (4) received at least 1 cycle of ICI agents. The ICI agents used were nivolumab (12 patients), pembrolizumab (23 patients), atezolizumab (4 patients), toripalimab (2 patients), Sintilimab (38 patients), durvalumab (3 patients), tislelizumab (5 patients), camrelizumab (5 patients), nivolumab followed by pembrolizumab (1 patient), nivolumab followed by pembrolizumab and Sintilimab (1 patient), and nivolumab followed by toripalimab and durvalumab (1 patient). The exclusion criteria were: (1) patients with a histological type other than adenocarcinoma or squamous carcinoma (exclude 13 patients); (2) had a second primary malignancy; (3) hematological disease or autoimmune diseases; (4) insufficient clinical or laboratory data (exclude 14 patients). All patients were clinically staged using the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system.[22] The study was approved by the ethics committee of Fujian Medical University Cancer Hospital, Fuzhou, China (YK2021-009-01).

2.2 Data collection

The clinical information included age, gender, karnofsky performance status (KPS), smoking history, tumor histology, clinical stage, PD-L1 expression, molecular alterations, treatment data, and peripheral blood biomarkers consisted of absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte (PLR), prognostic nutritional index (PNI), systemic inflammation index (SII), and systemic inflammation response index (SIRI). Peripheral blood biomarkers were collected from one week before the initial of ICIs treatment and within 3–4 weeks after the initial of ICIs treatment. The LMR,

NLR, PLR, PNI, SII, and SIRI were calculated as follows: $LMR = ALC / AMC$, $NLR = ANL / ALC$, $PLR = \text{Platelet count} / ALC$, $PNI = 10 \times \text{Serum Albumin level} + 0.005 \times ALC$, $SII = ANC \times \text{Platelet count} / ALC$, and $SIRI = ANC \times AMC / ALC$. All peripheral blood biomarkers cut-offs were obtained using the median value.

2.3 Endpoints

The primary endpoints included overall survival (OS) and progression-free survival (PFS). OS was defined as the time between initial ICIs treatment and death for any reason or the last follow-up. PFS was measured from the first time of ICIs treatment to the disease progression or death due to any cause. The secondary endpoint was the development of IRP. The time to onset of IRP was ranged from the start of ICIs therapy to the development of IRP. The IRP was reviewed by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. All patients were followed up until death or the last follow-up. The median follow-up period was 10 months (range 2–38 months).

2.4 Statistical analysis

A Chi-squared test or Fisher exact test was used to compare categorical variables and a Mann–Whitney U test was used to compare continuous variables. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Variables with a P-value ≤ 0.15 in the univariate analysis was included in the multivariable analyses. Multivariate analysis was carried out to identify independent prognostic factors related to OS and PFS. Logistic regression analysis was applied to explore the correlation between peripheral blood markers and the onset of IRP. All analyses were considered as statistically significant with a two-sided P-value of < 0.05 , and were performed using SPSS 24.0 (IBM, Armonk, NY, USA).

3. Results

3.1 The characteristics of patients

A total of 95 NSCLC patients treated with ICIs were included in our study. The characteristics of patients were given in Table 1. Of the 95 patients, 76 (80.0%) were males, 34 (35.2%) were ≥ 65 years, 60 (57.0%) had adenocarcinoma, and 75 (78.9%) had a history of smoking. In addition, there were 37 (38.9%) patients at stage III and 58 (61.9%) at stage IV. The PD-L1 expression in 0, 1–49%, and $\geq 50\%$ were 5.3%, 15.8%, and 18.9%, respectively. 4 patients had an EGFR mutation, 9 patients had a KRAS mutation, and none had ALK/ROS1 fusion. 31 (32.6%) patients had received prior thoracic radiation therapy, 87 (91.6%) had undergone chemotherapy, and 11 (11.6%) had treated prior curable operation. ICIs were received as first-line treatment in 42 patients (44.2%), and as second-line or later-line treatment in 53 patients (55.8%).

Table 1
Characteristics of patients treated with ICIs

Variable	Patients treated with ICIs (n = 95),n (%)
Age	
< 65	61(64.2)
≥ 65	34(35.2)
Gender	
Male	76(80.0)
Female	19(20.0)
Smoking	
Yes	75(78.9)
No	20(21.1)
KPS	
80	61(64.2)
90	34(35.8)
Histology	
Adenocarcinoma	57(60.0)
Squamous cell carcinoma	38(40.0)
Clinical stage	
III	37(38.9)
IV	58(61.9)
Prior thoracic radiotherapy	
Yes	31(32.6)
No	64(67.4)
Combine chemotherapy	
Yes	87(91.6)
No	8(8.4)
Prior curable operation	
Yes	11(11.6)
No	84(88.4)

Variable	Patients treated with ICIs (n = 95),n (%)
Molecular alterations	
EGFR or ALK/ROS1(+)	13(13.7)
(-)/not done	89(86.3)
PD-L1 expression	
0	5(5.3)
1–49	15(15.8)
≥ 50	18(18.9)
Not done	57(52.6)
Line of immunotherapy	
First line	42(44.2)
Further lines	53(55.8)
Pretreatment peripheral blood biomarkers Median (IQR)	
ANC	4.9(3.5–6.3)
ALC	1.5(1.1–2.0)
AMC	0.51(0.39–0.69)
LMR	2.98(1.84–4.32)
NLR	3.15(2.21–5)
PLR	175(122.86–245)
PNI	45(40.1–51)
SII	846.61(514.8–1356)
SIRI	1.52(1.01–3.1)
Post-treatment peripheral blood biomarkers Median (IQR)	
ANC	4.9(4–6.4)
ALC	1.5(1.1–1.9)
AMC	0.51(0.41–0.69)
LMR	3.12(2.2–4)
NLR	3.29(2.31–5.55)
PLR	175(121.36–247.14)

Variable	Patients treated with ICIs (n = 95),n (%)
PNI	46(40.6–49.5)
SII	846.40(527.06–1395.68)
SIRI	1.69(1.09–3.08)

Abbreviations: ICIs, immune checkpoint inhibitors; KPS, karnofsky performance status; PD-L1, programmed cell death-Ligand 1; IQR, interquartile range; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte; PNI, prognostic nutritional index; SII, systemic inflammation index; SIRI, systemic inflammation response index.

3.2 Univariate and multivariate cox analysis for PFS and OS

Univariate and multivariate cox analysis for OS and PFS were detailed in Table 2 and Table 3, respectively. As shown in Table 2, in Univariate cox analysis, the factors significantly correlated with OS were clinical stage ($P = 0.023$), prior thoracic radiotherapy ($P = 0.014$), Molecular alterations ($P = 0.046$), pretreatment NLR ($P = 0.033$), pretreatment PLR ($P = 0.041$), pretreatment PNI ($P = 0.023$), pretreatment SII ($P = 0.013$), post-treatment LMR ($P = 0.032$), post-treatment LMR ($P = 0.010$), and post-treatment SIRI ($P = 0.018$). In Multivariate Cox analysis, only prior thoracic radiotherapy (HR: 0.180, 95%CI: 0.067–0.487, $P = 0.001$), pretreatment ALC (HR: 0.113, 95%CI: 0.113–0.863, $P = 0.025$), and post-treatment SIRI (HR: 4.199, 95%CI: 1.058–16.662, $P = 0.041$) were independent prognostic factors for OS. Similarly, the multivariate cox analysis indicated that prior thoracic radiotherapy (HR: 0.239, 95%CI: 0.100–0.570, $P = 0.001$), pretreatment ALC (HR: 0.333, 95%CI: 0.129–0.857, $P = 0.023$), pretreatment PNI (HR: 2.750, 95%CI: 1.033–7.322, $P = 0.043$), post-treatment PLR (HR: 2.213, 95%CI: 1.039–4.715, $P = 0.040$), and post-treatment SIRI (HR: 3.160, 95%CI: 1.046–9.551, $P = 0.041$) were independent predictors of PFS (Table 3).

Table 2

Univariate and multivariate cox analyses of factors associated with overall survival in NSCLC patients treated with ICIs.

Variable	Univariate analysis	Multivariate analysis
	HR (95% CI), P value	HR (95% CI), P value
Age(< 65 vs. ≥65)	1.269 (0.716–2.247), 0.414	
Gender(Female vs. Male)	0.988 (0.472–2.067), 0.974	
Smoking(No vs. Yes)	1.129 (0.541–2.354), 0.746	
KPS(80 vs. 90)	1.218 (0.691–2.149), 0.495	
Histology(Squamous vs. Adenocarcinoma)	0.876 (0.495–1.550), 0.649	
Clinical stage(III vs. IV)	2.129 (1.109–4.087), 0.023	1.551 (0.630–3.820), 0.340
Prior thoracic radiotherapy(No vs. Yes)	0.426 (0.216–0.841), 0.014	0.180 (0.067–0.487), 0.001
Combine chemotherapy(No vs. Yes)	1.500 (0.462–4.867), 0.500	
Prior curable operation(No vs. Yes)	0.412 (0.128–1.328), 0.138	0.501 (0.114–2.206), 0.361
Molecular alterations(No/not done vs. Yes)	2.115 (1.014–4.410), 0.046	2.321 (0.903–5.965), 0.080
PD-L1 expression	-	
0 vs. 1–49	0.894 (0.244–3.276), 0.866	
0 vs. ≥50	1.261 (0.343–4.634), 0.727	
Line of immunotherapy(First line vs. Further lines)	1.002 (0.570–1.761), 0.994	
Pretreatment peripheral blood biomarkers		
ANC(≤ 4.9 vs. >4.9)	1.593 (0.893–2.841), 0.115	1.547 (0.622–3.848), 0.348
ALC(≤ 1.5 vs. >1.5)	0.574 (0.320–1.027), 0.062	0.312 (0.113–0.863), 0.025

Variable	Univariate analysis	Multivariate analysis
	HR (95% CI), P value	HR (95% CI), P value
AMC(≤ 0.51 vs. >0.51)	1.218 (0.684–2.168), 0.503	
LMR(≤ 2.98 vs. >2.98)	0.629 (0.357–1.110), 0.110	1.135 (0.380–3.391), 0.821
NLR(≤ 3.15 vs. >3.15)	1.859 (1.051–3.290), 0.033	1.244 (0.361–4.292), 0.729
PLR(≤ 175 vs. >175)	1.810 (1.024–3.198), 0.041	0.681 (0.264–1.754), 0.426
PNI(≤ 45 vs. >45)	0.512 (0.287–0.910), 0.023	2.684 (0.893–8.068), 0.079
SII(≤ 846.61 vs. >846.61)	2.064 (1.162–3.665), 0.013	3.562 (0.888–14.286), 0.073
SIRI(≤ 1.52 vs. >1.52)	1.533 (0.869–2.704), 0.140	0.262 (0.096–1.360), 0.132
Post-treatment peripheral blood biomarkers		
ANC(≤ 4.9 vs. >4.9)	1.733 (0.978–3.073), 0.060	1.737 (0.675–4.467), 0.252
ALC(≤ 1.5 vs. >1.5)	0.721 (0.408–1.275), 0.261	
AMC(≤ 0.51 vs. >0.51)	1.197 (0.682–2.099), 0.531	
LMR(≤ 3.12 vs. >3.12)	0.534 (0.301–0.948), 0.032	1.109 (0.348–3.532), 0.861
NLR(≤ 2.31 vs. >2.31)	1.373 (0.773–2.437), 0.279	
PLR(≤ 175 vs. >175)	1.752 (0.991–3.095), 0.054	2.477 (0.969–6.181), 0.058
PNI(≤ 46 vs. >46)	0.581 (0.326–1.036), 0.066	0.823 (0.333–2.033), 0.673
SII(≤ 846.4 vs. >846.4)	2.149 (1.205–3.832), 0.010	0.347 (0.103–1.166), 0.087
SIRI(≤ 1.69 vs. >1.69)	1.992 (1.125–3.527), 0.018	4.199 (1.058–16.662), 0.041

Abbreviations: NSCLC, non-small lung cancer; HR, hazard ratio; CI, confidence interval; KPS, karnofsky performance status; PD-L1, programmed cell death-Ligand 1; ANC, absolute neutrophil count; ALC,

absolute lymphocyte count; AMC, absolute monocyte count; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte; PNI, prognostic nutritional index; SII, systemic inflammation index; SIRI, systemic inflammation response index.

Table 3

Univariate and multivariate cox analyses of factors associated with progress-free survival in NSCLC patients treated with ICIs.

Variable	Univariate analysis	Multivariate analysis
	HR (95% CI), P value	HR (95% CI), P value
Age(< 65 vs. ≥65)	1.266 (0.744–2.155), 0.385	
Gender(Female vs. Male)	1.450 (0.683–3.076), 0.333	
Smoking(No vs. Yes)	1.631 (0.770–3.454), 0.201	
KPS(80 vs. 90)	1.218 (0.691–2.149), 0.495	
Histology(Squamous vs. Adenocarcinoma)	0.902 (0.553–1.526), 0.702	
Clinical stage(III vs. IV)	1.689 (0.958–2.975), 0.070	1.023 (0.471–2.221), 0.954
Prior thoracic radiotherapy(No vs. Yes)	0.507 (0.277–0.928), 0.028	0.239 (0.100–0.570), 0.001
Combine chemotherapy(No vs. Yes)	2.009 (0.624–6.467), 0.242	
Prior curable operation(No vs. Yes)	0.426 (0.154–1.181), 0.101	0.327 (0.095–1.126), 0.076
Molecular alterations(No/not done vs. Yes)	1.958 (0.983–3.901), 0.056	2.145 (0.956–4.814), 0.064
PD-L1 expression		
0 vs. 1–49	0.522 (0.172–1.581), 0.250	
0 vs. ≥50	0.804 (0.275–2.354), 0.691	
Line of immunotherapy(First line vs. Further lines)	0.936 (0.555–1.578), 0.805	
Pretreatment peripheral blood biomarkers		
ANC(≤ 4.9 vs. >4.9)	1.552 (0.916–2.630), 0.102	1.287 (0.639–2.589), 0.480
ALC(≤ 1.5 vs. >1.5)	0.605 (0.605–1.030), 0.064	0.333 (0.129–0.857), 0.023

Variable	Univariate analysis	Multivariate analysis
	HR (95% CI), P value	HR (95% CI), P value
AMC(≤ 0.51 vs. >0.51)	1.319 (0.776–2.240), 0.306	
LMR(≤ 2.98 vs. >2.98)	0.665 (0.395–1.121), 0.125	1.330 (0.605–2.925), 0.478
NLR(≤ 3.15 vs. >3.15)	1.437 (0.854–2.418), 0.172	
PLR(≤ 175 vs. >175)	1.579 (0.938–2.658), 0.086	0.810 (0.344–1.911), 0.631
PNI(≤ 45 vs. >45)	0.640 (0.380–1.077), 0.093	2.750 (1.033–7.322), 0.043
SII(≤ 846.61 vs. >846.61)	1.727 (1.024–2.910), 0.040	1.802 (0.669–4.855), 0.244
SIRI(≤ 1.52 vs. >1.52)	1.392 (0.829–2.336), 0.211	
Post-treatment peripheral blood biomarkers		
ANC(≤ 4.9 vs. >4.9)	1.209 (0.715–2.047), 0.479	
ALC(≤ 1.5 vs. >1.5)	0.703 (0.416–1.188), 0.188	
AMC(≤ 0.51 vs. >0.51)	1.159 (0.692–1.941), 0.576	
LMR(≤ 3.12 vs. >3.12)	0.613 (0.364–1.035), 0.067	1.080 (0.429–2.719), 0.870
NLR(≤ 2.31 vs. >2.31)	1.188 (0.702–2.010), 0.521	
PLR(≤ 175 vs. >175)	1.518 (0.902–2.554), 0.116	2.213 (1.039–4.715), 0.040
PNI(≤ 46 vs. >46)	0.689 (0.412–1.185), 0.183	
SII(≤ 846.4 vs. >846.4)	1.689 (1.001–2.849), 0.050	0.477 (0.204–1.119), 0.089
SIRI(≤ 1.69 vs. >1.69)	1.719 (1.021–2.895), 0.042	3.160 (1.046–9.551), 0.041

3.3 Immune prognostic factors for risk stratification

Pretreatment ALC and post-treatment SIRI were considered as significant favorable prognostic factors for both OS and PFS. The Kaplan-Meier curves for OS and PFS were presented in Fig. 1. The median OS and PFS among patients who had post-treatment SIRI > 1.69 were significantly shorter than that post-treatment SIRI ≤ 1.69 (OS: 5 months vs 11 months, P = 0.013; PFS: 3 months vs 8 months, P = 0.031). Furthermore, the median OS and PFS among patients who had pretreatment ALC > 1.5 was longer than that pretreatment ALC ≤ 1.5 (OS: 9 months vs 7 months, P = 0.052; PFS: 7 months vs 5 months, P = 0.050). Based on these risk factors, we then classified patients into 3 categories: low-risk group: ALC > 1.5 and SIRI ≤ 1.69 (n = 28); medium-risk group: ALC > 1.5 or SIRI ≤ 1.69 (n = 35); high-risk group ALC ≤ 1.5 and SIRI > 1.69 (n = 32). Kaplan-Meier analysis showed the 1-year OS rates of 69.2%, 63.6%, 27.1% in low-risk, medium-risk, and high-risk group respectively (P = 0.001) (Fig. 2A). In addition, the PFS of high-risk group were also significantly shorter than that of patients in low-risk or medium-risk group (P = 0.007) (Fig. 2B).

3.4 The associations between IRP with peripheral blood biomarkers and outcomes

In our study, 24 patients developed IRP attributed to PD-1/PD-L1 inhibitors. Among these patients, 12.5% (3/24) had grade 1, 66.7% (16/24) had grade 2, 12.5% (3/24) had grade 3, and 8.3% (2/24) had grade 4. As showed in Table 4, patients with IRP had significantly higher post-treatment NLR than those without IRP (the median 4.23 versus 3.07, P = 0.045). Logistic regression analysis (Table 5) revealed that post-treatment NLR was a risk factor for the occurrence of IRP. Patients with post-treatment NLR > 3 were associated with a significantly higher risk for IRP than that NLR ≤ 3 (HR: 2.917, 95%CI: 1.037–8.206, P = 0.043).

Table 4
Characteristics among patients who with or without IRP.

Variable	IRP (n = 24)	No IRP (n = 71)	P Value
Age			0.487
< 65	14(58.3)	47(66.2)	
≥ 65	10(41.7)	24(33.8)	
Gender			0.773
Male	20(83.3)	56(78.9)	
Female	4(16.7)	15(21.1)	
Smoking			0.385
Yes	21(87.5)	54(76.1)	
No	3(12.5)	17(23.9)	
KPS			0.772
80	16(66.7)	45(63.4)	
90	8(33.3)	26(36.6)	
Histology			0.247
Adenocarcinoma	12(50.0)	45(63.4)	
Squamous cell carcinoma	12(50.0)	26(36.6)	
Clinical stage			0.424
III	11(45.8)	26(36.6)	
IV	13(54.2)	45(63.4)	
Prior thoracic radiotherapy			0.275
Yes	10(41.7)	21(29.6)	
No	14(58.3)	50(70.4)	
Combine chemotherapy			1.000
Yes	22(91.7)	65(91.5)	
No	2(8.3)	6(8.5)	
Prior curable operation			1.000
Yes	3(12.5)	8(11.3)	
No	21(87.5)	63(88.7)	

Variable	IRP (n = 24)	No IRP (n = 71)	P Value
Molecular alterations			1.000
EGFR or ALK/ROS1(+)	3(12.5)	10(14.1)	
(-)/not done	21(87.5)	61(85.9)	
PD-L1 expression			0.134
0	2(8.3)	3(4.2)	
1–49	4(16.7)	11(15.5)	
≥ 50	8(33.3)	10(14.1)	
Not done	14(58.3)	24(33.8)	
Line of immunotherapy			0.256
First line	13(54.2)	29(40.8)	
Further lines	11(45.8)	42(59.2)	
Pretreatment peripheral blood biomarkers Median (IQR)			
ANC	4.35(3.38–6.78)	4.9(3.5–6.2)	0.448
ALC	1.40(1.20–1.80)	1.5(1.1–2)	0.938
AMC	0.51(0.41–0.76)	0.51(0.37–0.68)	0.700
LMR	3.00(2.17–3.92)	2.91(1.69–4.39)	0.956
NLR	3.11(2.23–4.64)	3.19(2.2–5.74)	0.771
PLR	163.61(123.04–240.19)	178.33(122.35–246.67)	0.675
PNI	46.25(42.35–50.1)	44.6(39.9–51.7)	0.647
SII	897.58(430.73–1254)	775.38(526.5–1584.6)	0.613
SIRI	1.60(1.12–2.31)	1.51(1.00–3.12)	0.794
Post-treatment peripheral blood biomarkers Median (IQR)			
ANC	5.7(4.45–7.80)	4.7(3.7–6.1)	0.059
ALC	1.40(0.73–2.35)	1.5(1.2–1.8)	0.487
AMC	0.55(0.28–0.74)	0.51(0.42–0.68)	0.861
LMR	3.12(2.07–3.91)	3.12(2.2–4.2)	0.837
NLR	4.23(2.97–7.63)	3.07(2.23–5.13)	0.045
PLR	170.72(103.33–314.33)	180(12.35–245)	0.820

Variable	IRP (n = 24)	No IRP (n = 71)	P Value
PNI	46(39.10–50.35)	46(41.2–49.5)	0.706
SII	937.57(656.70–1552.11)	790.86(522.2–1378.91)	0.262
SIRI	2.4(1.22–3.31)	1.56(1.04–2.71)	0.134

Abbreviations: IRP, immune-related pneumonitis; KPS, karnofsky performance status; PD-L1, programmed cell death-Ligand 1; IQR, interquartile range; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte; PNI, prognostic nutritional index; SII, systemic inflammation index; SIRI, systemic inflammation response index.

We also found that among patients with post-treatment NLR > 3, 3 (16.7%) had grade 1 ICI-pneumonitis, 10 (55.6%) had grade 2, 3 (16.7%) had grade 3, and 2 (11.1%) had grade 4. For post-treatment NLR ≤ 3, all patient developed grade 2 ICI-pneumonitis. But it was no significant difference in the distribution of grade between post-treatment NLR > 3 group and post-treatment NLR ≤ 3 group (P = 0.280) (Fig. 3A). In addition, we observed that most of patients (18/24) developed IRP within the first 3 months after the start of ICIs treatment, and the time to IRP onset in post-treatment NLR > 3 group was shorter than in post-treatment NLR ≤ 3 group (Fig. 3B). The median onset time of IRP was 2 months (range 1–18 months), and the median IRP onset time in post-treatment NLR > 3 group was 1.5 months (range 1–16 months), and 6.5 months (range 1–18 months) in post-treatment NLR ≤ 3 group.

Table 5
Univariate logistic regression analysis was performed to identify the risk of IRP in different cut-off values of post-treatment NLR.

Variable	HR (95% CI)	p-value
Post-treatment NLR(≤ 2 vs. >2)	1.875(0.492–7.141)	0.357
Post-treatment NLR(≤ 3 vs. >3)	2.917(1.037–8.206)	0.043
Post-treatment NLR(≤ 4 vs. >4)	2.314(0.903–5.934)	0.081
Post-treatment NLR(≤ 5 vs. >5)	1.472(0.540–4.014)	0.450
Post-treatment NLR(≤ 6 vs. >6)	2.727(0.940–7.909)	0.065

Median OS and PFS were similar in patients who developed IRP compared with those who did not, however, patients with grade ≥ 3 IRP were significantly associated with shorter OS (8 months versus 4 months, P = 0.04) and PFS (6.5 months versus 3 months, P = 0.054) (Fig. 4).

4. Discussion

The role of immunotherapy in the treatment of NSCLC has been increasingly emphasized, and its application in clinical practice largely changes the treatment and prognosis of NSCLC patients.[4–6, 8] In this study, a total of 95 stage III/IV NSCLC patients treated with ICIs therapy was retrospectively analyzed. We found that both pretreatment ALC and post-treatment SIRI were useful predictors of outcomes in NSCLC patients receiving ICIs. Then we established a novel risk stratification based on these prognostic factors. To our knowledge, this is the first study to combine pretreatment ALC with post-treatment SIRI for predicting outcomes in patients treated with ICIs. Furthermore, our results showed that post-treatment NLR was a risk factor for the occurrence of IRP.

Currently, a growing body of studies illustrated that the clinical value of peripheral blood biomarkers which could be helpful for predicting treatment outcomes in different solid tumors, including NSCLC.[16–20] Lymphocyte is one of peripheral blood biomarkers which is a vital indicator of the immune system, reflecting the immune system activation, and play a fundamentally important role in tumor proliferation and migration.[23–26] Previous studies have reported that the lymphopenia correlated with worse outcomes in cancer patients.[27–29] Ryoko et.al. found that pretreatment ALC less than 1.5 associated with adverse survival.[28] Another analysis of patients with advanced breast cancer, sarcoma, and lymphoma, suggested that lymphopenia was an independent predictor of survival.[29] In our study, we found that pretreatment ALC less than 1.5 predicted adverse OS and PFS for patients treated with ICIs. The mechanism of cancer immunotherapy is to promote the activity of cytotoxic T lymphocytes (CTLs) and assist in the activation of tumor-specific CTLs in lymphoid organs, thus establishing an efficient and durable anti-tumor immune microenvironment for anti-tumor therapy.[30] Therefore, it is not difficult to understand that a higher pretreatment ALC is beneficial to improve the survival of patients receiving ICIs.

Another peripheral blood biomarker is the systemic inflammation response index (SIRI), which combined ANC, ALC, and AMC, has been proved to be an effective prognostic biomarkers in different cancers such as esophageal squamous cell carcinoma, non-small cell lung cancer, pancreatic cancer, gastric adenocarcinoma, clear cell renal cell carcinoma.[20, 31–34] Geng et al. suggested that SIRI was an independent prognostic indicator for ESCC patients after the radical surgery.[33] and Hu et al. proposed pretreatment SIRI was an independent predictor of outcomes in stage III NSCLC patients who undergoing chemoradiotherapy.[20] But few studies accessed the effect of SIRI for patients receiving immunotherapy. As far as we know, the present study was the first to demonstrate predictive roles of SIRI for prognosis of III/IV stage NSCLC patients treated with ICIs and revealed that high post-treatment SIRI was significantly associated with poor OS and PFS. Then, we established a novel risk stratification based on pretreatment ALC and post-treatment SIRI. Patients were classified into 3 categories: low-risk group: $ALC > 1.5$ and $SIRI \leq 1.69$; medium-risk group: $ALC > 1.5$ or $SIRI \leq 1.69$; high-risk group: $ALC \leq 1.5$ and $SIRI > 1.69$. Survival analysis showed 1-year OS rates of 69.2%, 63.6%, 27.1% in low-risk, medium-risk, and high-risk group respectively ($P = 0.001$). In addition, PFS of high-risk group were also significantly shorter than that patients in low-risk or medium-risk group ($P = 0.007$). Given that ALC and SIRI are easily obtainable, a simple immune risk stratification based on these factors may easily predict survival in III/IV NSCLC treated with ICIs in clinical practice.

Although immunotherapy has brought hope to patients with advanced tumors in recent years, the immune-related adverse effects (irAEs) it brings have also drawn attention.[10] Immune-related pneumonitis (IRP) is a rare but potential fatal irAE that is related to poor outcomes.[11–14] It reported that the incidence rate of all-grade and grade 3 or more IRP were almost 5.4–19.0% and 2.6–12.2% respectively in the clinical setting.[35–37] Our study presented a real-world observation concerning the onset of IRP by ICIs therapy in clinical practice. 24 (25.2%) patients developed IRP attributed to PD-1/PD-L1 inhibitors. Among these patients, 12.5% (3/24) had grade 1 IRP, 66.7% (16/24) had grade 2 IRP, 12.5% (3/24) had grade 3 IRP, and 8.3% (2/24) had grade 4 IRP. Median OS and PFS were similar in patients who developed IRP compared with those who did not, however, patients with grade ≥ 3 IRP were associated with shorter OS (8 months versus 4 months, $p = 0.04$) and PFS (6.5 months versus 3 months, $p = 0.054$).

Given severity and worse outcomes of IRP, many scholars have tried to identify reliable predictors for the occurrence of IRP. They suggested that IRP may be associated with tumor histology types, smoking history, presence of preexisting interstitial lung disease.[38, 39] However, no reliable predictive biomarkers were currently used to predict the risk of IRP onset. Therefore, our study also explored an association between IRP and the peripheral blood biomarkers. Intriguingly, we observed that higher post-treatment NLR showed an increased the IRP onset. Patients with post-treatment $\text{NLR} > 3$ were corrected with a significantly higher risk for developing IRP than that post-treatment $\text{NLR} \leq 3$ (HR: 2.917, 95%CI: 1.037–8.206, $P = 0.043$). There were few studies indicated that the NLR reflected the systemic immune status and may be regarded as a predictor of IRP in patients with ICIs therapy.[40, 41] A study by Ryosuke et al. confirmed that NLR could well predict the onset and severity of IRP. They also showed that a considerable elevated NLR during the development of IRP.[40] Furthermore, Fujisawa et al. Also found similar results of elevated neutrophils and decreased lymphocytes in grade 3 and 4 IRP.[41] The precise mechanism of higher NLR associated with the development of IRP is still unclear, and further in-depth studies are needed to validate our results and elucidate the mechanisms it involved.

In addition, we also explored the correction between NLR and the time to IRP onset, and found that most of patients developed IRP within the first 3 months after the start of ICIs treatment, and the onset time in post-treatment $\text{NLR} > 3$ group was shorter than in post-treatment $\text{NLR} \leq 3$ group. The median onset time in post-treatment $\text{NLR} > 3$ group was 1.5 months (range 1–16 months), and 6.5 months (range 1–18 months) in post-treatment $\text{NLR} \leq 3$ group. Therefore, for those patients with post-treatment $\text{NLR} > 3$, we should be alert to the development of IRP in the first 3 months after ICIs therapy and adopt a timely treatment strategy.

The present study has several limitations. Firstly, this is a retrospective study, so there may be selective bias in our study. Secondly, there are small numbers of eligible patients, and all patients come from a single institution. Accordingly, larger prospective studies are needed to confirm our results. Third, our current study only explored parameters that are commonly used and easily accessible in clinical practice, but other relevant variables involving genomics and radiomics may provide more valuable information to improve the predictive accuracy of IRP as well as the prognosis of patients treated with ICIs.

5. Conclusion

Our data indicated that pretreatment ALC and post-treatment SIRI appeared to be biomarkers of outcome in stage III/IV NSCLC patients treated with ICIs. A novel risk stratification was established basing on these prognostic factors. Patients were classified into 3 categories: low-risk group: $ALC > 1.5$ and $SIRI \leq 1.69$; medium-risk group: $ALC > 1.5$ or $SIRI \leq 1.69$; high-risk group: $ALC \leq 1.5$ and $SIRI > 1.69$. Furthermore, our study also shows that post-treatment $NLR > 3$ were likely to develop IRP of patients who receiving ICIs. A prospective study to validate the significance of peripheral blood biomarkers is necessitated.

Declarations

Ethics Approval and consent to participate

This retrospective study was approved by the ethics committee of the Fujian Province Cancer Hospital (YK2021-009-01). All patients provided written informed consent prior to treatment, and all information was anonymized prior to analysis.

Guideline statement

All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare the submitted work was not carried out in the presence of any personal, professional or financial relationships that could potentially be construed as a conflict of interest.

Contributions:

(I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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- ## Figures

Analysis of overall survival for patients according to post-treatment systemic inflammation response index (SIRI) (A), pretreatment absolute lymphocyte count (ALC) (C), and analysis of progression-free survival for patients according to post-treatment SIRI (B), pretreatment ALC (D).

Figure 2

Overall survival (A) and Progression-free survival (B) curves of the risk stratification according to post-treatment systemic inflammation response index (SIRI) and pretreatment absolute lymphocyte count.

Figure 3

Comparison of the grade distribution of immune-related pneumonitis (IRP) in the patients with post-treatment neutrophil-to-lymphocyte ratio (NLR) ≤ 3 and >3 (A), and comparison of the time to develop IRP in the patients with post-treatment NLR ≤ 3 and >3 .

Figure 4

Analysis of overall survival (OS) (A) and progression-free survival (PFS) (B) for patients with or without immune-related pneumonitis (IRP), and analysis of OS (C) and PFS (D) for patients according to the grades of IRP.