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ORIGINAL RESEARCH

The Predictive Value of NLR, PLR, LMR, NPAR and D-Dimer on the Efficacy and Prognosis of First-Line Immunotherapy for Extensive-Stage Small Cell Lung Cancer

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Purpose: To investigate the predictive value of peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), neutrophil percentage-to-albumin-ratio (NPAR), and D-dimer in the efficacy and prognosis of immunotherapy for extensive-stage small cell lung cancer (ES-SCLC).

Patients and Methods: A total of 70 ES-SCLC were included. The diagnostic performance of inflammatory indexes and D-dimer in predicting the efficacy and prognosis of immunotherapy was evaluated using receiver operating characteristic curve (ROC). Disease control rate (DCR) was used as the assessment indicator for immunotherapy efficacy, and progression free survival (PFS) > 6 months was used as the judgement indicator for better prognosis. Using Lasso regression and logistic multivariate analysis to predict the efficacy and prognosis of immunotherapy, and the optimal cut-off value was determined according to the area under the ROC curve. Kaplan-Meier survival analysis was applied to compare survival differences between groups.

Results: At baseline, PLR can predict the efficacy of immunotherapy in ES-SCLC patients, but cannot predict their prognosis. After two cycles of immunotherapy, NLR can not only predict the efficacy and prognosis of immunotherapy, but also be identified as an independent predictor of long-term PFS in multivariate analysis (P<0.01). The long-term PFS rate of the low NLR2 group (<2.2) was significantly higher than that of the high NLR2 group (≥ 2.2) (P<0.001), with median PFS of 4.83 months vs 9.9 months, respectively, P<0.001.

Conclusion: After two cycles of chemotherapy combined with immunotherapy, the efficacy and prognosis of NLR and ES-SCLC immunotherapy are closely related and can serve as effective and reliable predictive indicators.

Keywords: inflammatory indicators, D-dimer, immunotherapy, therapeutic effect prediction

Introduction

On April 4, 2024, the National Cancer Institute published cancer statistics for all regions of the world in 2022, and lung cancer is a malignant tumor with the highest incidence and the leading cause of cancer deaths in China and globally. Among them, small cell lung cancer (SCLC) accounts for 13%-17% of lung cancers.[1] SCLC is known for its high malignancy and early metastatic tendency, resulting in many patients being diagnosed with advanced disease and thus poor prognosis.[2,3] With the rapid development of tumor immunotherapy, immune checkpoint inhibitors (ICIs) have significantly improved progression free survival (PFS) and overall survival (OS) in SCLC. However, immunotherapy

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does not benefit all patients with advanced SCLC. Therefore, it is necessary to find suitable biomarkers to screen the superior population for immunotherapy.

Currently, the most commonly used clinical predictor of immunotherapy efficacy is programmed cell death ligand-1 (PD-L1) expression, but its predictive value is limited and unstable Tumor mutation burden (TMB) has been proved to be an effective and independent biomarker for predicting the efficacy of immunotherapy, but there are many shortcomings, such as the TMB detection platform is not standardized, and TMB is not fully correlated with the response rate of ICIs, which limits its wide application in the clinic.

More and more evidence shows that the inflammatory microenvironment is closely related to the occurrence and development of tumors and the prognosis of patients; the inflammatory response is closely related to tumor immunity, and inflammatory cells can regulate the activity of immune cells in the tumor microenvironment through a series of inflammatory mediators, leading to dysregulation of the immune state of the body, which is mainly manifested in the peripheral blood as the alteration of the levels and ratios of various inflammatory cells.[4,5] Among many inflammatory indicators, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) have been shown to correlate with immunotherapy efficacy and prognosis in several solid tumors.[6–8] However, the relationship between NLR, PLR, LMR and SCLC immunotherapy efficacy and prognosis prognosis has not been conclusively established. Neutrophil percentage-to-albumin ratio (NPAR) is a biomarker of inflammation and trophic state, NPAR = (neutrophil percentage (%) / albumin concentration (g/dL)), which has been found to be associated with a variety of disease states, including cardiovascular diseases, infections, malignancies etc. Fewer studies have been conducted on D-dimer and immunotherapy. The present study was therefore conducted to investigate this.

Materials and Methods

General Information

We retrospectively collected data on patients with extensive-stage small cell lung cancer (ES-SCLC) diagnosed and treated from January 2021 to December 2024 at the First Affiliated Hospital of Anhui Medical University. This study followed the standards established by the Declaration of Helsinki. The inclusion criteria were as follows: (1) clear pathological diagnosis of SCLC with clinical stage of ES- SCLC. (2) Eastern Cooperative Oncology Group (ECOG) physical status score: 0–2. (3) complete clinical data, including complete laboratory and imaging examinations with measurable lesions. Exclusion criteria were as follows: (1) age < 18 years. (2) comorbid hematologic diseases, immune system diseases, or other malignancies, etc. (3) previous long-term treatment with hormones or hematopoietic factors. (4) incomplete statistical and treatment-related data.

Treatment Regimen and Follow-Up

Patients received immunotherapy (Atezolizumab, Duvalimumab, Serplulimab, Triprolizumab) in combination with chemotherapy as a first-line treatment regimen and received at least 2 courses of antitumor therapy until the patients experienced disease progression, intolerable adverse effects, or death. Follow-up visits were conducted by regular visits to the hospital or by telephone. The start of follow-up was on April 01, 2021, and the last visit was on July 01, 2025, and 4 patients were lost to follow-up (excluded during statistical analysis).

Data Collection

Data collected included: demographic and baseline characteristics of patients (gender, age, smoking status, body mass index (BMI), and presence or absence of brain metastases at initial diagnosis); and laboratory tests for neutrophils, percentage of neutrophils, lymphocytes, platelets, monocytes, albumin, and D-dimer before treatment and after 2 cycles (±3 days) of treatment. Disease control rate (DCR) as the primary efficacy endpoint was assessed by two independent radiologists (each with >5 years of experience) according to RECIST v1.1 criteria. Discrepancies were resolved by a third senior radiologist. Discrepancies were resolved by consulting a third senior radiologist. PFS was defined as the time from the initiation of treatment to disease progression or death. Based on the median PFS of 5.2 months in the IMpower133 trial, a PFS of >6 months was defined as “long-term PFS”.[9]

Statistical Analysis

SPSS (v22.0) and R (v4.4.0) software were used to statistically analyze the study data. Count data were expressed as rate (%) and $\chi 2$ test was used. Receiver operating characteristic (ROC) curves were plotted, and patients were grouped by applying the best cut-off value selected by the area under the curve (AUC). The optimal cut-off value for survival was calculated using the surv_cutpoint() function in the survminer package of R software, and the survival curve was plotted using Kaplan-Meier survival analysis, and the Log rank test was performed to compare the differences in survival between the groups, and the Logistic model was used for multivariable analysis to screen out the independent predictive factors, and the statistical test was a two-sided probability test level $\alpha=0.05$, $P<0.05$ indicated that the difference was statistically significant.

Results

Patient Clinical Characteristics

This study included a total of 70 ES-SCL patients with complete information and follow-up data, including 67 (95.7%) males and 3 (4.3%) females, aged 65.5±8.4 years. Among them, 16 patients (22.9%) had brain metastases. After 2 courses of treatment, all patients were evaluated for imaging efficacy, of which 0 cases (0%) were complete response (CR), 38 cases (54%) were partial response (PR), 22 cases (31%) were stable disease (SD), 10 cases (14%) were progressive disease (PD), ORR was 54.3%, and DCR was 85.7%. Then we divided all patients into two groups according to the efficacy of the 2 courses of treatment, which were divided into the effective group (CR+PR+SD) and the ineffective group (PD), and the results showed that different age groupings had a significant effect on the efficacy, and the rate of PD after 2 cycles of treatment was significantly higher in patients aged >65 than in patients aged ≤65 (25% vs2.9%, P=0.008), and the differences in the remaining factors were not statistically significant, as detailed in Table 1.

Table 1 Relationship Between Clinical Parameters and Therapeutic Efficacy

Clinical Parameters	ALL	Efficacy Evaluation After 2 Cycles		*P*-value
		CR+PR+SD	PD	
Gender	70	60 (85.7%)	10 (14.3%)	0.63
Male	67	57 (85.1%)	10 (14.9%)	
Female	3	3 (100%)	0	
Age				0.008
>65 years	36	27 (75%)	9 (25%)	
≤65 years	34	33 (97.1%)	1 (2.9%)	
BMI				0.22
<18.5	6	6 (100%)	0	
18.5≤BMI<24	49	43 (87.6%)	6 (12.4%)	
BMI≥24	15	11 (73.3%)	4 (26.7%)	
Smoking				0.51
Yes	45	39 (86.7%)	6 (13.3%)	
No	25	21 (84%)	4 (16%)	
Brain metastasis				0.28
Yes	16	15 (93.8%)	1 (6.2%)	
No	54	45 (83.3%)	9(16.7%)	
Drugs				0.65
Atezolizumab	20	17 (85.0%)	3 (15.0%)	
Duvalimumab	15	12 (80.0%)	3 (20.0%)	
Serplulimab	12	8 (66.7%)	4 (33.3%)	
Triprolizumab	23	17 (73.9%)	6 (26.1%)	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BMI, body mass index.

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Validation of the Predictive Efficacy of NLR, PLR, LMR, NPAR, and D-Dimer on the Efficacy and Prognosis of Immunotherapy Before and After Immunotherapy

The ROC curves of NLR, PLR, LMR, NPAR, and D-dimer for predicting the efficacy of ES-SCLC immunotherapy were plotted using patients who achieved objective remission as positive samples and patients who did not achieve objective remission as negative samples, and the results showed that the AUC of NLR and its 95% CI were 0.78 (0.68, 0.89), the AUC of PLR and its 95% CI was 0.82 (0.72, 0.92), and LMR had the highest predictive efficacy with an AUC value and its 95% CI of 0.84 (0.75, 0.94), as shown in Figure 1 and Table 2. Similarly, we plotted the ROC curves of NLR2, PLR2, LMR2, NPAR2, and D-dimer2 for predicting the efficacy of immunotherapy after 2 cycles of treatment, and found that the AUC values of NLR2, PLR2, LMR2, and NPAR2 for predicting the efficacy of immunotherapy were 0.71 [95% CI (0.58–0.83)], 0.68 [95% CI (0.56–0.81)], 0.72 [95% CI (0.6–0.84)], and 0.69 [95% CI (0.55–0.81)], as shown in Figure 2 and Table 3. Then, we conducted univariate and multivariate logistic proportional hazards regression analyses using inflammatory markers and D-dimer as factors affecting the efficacy of immunotherapy before and after treatment. The results of Lasso univariate regression analysis showed that PLR and NLR2 may be factors affecting the efficacy of immunotherapy ($P<0.05$). Further multivariate logistic regression analysis showed that NLR2 is an independent risk factor for the efficacy of immunotherapy in ES-SCLC patients ($P=0.004$) (Table 4 and Table 5).

In order to further observe whether the inflammatory indicators at baseline and after 2 cycles of immunotherapy affected the long PFS of patients, the ROC curves of NLR, PLR, LMR, NPAR, and D-dimer for predicting long PFS were plotted, and the results showed that the diagnostic value of the inflammatory indicators the D-dimear at baseline and for predicting PFS were low (Figure 3 and Table 6), and in the ROC curves of the inflammatory indicators after 2 cycles of therapy, we found that the AUC of NLR2, PLR2, LMR2, NPAR2, and D-dimer2 for predicting PFS were 0.75 [*95% CI* (0.64–0.87)], 0.64 [*95% CI* (0.51–0.77)], 0.77 [*95% CI* (0.66–0.89)], 0.69 [95% CI (0.57–0.83)], 0.65 [*95% CI* (0.52–078)], in which NLR2 and LMR2 showed good predictive diagnostic value, as shown in Figure 4 and Table 7. Similarly, we conducted Lasso regression analysis on all inflammation indicators before and after treatment as factors affecting long-term PFS. Univariate analysis showed that NLR2 may be a predictor of long-term PFS ($P<0.05$) (Table 8). Subsequently, indicators with P values less than 0.2 (NLR2, NPAR2) were further included in multivariate analysis, and the results showed that NLR2 may be an independent predictor of long-term PFS in ES-SCLC patients receiving immunotherapy ($P=0.012$) (Table 9).

Use ROC curve to determine the optimal threshold for predicting long PFS with NLR2, and divide patients into high NLR2 group (≥ 2.2) and low NLR2 group (<2.2) based on the optimal threshold. Use chi square test to compare the incidence of long PFS between the two groups. The long-term progression free survival rate of the low NLR2 group was significantly higher than that of the high NLR2 group (89.5% vs 37.3%, $P<0.001$) (Table 10). Meanwhile, use the survv_cutpoint() function in the survminer package of R software to calculate the optimal critical value for survival.

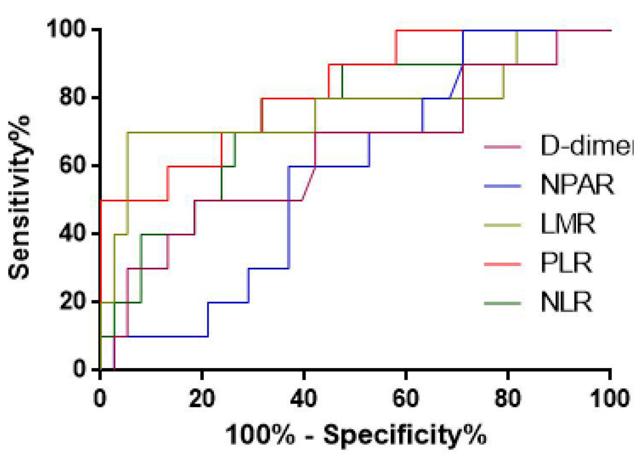

Figure 1 Area under the ROC curve for predicting therapeutic efficacy with different parameters at baseline.

Table 2 Diagnostic Performance of Baseline Inflammatory Markers in Predicting Immunotherapy Efficacy

Inflammatory Indicators	*AUC*	*95% CI*	*P*
NLR	0.78	0.68–0.89	<0.001
PLR	0.82	0.72–0.92	<0.001
LMR	0.84	0.75–0.94	<0.001
NPAR	0.52	0.39–0.67	0.68
D-dimer	0.59	0.45–0.72	0.21

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; NPAR, Neutrophil percentage-to-albumin ratio; AUC, area under the curve.

Kaplan Meier survival analysis was used to plot survival curves for the NLR2 subgroup, and a Log rank test was performed. The results showed a significant survival difference between the two groups (P=0.0037) (Figure 5).

Discussion

Studies have shown that inflammation induced by the tumor microenvironment promotes tumor cell initiation, proliferation, hematopoietic dissemination, and survival, and it has been demonstrated that cellular inflammatory responses correlate with the prognosis of immunotherapy for a variety of tumors.[10,11]

Neutrophils form part of the tumor microenvironment and play an important role in tumor progression and treatment resistance. It has been shown that tumor-induced neutrophils secrete a variety of pro-tumorigenic substances that facilitate the formation of the tumor microcirculation, as well as recruiting tumor cells to proliferate, promote angiogenesis and adaptive immune responses, and also inhibit cytotoxic CD8+ T lymphocytes through the production of inducible nitric oxide synthase. In conclusion, it involves interfering with biological behaviors such as growth and reproduction of tumor cells, which can stimulate tumor cell progression and lead to tumor deterioration.[12,13]

As an important indicator of inflammatory response, lymphocytes have a specific immune recognition function, and they can play an important role in the anti-tumor process by releasing a series of cytokines that activate anti-tumor immunity.[14] Lymphocytes can not only kill tumor cells directly, but also are particularly critical in anti-tumor immunotherapy, for example, programmed death receptor-1 (PD-1) inhibitors can release the inhibitory effect of PD-1/PD-L1 signaling pathway on the immune system, up-regulate the number and activity of T-lymphocytes in vivo, and restore the T-cells of the body's anti-tumor response.[15,16] Therefore, elevated NLR indicates excessive neutrophilia and lymphocyte depletion, which contributes to tumor growth and proliferation, and may serve as a predictor of poor anti-tumor

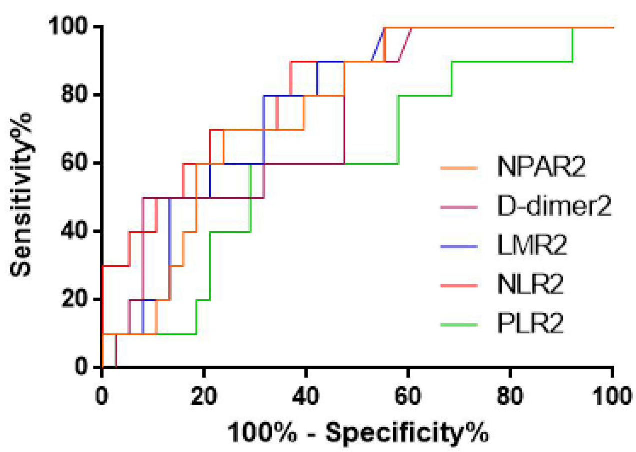

Figure 2 ROC curve area under different parameters for predicting therapeutic efficacy after 2 cycles.

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Table 3 Diagnostic Performance of Inflammatory Markers in Predicting the Efficacy of Immunotherapy After 2 Cycles

Inflammatory Indicators	***AUC***	***95% CI***	***P***
NLR2	0.71	0.58–0.83	0.003
PLR2	0.68	0.56–0.81	0.008
LMR2	0.72	0.6–0.84	0.002
NPAR2	0.69	0.55–0.81	0.008
D-dimer2	0.62	0.49–0.75	0.08

Table 4 Lasso Regression Analysis of Inflammatory Indicators for Predicting the Efficacy of Immunotherapy

Parameter	**Standardized Coefficient**	**t**	**P**
NLR	−0.026568	−0.973813	0.334125
PLR	−0.002585	−4.504494	0.000032
LMR	0.029674	1.157618	0.251685
NPAR	0	0	1
D-dimer	0	0	1
NLR2	−0.047081	−2.808321	0.006742
PLR2	−0.000523	−0.855591	0.395685
LMR2	0.033514	1.750821	0.085175
NPAR2	−0.014925	−1.332155	0.187932
D-dimer2	0	0	1
Dependent variable: DCR			

Table 5 Multivariate Analysis of Inflammation Indicators Predicting the Efficacy of Immunotherapy

Parameter	**Multivariate Analysis**				
	β	***S. E.***	***Wald***	***OR (95% CI)***	***P***
PLR	0.007	0.004	3.393	1.007 (1–1.015)	0.065
NLR2	0.45	0.156	8.358	1.568 (1.156–2.126)	0.004

immunotherapy efficacy, which is consistent with the results of the present study, in which NLR2 was an independent risk factor for predicting the efficacy of immunotherapy in patients with ES-SCLC.

Elevated platelets accelerate tumor progression by promoting neovascularization and the production of adhesion molecules.[17,18] In a recent study, Hinterleitner et al found that PD-L1 protein was able to translocate from NSCLC tumor cells to platelets, and platelets expressing PD-L1 inhibited the infiltration of CD4+ and CD8+ T lymphocytes.[14] Taken together, peripheral platelets may reflect PD-L1 expression on tumors, and high PLR may impair the efficacy of ICIs. These findings provide some evidence for the predictive value of PLR for immunotherapy. After entering the tumor microenvironment, monocytes differentiate into tumor-associated macrophages, which produce tumor necrosis factor α and vascular endothelial growth factor to promote tumor microvascular growth and accelerate tumor cell invasion and metastasis, and at the same time, monocytes can directly provide trophic factors to promote tumor cell development.[19,20] Studies have reported that tumor-associated macrophages can further inhibit the function of cytotoxic T cells and contribute to tumor proliferation and invasion by acting on the PD-1/PD-L1 signaling pathway.[21] Thus reduced LMR may be associated with poor tumor prognosis.

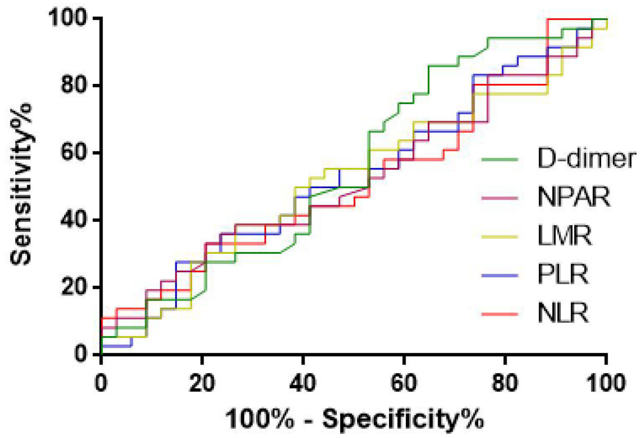

Figure 3 Area under the ROC curve for predicting prognosis with different parameters at baseline.

There are many types of proteins in plasma, among which plasma albumin has the highest concentration and is a key substance for maintaining normal physiological activities of the body. Albumin is synthesized by the liver, and tumor patients often have lower albumin due to nutritional depletion and compromised liver function, etc. Elevated NPAR reflects, to a certain extent, the imbalance between tumor-induced inflammation and nutritional status as well as the increased risk of infections, and inflammation promotes tumor growth, invasion, and metastasis. Several studies have shown that NPAR can be used as a reference indicator for the prognosis of tumor patients.[22,23] For example, in a variety of cancers such as lung cancer and gastric cancer, higher NPAR values often suggest that patients have a poorer prognosis and may have a shorter survival period, and it reflects the effect of a patient's physical condition on the tumor in a more comprehensive way than the neutrophil percentage or albumin index alone.[24]

D-dimer levels are often elevated in tumor patients, and it reflects the activation status of coagulation and fibrinolytic systems in tumor patients. High levels of D-dimer can promote the immune escape of tumor cells and reduce the killing of tumor cells by affecting immune cell functions, such as inhibiting natural killer cell (NK cell) activity.[25] D-Dimer can affect the expression and release of cytokines in the tumor microenvironment, such as promoting the production of vascular endothelial growth factor (VEGF), which facilitates tumor angiogenesis, as well as altering the recruitment and function of immune cells to create an immune microenvironment that favors tumor growth. In some immunotherapies, monitoring changes in D-dimer levels may be helpful in assessing efficacy. For example, in the treatment of ICIs, patients with low D-dimer levels before treatment may respond better to immunotherapy and have longer survival.[26]

In conclusion neutrophils, platelets, monocytes, lymphocytes, and D-dimer are widely involved in the process of tumor immunotherapy, so the levels of NLR, PLR, LMR, NPAR, and D-dimer in the peripheral blood may be an ideal indicator to predict the efficacy of tumor immunotherapy.

A study from 2021 found that early-stage SCLC patients with NLR < 5 after 6 weeks of immunotherapy had a significantly longer median PFS than those with NLR ≥ 5 (NR vs 3.2 months; *HR* = 0.29, *95% CI* 0.09–0.96, *P* = 0.04);

Table 6 Diagnostic Performance of Baseline Inflammatory Markers for Predicting Long-Term PFS

Inflammatory Indicators	*AUC*	*95% CI*	*P*
NLR	0.52	0.38–0.66	0.76
PLR	0.54	0.4–0.67	0.07
LMR	0.52	0.39–0.66	0.71
NPAR	0.53	0.39–0.67	0.71
D-dimer	0.56	0.43–0.7	0.37

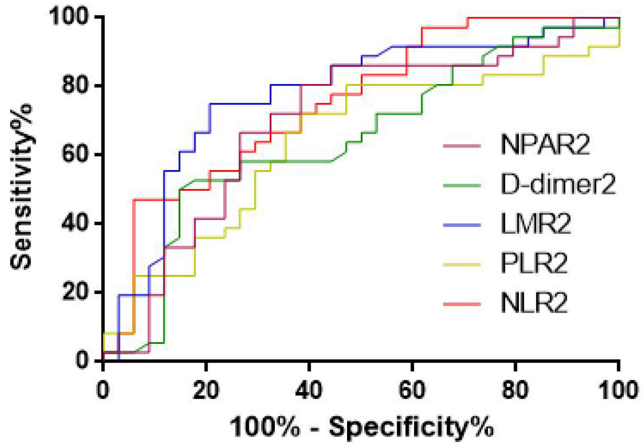

Figure 4 Area under the ROC curve for predicting prognosis with different parameters after 2 cycles.

in the NLR < 5 group, 9/28 patients developed PD at 6 weeks post-treatment with an ORR was 67.9% in the NLR ≥ 5 group, 7/13 patients developed PD 6 weeks after treatment, with an ORR of 46.2%.[27]

In another immunotherapy study in patients with renal cancer, the authors found that NLR after 6 weeks of treatment had a higher predictive efficacy for ORR, PFS, and OS compared with baseline, and could be an independent risk factor for ORR.[28] This is similar to the results of the our study, in which NLR2 could be an independent risk factor for immunotherapy efficacy in ES-SCLC patients, although the efficacy metric in this study was DCR. Similar to Suh et al,[29] we found that baseline NLR in ES-SCLC patients receiving immunotherapy was less correlated with response to

Table 7 Diagnostic Performance of Inflammatory Markers Predicting Long-Term PFS After 2 Cycles of Treatment

Inflammatory Indicators	*AUC*	*95% CI*	*P*
NLR2	0.75	0.64–0.87	<0.001
PLR2	0.64	0.51–0.77	0.043
LMR2	0.77	0.66–0.89	<0.001
NPAR2	0.69	0.57–0.83	0.004
D-dimer2	0.65	0.52–0.78	0.032

Table 8 Lasso Regression Analysis of Inflammatory Markers for Predicting Long-Term PFS in Immunotherapy

Parameter	Standardized Coefficient	t	*P*
NLR	0.013	0.37352	0.710101
PLR	−0.000506	−0.670518	0.505144
LMR	0	0	1
NPAR	0.010549	0.596765	0.552947
D-dimer	0	0	1
NLR2	−0.052244	−2.367809	0.021191
PLR2	−0.000561	−0.697911	0.487974
LMR2	0.020032	0.795162	0.429707
NPAR2	−0.021032	−1.426403	0.159022
D-dimer2	0	0	1
Dependent variable: long-term PFS			

Table 9 Multivariate Analysis of Inflammation Indicators Predicting Immune Therapy Long-Term PFS

Parameter	Multivariate Analysis				
	β	*S. E.*	*Wald*	*OR (95% CI)*	*P*
NLR2	0.463	0.184	6.345	1.59 (1.108–2.28)	0.012
NPAR2	0.099	0.074	1.823	1.104 (0.956–1.276)	0.177

Table 10 Correlation Analysis Between Cut-off Values of Inflammatory Markers and Prognosis

Inflammatory Indicators	Cut-off Values	PFS>6 Months		*mPFS*	*95% CI*	*χ2*	*P*
		Yes	No				
NLR2	≥2.2	19	32	4.83	4.07–6.03	15.11	<0.001
	<2.2	17	2	9.9	7.33–11.17		

treatment, whereas post-treatment NLR was independently associated with efficacy, and our study also found that the rate of long PFS was significantly higher in the low NLR2 group (<2.2) than in the high NLR2 group (≥2.2) (89.5% vs.37.3%, $P < 0.001$). Two similar studies on ES-SCLC both demonstrated that elevated NLR and serum lactate dehydrogenase (LDH) concentrations prior to immunotherapy are independent adverse prognostic factors associated with reduced OS.[30,31] A meta-analysis of gastric cancer patients receiving immunotherapy included 17 studies evaluating a total of 1566 gastric cancer patients treated with ICIs, and the final results of the analysis also noted that high levels of NLR were associated with poorer OS and PFS.[32] Another study examining factors influencing the prognosis of ES-SCLC patients following first-line chemoradiotherapy also included the NLR value at the first cycle post-immunotherapy, but did not find it to independently affect prognosis.[33] Conclusions remain inconsistent, and further large-scale, multicenter studies are needed to validate these findings.

Previous studies have suggested that there may be a dynamic equilibrium in PLR as platelets continue to proliferate after immunotherapy, and at the same time, PD-1 inhibitors alter the negative regulation of T-cells and thus cause an increase in lymphocytes.[15] A systematic review published in 2022 included 21 studies involving 2312 patients with advanced lung cancer receiving immunotherapy.[34] In addition, patients with elevated PLR had lower ORR and DCR. Furthermore, in advanced NSCLC, high PLR was significantly associated with poor OS and PFS; however, in advanced SCLC, PLR was not associated with OS and PFS. However, studies have also shown that in SCLC, patients with higher baseline PLR levels (PLR > 190) exhibit shorter progression-free survival.[13] Our study did

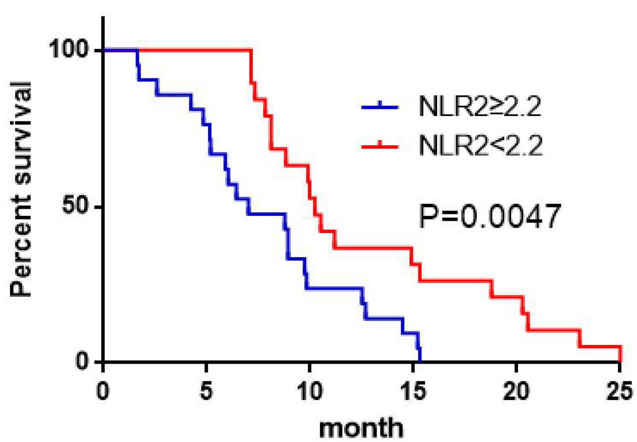

Figure 5 Correlation analysis between high and low subgroups of NLR2 and prognosis.

not observe any correlation between PLR levels before or after treatment and long PFS. In univariate analysis, baseline PLR levels were significantly associated with treatment efficacy but did not constitute an independent risk factor for treatment response. LMR was initially identified as a prognostic indicator in hematologic malignancies, and subsequently a growing number of studies have shown prognostic relevance in numerous solid tumors, including gastric and breast cancers in addition to melanoma.[35,36] A growing number of studies have found that LMR can be used as a prognostic biomarker for lung cancer and that low LMR is associated with a poorer prognosis in lung cancer patients.

NPAR has been used for prognostic assessment of many non-cancerous diseases, such as cardiovascular diseases, liver- and kidney-related diseases, etc., whereas there are still fewer studies on the relationship between NPAR and cancer immunotherapy.[37,38] While our study found no predictive value for NPAR in ES-SCLC treated with immunotherapy, a 2022 modeling study in advanced lung cancer identified it as a promising prognostic biomarker.[39] It demonstrates similar value in other cancer types. For instance, an oral cancer study indicated that high NPAR (≥16.93) was an independent risk factor for poor OS (HR: 2.697; 95% CI: 1.761–4.130; P< 0.001).[22] Another recent study on NPAR and breast cancer incidence and mortality also indicated that NPAR may serve as a dual biomarker for risk assessment and prognostic evaluation of breast cancer.[40]

Conclusions

In summary, we found through a small sample study that NLR2 can serve as a biomarker for predicting the efficacy and prognosis of immunotherapy for male ES-SCLC, but further prospective, large-scale, multicenter studies are still needed for rigorous validation.

Data Sharing Statement

The datasets generated and/or analyzed during this current study may be made available upon reasonable request to the corresponding author, MHD.

Ethics Approval and Consent to Participate

This research protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. All patient information pathologically diagnosed with small cell carcinoma of the lung was obtained from the First Affiliated Hospital of Anhui Medical University: Scientific Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University—PJ2025-07-24. Due to the retrospective nature of this research project, the collected data does not cause any additional harm to patients, and all information is limited to this research project, protecting the privacy and personal information of patients. Therefore, the ethics committee approves the exemption of informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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