

Neutrophil–lymphocyte ratio (NLR) predicted prognosis for advanced non-small-cell lung cancer (NSCLC) patients who received immune checkpoint blockade (ICB)

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Purpose: The aim of this study was to identify the prognostic value of blood neutrophil–lymphocyte ratio (NLR) in patients with advanced non-small-cell lung cancer (NSCLC) who received immune checkpoint blockade (ICB) therapy.

Materials and methods: 147 advanced NSCLC patients were enrolled in this study from June 30, 2013, to August 30, 2017. Survival analysis used the Kaplan and Meier methodology. The mean follow-up time was 2.6 years. The phenotypic T cells subtypes were evaluated by flow cytometry.

Results: Of these patients, receiver operating characteristic (ROC) curves analysis were used to confirm the cut-off value, and patients were stratified into NLR>2.5 (n=88) and NLR≤2.5 (n=59) groups. Survival analysis showed that patients with NLR≤2.5 had significantly favorable overall survival (OS) and progression-free survival (PFS) compared with patients with NLR>2.5. After stratified with the tumor mutational burden (TMB), we further found that patients with NLR≤2.5 had significantly favorable OS and PFS compared with patients with NLR>2.5 in the group of patients with TMB>10, while in group patients with TMB≤10, patients with NLR≤2.5 had no significantly favorable OS and PFS compared with patients with NLR>2.5. The CD3⁺ and CD8⁺/CD28⁺ T cell subsets were significantly increased in patients with NLR≤2.5 ($P<0.05$), while the CD8⁺/CD28⁻ and CD4⁺/CD25⁺ cell subsets were significantly decreased in patients with NLR≤2.5 ($P<0.05$).

Conclusion: High NLR value independently predicted poorer survival in advanced NSCLC patients received ICB therapy. The NLR may help oncologists to predict outcomes of patients received ICB and choose alternative therapies for patients with high NLR value.

Keywords: NLR, NSCLC, ICB

Introduction

Lung cancer, one of the most common cancers with high degree of malignancy, is a devastating disease with a poor prognosis worldwide.^{1–4} Approximately 85% of the lung cancers are diagnosed as non-small-cell lung cancer (NSCLC), which composed of 2 major histology subtypes: squamous (SQ) and non-squamous (non-SQ) carcinoma. A large proportion of patients are diagnosed at advanced-stage in this world, which would be the leading cause of cancer-related mortality. Newer therapeutic modalities for NSCLC have focused on targeting the immune system.⁵

Immune checkpoint blockade (ICB), which has been approved as second-line treatment of advanced NSCLC, has led to paradigm shifts in the use of

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manipulation of immune cells to control tumor growth. Therapy targeting the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) checkpoint has produced an impressive response rate in patients with multiple treatment-refractory metastatic diseases.⁶ Although high levels of PD-L1 expression may indicate a greater possibility of response to anti-PD-1/PD-L1 treatment of ICB, PD-L1 expression detected by immunohistochemistry (IHC) is based on tumor histology and space changes and temporal factors (for example, the time and location frame of the biopsy). In addition, it has been reported that some patients with little or no PD-L1 expression also benefit from treatment of ICB.⁷

Recent studies have shown that the status of tumor-infiltrating lymphocyte (TIL) could predict response to anti-PD-1 or PD-L1 treatment.⁸ Patients with high T effect or interferon-related gene expression showed improved both progressive PFS and OS with anti-PD-1 or PD-L1 therapy.⁹ A predictive model based on the expression of CD8 was established by detecting tumor biopsies before and during anti-PD-1 treatment against melanoma.¹⁰ In a mouse model, Tang et al showed that adequate T cell infiltration but not PD-L1 expression is more significant and critical for tumor response to checkpoint blockade.¹¹ Moreover, tumor mutation burden (TMB) has become a potential measure of genomic instability and neoantigens used to predict tumor response to immunotherapy, including ICB and adoptive cell therapy. Previous studies have shown that the higher non-synonymous mutation burden assessed by whole exome sequencing is objectively related to patients with NSCLC treated with ICB.¹² In addition to whole exon sequencing, the prediction accuracy of the tumor mutation burden was reported using a comprehensive genomic analysis in NSCLC.¹³

Increasing evidence showed that systemic inflammatory activation in cancer cells predicted tumor progression by inducing cancer proliferation and metastasis or promoting angiogenesis.¹⁴ The neutrophil-lymphocyte ratio (NLR), which has been considered as a member of the marker of the systemic inflammation response, is valuable for predicting the prognosis of various cancers.^{15,16} Clearly, challenges remain to identify reliable, cost-effective biomarkers to determine which patients are most likely to benefit from ICB and avoid unnecessary immune-related adverse events.

In the present study, we evaluated the prognostic value of NLR in advanced NSCLC patients received treatment of anti-PD-1 inhibitors. The relationship between the NLR

and immune cells phenotypes and other clinical characteristics was further analyzed.

Patients and methods

Study design and participants

The cohort included 147 consecutive NSCLC patients between June 30, 2013, and August 30, 2017, retrospectively. The study was approved by the Regional Ethics Review Committee of the Cancer Center of the Capital Medical University. Patients were treated according to the ethical principles of the Helsinki Declaration concerning medical research in human subjects. All patients provided informed written consent prior to entering the study. Patients need to meet the following inclusion criteria: Participants are between 18 and <80 years old; Eastern Cooperative Oncology Group performance status (ECOG-PS)¹⁷ ≤ 2 ; Histology or cytology confirmed unresectable, locally advanced or metastatic NSCLC; No immunotherapy was performed prior to this study. If the patient has a concurrent malignancy other than NSCLC, a severe, uncontrolled disease or psychiatric disorder that limits the ability to meet the research requirements, then the patient is excluded.

Pretreatment evaluation

Each patient recorded a medical history and physical examination results. Each patient also had an electrocardiogram, a computed tomography scan of the abdomen and pelvis (as well as the chest, if needed), serum chemistry and CBC, and urine analysis.

Procedures

Receipt of radiotherapy, adjuvant chemotherapy, and number of previous lines of palliative intent chemotherapy preceding PD-1 antibody treatment were recorded. The chemotherapy choices were following platinum-based chemotherapy regimens for 4 to 6 cycles: carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel. PD-1 inhibitors were administered according to standard dosing: nivolumab 3 mg/kg body weight every 2 weeks and pembrolizumab 2 mg/kg body weight every 3 weeks. Adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0) and response to treatment was assessed by the Response Evaluation Criteria in Solid Tumors (www.cancer.gov/).

Tissue IHC

Tissue staining was performed retrospectively on a subset of 86 patients with IHC-accessible tissue. All of these patients were treated with an immunological checkpoint blockade. Of all patients treated with immunological checkpoint block, 61 were excluded due to inaccessible pathology or insufficient IHC samples (eg, samples obtained by fine needle aspiration biopsy). Tissue staining was performed on PD-L1 (tumor), PD-L1 (Immunomicroenvironment), CD3, CD4, CD8, CD25, and CD56. The primary antibody against PD-L1 (SP263, Ventana) was used according to the manufacturer instructions. primary antibody of anti-CD3-FITC/anti-CD56-RPE (Dako), anti-CD3-FITC (fluorescein isothiocyanate), anti-CD4-RPE, anti-CD8-RPE, anti-CD45RO, and anti-CD4-FITC/anti-CD25-PE (BD Biosciences) were used. The sample was read and explained by the attending pathologist. The data report the percentage of cells stained for each particular marker.

Definition of TMB

TMB is determined by Foundation Medicine. Calculate TMB by including all substitutions and insertions in the entire somatic cell, coding, and sequencing length.^{18,19} Synonymous mutations were included given their potential to promote genomic instability. Noncoding alterations were excluded. TMB was calculated in mutations per megabase pair. TMB categories were determined by Foundation Medicine on the basis of the following ranges, rounded to the nearest whole number: low (0–10), intermediate (11–19), high (20–34), and very high (35 and above).

Analysis of the circulating immune response

Peripheral venous blood was obtained from each patient at various time points. Whole blood (100 mL) was incubated with primary antibody in the dark for 15 mins at 4°C. anti-CD3-FITC/anti-CD56-RPE (Dako), anti-CD3-FITC (fluorescein isothiocyanate), anti-CD4-RPE, anti-CD8-RPE, anti-CD45RO and anti-CD4-FITC/anti-CD25-PE (BD Biosciences). After 10 mins of hemolysis, the samples were centrifuged at 1,500 rpm for 10 mins at room temperature, then washed twice in PBS and subjected to flow cytometry analysis. Three-color flow cytometry analysis was performed using FC500 (Beckman-Coulter) and CXP analysis software (Beckman-Coulter) to determine the cell phenotype. Lymphocytes are gated by forward scatter and side scatter. The analysis will collect 5,000 gated events.

Statistical methods

Continuous variables were expressed as mean±SD (standard deviation) and compared using a two-tailed unpaired Student's *t*-test; categorical variables were compared using χ^2 or Fisher analysis. The predictive performance of NLR was measured using the area under receiver operating characteristic (ROC) curve (AUC).²⁰ Survival analysis used the Kaplan and Meier methodology.²¹ A Cox proportional hazards regression approach²² was used for evaluating PFS and OS, which was the primary end-point. Univariate analysis of possible prognostic variables, using a factor at a time, followed by a multivariate model combining all factors. Results were reported as hazard ratio (HR) and 95% confidence interval (CI). HR >1 indicates an increase in risk relative to the reference category. A confidence interval that does not include a value of 1 indicates a statistical significance of 5% level. All statistical evaluations were performed using SPSS software (Statistical Package for the Social Science, version 15.0, SPSS Inc, Chicago, IL). Values of $P < 0.05$ were considered to be statistically significant in all analyses.

Results

Patients' characteristics

The 147 patients in this study were treated with immune checkpoint blockade including nivolumab and pembrolizumab. We then performed ROC curves analysis to stratify all patients into $NLR > 2.5$ ($n=88$) and $NLR \leq 2.5$ ($n=59$) groups according to the prognosis of patients with NSCLC. Characteristics of all patients are detailed in [Table 1](#). There were no significant differences in relevant baseline characteristics of age, gender, histologic subtypes, PD-1 antibodies, TMB, presence of EGFR/KRAS Mutations, No. prior lines of treatment, TNM stages, and site of metastasis between the two groups divided by NLR, as shown in [Table 1](#). There were significant differences in ECOG-PS status ($P=0.008$), smoking status ($P=0.024$), and expression of PD-L1 ($P=0.048$) between the two groups divided by NLR.

Survival analysis of patients with NSCLC with respect to NLR

In this study, we performed ROC analysis to confirm 2.5 as the cut-off value of NLR according to the survival of patients with NSCLC ([Figure 1](#)). After then, we performed survival analysis to identify the factors associated with prognosis of patients with NSCLC received PD-1 antibodies. The results showed that patients with $NLR \leq 2.5$ had significantly favorable OS

Table I Demographics and baseline characteristics of patients

Variable	All NSCLC patients (n=147)	NLR>2.5	NLR≤2.5	p
		(N=88)	(N=59)	
Age	57.6±10.6	58±10.3	56.3±11.2	0.318
Gender				0.191
Female	53	28	25	
Male	94	60	34	
ECOG-PS				0.008
0/1	80	40	40	
2	67	48	19	
Histologic subtype				0.471
Squamous	62	35	27	
Nonsquamous	85	53	32	
Smoking status				0.024
Minimal/never	56	27	29	
Current/former	91	61	30	
Patients receiving immunotherapy				0.181
Nivolumab	60	32	28	
Pembrolizumab	87	56	31	
PD-L1 staining				0.048
<1%	28	11	17	
1%-49%	42	25	17	
>50%	16	9	7	
Unknown	61	43	18	
Tumor mutational burden (mut/Mb)				0.567
TMB ≤10	73	42	31	
TMB >10	74	46	28	
Presence of EGFR/KRAS mutations				0.361
EGFR mutant/wild type	8/139	3/85	5/54	
KRAS mutant/wild type	12/135	7/81	5/54	
No. prior lines of treatment				0.426
0-1	94	54	40	
2+	53	34	19	
Chemotherapy regimens				0.651
Carboplatin plus pemetrexed	35	20	15	
Cisplatin plus pemetrexed	16	9	7	
Carboplatin plus gemcitabine	28	18	10	
Cisplatin plus gemcitabine	15	7	8	
Carboplatin plus paclitaxel	9	6	3	
TNM staging				0.861
III	61	36	25	
IV	86	52	34	
Site of metastasis				0.511
Liver	28	16	12	

(Continued)

Table 1 (Continued).

Variable	All NSCLC patients (n=147)	NLR>2.5	NLR≤2.5	p
		(N=88)	(N=59)	
Lung	33	15	18	
Peritoneum	17	11	6	
Others	21	13	8	

Note: Data are presented as n (%) or median (range). Statistically significant *P* values shown in bold.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD-I, programmed death I; PD-LI, programmed death ligand-I; NSCLC, non-small cell lung cancer; TMB, tumor mutational burden.

($P=0.009$, Figure 2A) and PFS ($P=0.017$, Figure 2B) compared with patients with $NLR>2.5$. Patients with $TMB>10$ had significantly favorable OS ($P=0.003$, Figure 2C) and PFS ($P=0.001$, Figure 2D) compared with patients with $TMB\leq 10$. After stratified with the variable of TMB, we further found that patients with $NLR\leq 2.5$ had significantly favorable OS ($P=0.003$, Figure 3A) and PFS ($P=0.001$, Figure 3B) compared with patients with $NLR>2.5$ in the group of patients with $TMB>10$, while in group patients with $TMB\leq 10$, patients with $NLR\leq 2.5$ had no significantly favorable OS ($P=0.251$, Figure 3C) and PFS ($P=0.325$, Figure 3D) compared with patients with $NLR>2.5$.

Predictors associated with clinical outcomes

Cox proportional hazards models were then used to quantify the prognostic significance of risk factors after multivariable

adjustment. A multivariable analysis was performed to assess the factors that demonstrated significant effects in univariate analysis. After adjusting for competing risk factors, $NLR\leq 2.5$ (HR: 2.165, 95% CI: 1.392–5.201, $P=0.012$), $TMB\leq 10$ (HR: 2.439, 95% CI: 1.243–5.493, $P=0.007$) and No. of sites metastasis (HR: 3.154, 95% CI: 1.229–6.593, $P=0.002$) remained independent predictors of PFS and OS. The details are shown in Figure 4.

Phenotypic analysis of peripheral blood immune cells

Phenotypic analysis of peripheral blood mononuclear cells before the treatment and at the end of the first cycle of therapy demonstrated that the $CD3^+$ and $CD8^+/CD28^+$ T cell subsets were significantly increased in patients with $NLR\leq 2.5$ ($P<0.05$), while the $CD8^+/CD28^-$ and $CD4^+/CD25^+$ cell subsets were significantly decreased in patients with $NLR\leq 2.5$ ($P<0.05$) (Figure 4). However, only $CD3^+$ T cell subsets were significantly increased in patients with $NLR>2.5$ ($P<0.05$) (Figure 5).

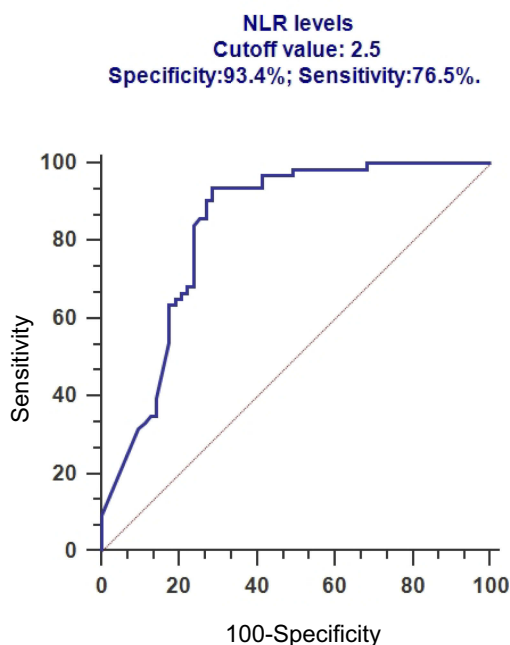


Figure 1 ROC analysis to confirm 2.5 as the cut-off value of NLR according to the survival of patients with NSCLC.

Treatment toxicity

Among both hematologic and nonhematologic adverse events, no significant differences were shown in various groups. Moreover, there were no significant differences in adverse events between the groups of patients with $NLR\leq 2.5$ and $NLR>2.5$, as shown in Table 2.

Discussion

Although PD-1 checkpoint inhibitors improved both OS and PFS for patients with NSCLC have been reported in several clinical trials,^{23,24} SQ-NSCLC and non-SQ-NSCLC showed differences in anti-PD-1 efficacy and response.²⁵ Compared with chemotherapy, ICBs demonstrated a delayed OS benefit but no statistically significant improvement in PFS for non-SQ-NSCLC. Moreover, treatment-related adverse events of

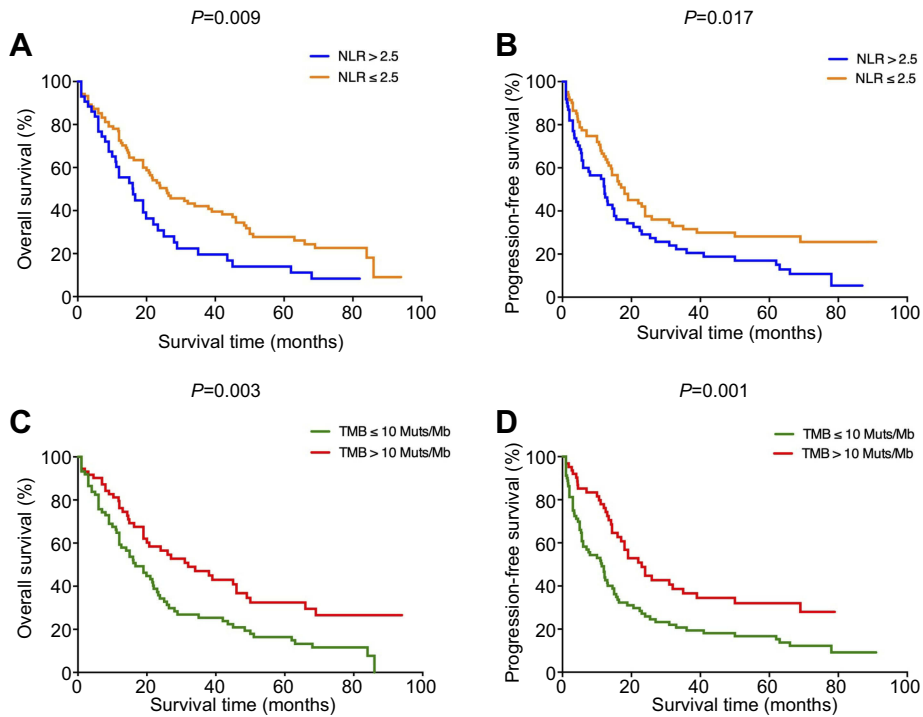


Figure 2 (A) Overall survival (OS) and (B) progression-free survival (PFS) for the different groups divided by NLR; (C) overall survival (OS) and (D) progression-free survival (PFS) for the different groups divided by TMB.

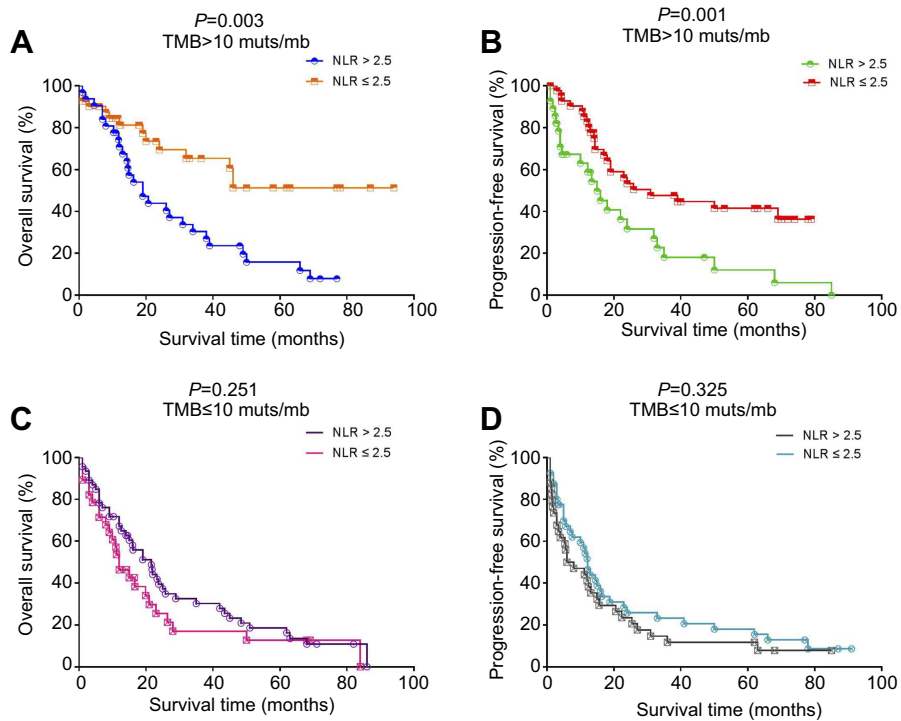


Figure 3 (A) Overall survival and (B) progression-free survival for patients with TMB>10 stratified by NLR; (C) overall survival and (D) progression-free survival for patients with TMB≤10 stratified by NLR.

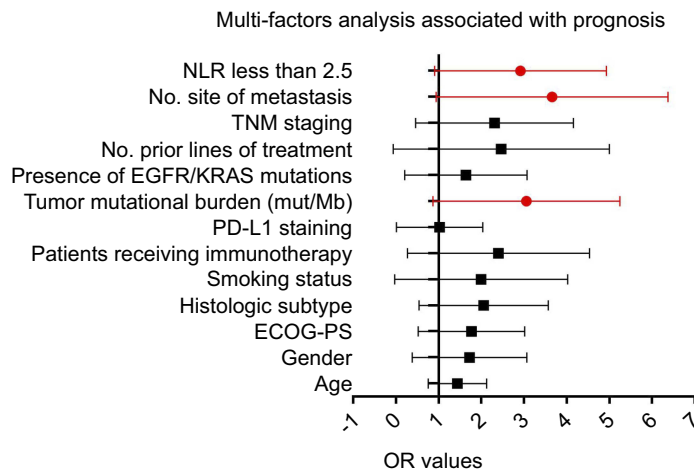


Figure 4 Cox proportional hazards models were used to quantify the prognostic significance of risk factors after multivariable adjustment.

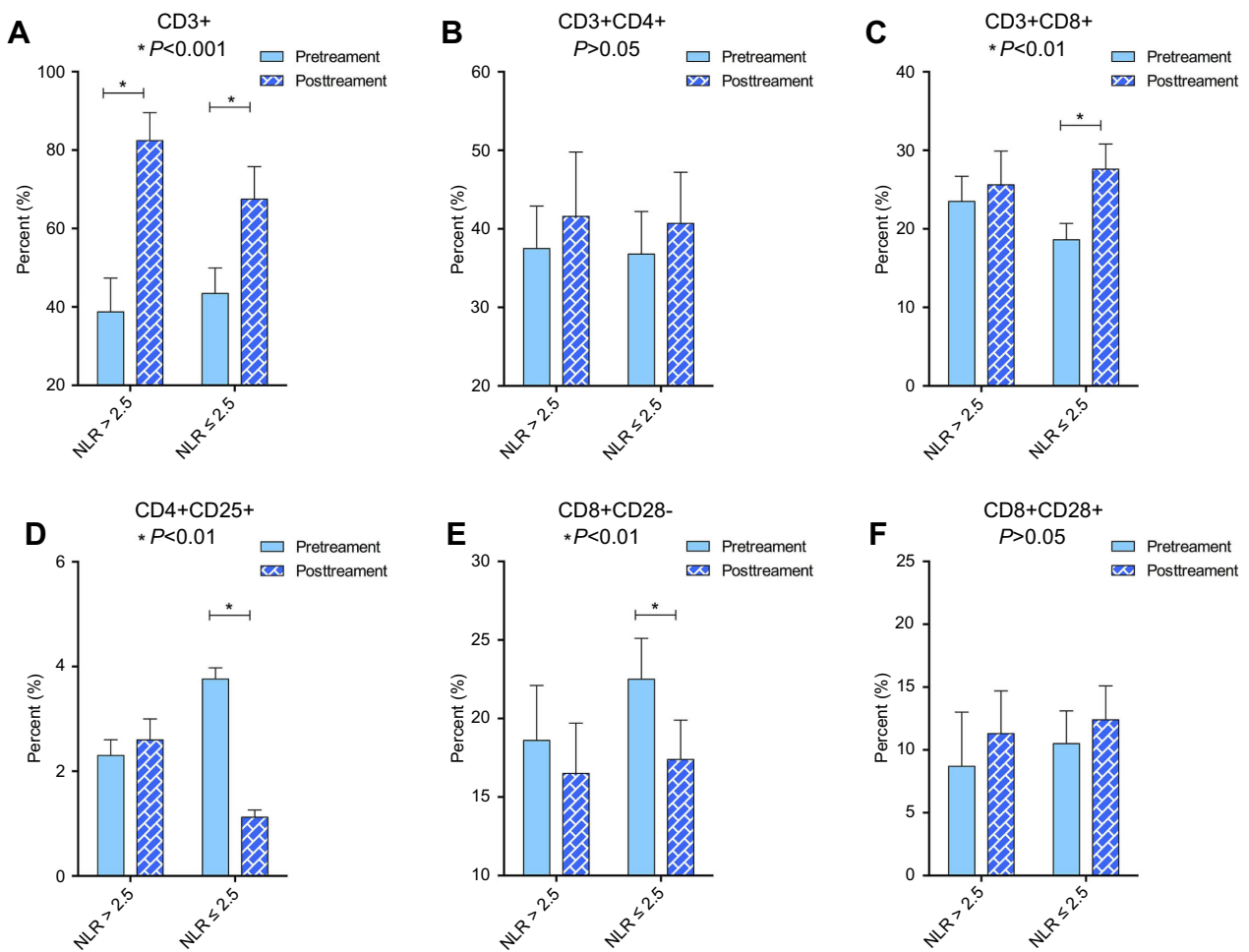


Figure 5 Peripheral blood T cell phenotype measurements via cytometry before and after treatment. **(A)** CD3+ T cell changed significantly in both groups; **(B)** CD3+CD4+ T cell did not change significantly; **(C)** CD3+CD8+ T cell changed significantly in group of NLR≤2.5; **(D)** CD4+CD25+ T cell changed significantly in group of NLR≤2.5; **(E)** CD8+CD28- T cell changed significantly in group of NLR≤2.5; **(F)** CD8+CD28+ T cell did not change significantly.

grade 3 or 4 were acceptable in the immunotherapy group compared with the chemotherapy group.^{26,27} ICBs plus chemotherapy are emerging as effective first-line treatment in

advanced NSCLC, but little is known about the magnitude of benefits and potential clinical predictors. pembrolizumab monotherapy has replaced chemotherapy as the first-line

Table 2 Hematological and nonhematologic adverse events

	NLR>2.5 (N=88)		NLR≤2.5 (N=59)	
	All grades, n (%)	Grade 3 or 4, n (%)	All grades, n (%)	Grade 3 or 4, n (%)
Leucopenia	12 (13.6%)	3 (3.4%)	8 (13.6%)	3 (5.1%)
Neutropenia	18 (20.1%)	0	7 (11.9%)	3 (5.1%)
Anemia	9 (10.2%)	3 (3.4%)	7 (11.9%)	3 (5.1%)
Thrombocytopenia	8 (9.1%)	0	8 (13.6%)	2 (3.4%)
Asthenia	10 (11.4%)	4 (4.5%)	8 (13.6%)	2 (3.4%)
Anorexia	9 (10.2%)	4 (4.5%)	8 (13.6%)	0
Nausea	9 (10.2%)	0	7 (11.9%)	2 (3.4%)
Vomiting	12 (13.6%)	0	7 (11.9%)	0
Diarrhea	12 (13.6%)	0	0	0
Fatigue	9 (10.2%)	0	0	0
Abdominal pain	0	0	0	0
Skin rash	0	0	3 (5.1%)	0
Hand-foot syndrome	3 (3.4%)	0	0	0
Pigmentation	4 (4.5%)	0	0	0
Stomatitis	2 (2.3%)	0	0	0
Lacrimation increased	8 (9.1%)	0	0	0
Tinnitus	2 (2.3%)	0	3 (5.1%)	0
ALT elevation	10 (11.4%)	2 (2.3%)	8 (13.6%)	0
AST elevation	5 (5.7%)	0	8 (13.6%)	0
Increased creatinine	2 (2.3%)	0	3 (5.1%)	0
Hyponatremia	4 (4.5%)	0	3 (5.1%)	0
Hypoalbuminemia	4 (4.5%)	0	7 (11.9%)	0

Note: Severity was graded according to National Cancer Institute Common Toxicity Criteria, version 4.0.

treatment for patients with PD-L1 tumor proportion score (TPS) of at least 50%,^{28,29} and pembrolizumab plus platinum and pemetrexed for those with nonsquamous histology irrespective of PD-L1 expression.^{30,31} Nevertheless, little is known about the magnitude of benefits and potential clinical predictors. Moreover, new data from anti-PD treatment clinical trials show that only about 15–25% of the NSCLC patients respond to immune checkpoint block therapy, and most patients have primary resistance.³²

This study showed that assessment of the NLR calculated from complete blood counts before treatments predicted survival of patients with advanced NSCLC independently. Patients with $NLR \leq 2.5$ had significantly favorable OS and PFS compared with patients with $NLR > 2.5$. After stratified with the variable of TMB, we further found that patients with $NLR \leq 2.5$ had significantly favorable OS and PFS compared with patients with $NLR > 2.5$ in the group of patients with $TMB > 10$, while in group patients with $TMB \leq 10$, patients with $NLR \leq 2.5$ had no significantly favorable OS and PFS compared with patients with $NLR > 2.5$. The result is consistent with previously published papers displaying that high NLR with

poor outcome in patients with lung cancer.^{33–35} Yet, the cutoff value of the NLR is inconsistent in these above studies, which reduces its clinical applicability. From our perspective, we believe that the impact of the NLR has been explored as a continuous explanatory variable, and it is affected by the patients baselines and therapeutic approaches. Various treatment prior to immunotherapy is an important factor in the oncologic outcome. In this study, patients receive chemotherapy including platinum, paclitaxel, gemcitabine, docetaxel, and so on. Consequently, we explored the pretreatment value of 2.5 as the most appropriate cutoff, not only the statistical sensitivity and specificity were taken into account but also the clinical significance. Our data indicated that the median OS of patients in $NLR > 2.5$ group was much shorter when compared with those in $NLR \leq 2.5$ group.

The mechanism underlying the potential prognostic value of NLR is mainly due to the significance of the infiltrated neutrophils and lymphocytes. The systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which benefits cancer progression via secreting interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-10 (IL-10),

tumor necrosis factor α (TNF- α), and vascular endothelial growth factor (VEGF).³⁶ VEGF is a proangiogenic factor contributes to cancer development especially through angiogenesis. Moreover, increased TNF- α and IL-10 issue in lymphocyte count decrease and lymphocyte dysfunction also. It is well known that lymphocyte depletion is likely reflection of an impaired T-lymphocyte-mediated antitumor response, which represents an adverse prognostic trait. In general, the relative ratio of elevated neutrophils and decreased lymphocytes could be a scientific marker for evaluating the systemic inflammatory response and outcome of individuals. And so, NLR is valuable as a potential indicator of prognosis to some degree.

By the way, this study is in small size and retrospective design. On the other hand, the relationship between survival and change of NLR after treatment apart from pretreatment can be investigated in future studies.

Conclusion

A high NLR value independently predicts poor survival in advanced NSCLC patients received ICB. The NLR may help oncologists evaluate outcomes of patients received immunotherapy and choose alternative therapies for patients with high NLR value.

Disclosure

The authors who have taken part in this study declared that they have nothing to disclose regarding funding or conflict of interest with respect to this manuscript.

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