Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios are associated with the efficacy of immunotherapy in stage III/IV non-small cell lung cancer

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Received April 2, 2022; Accepted June 1, 2022

DOI: 10.3892/ol.2022.13386

Abstract. Peripheral serological indicators are novel markers associated with prognosis in multiple malignant tumors. In the present study, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) were selected to construct a model that predicts long-term survival of patients with stage IIIB-IV non-small cell lung cancer (NSCLC) who received treatment with an anti-programmed cell death protein-1 (PD-1) monoclonal antibody. A total of 133 patients were eligible for the present retrospective study (January 2019-February 2021). The area under the receiver operating characteristic curve was used to compare the diagnostic value of PLR and NLR, and combined PLR and NLR. The objective response rate and disease control rate of each group were obtained and the differences were compared using the χ^2 test. The prognostic value of these indicators was assessed using the Kaplan-Meier method. Cox regression analysis was used to evaluate risk factors associated with long-term survival. Statistically significant parameters were included in the nomogram. Based on the median PLR and NLR values, the patients were divided into high PLR (H-PLR) (PLR >200.00, 67 patients) and low PLR (L-PLR) (PLR ≤200.00, 66 patients), and high NLR (H-NLR) (NLR >3.56, 65 patients) and low NLR (L-NLR) (NLR ≤3.56, 68 patients) groups. Immune-related adverse events (irAEs) occurred in 22 patients (16.5%) during the observation period, including 18 grade 2-3 irAEs and 4 grade 4 cases. H-NLR and H-PLR were associated with poor progression-free (PFS) and overall survival (OS) in the present study. NLR was an independent prognostic factor for PFS [hazard ratio (HR): 0.201, 95% confidence interval (CI): 0.060-0.670; P=0.009) and OS (HR: 0.413, 95% CI: 0.226-0.754; P=0.004) in this patient group. Therefore, NLR may be used in the prognostication of patients with stage IIIB-IV NSCLC treated with PD-1 inhibitors. These serological markers may be used in combination with established immunomarkers to help predict outcomes.

Introduction

Global cancer statistics in 2020 revealed that there were 2.22 million new diagnoses of lung cancer (LC), with a corresponding death rate of ~1.8 million worldwide (1) Non-small cell LC (NSCLC) accounts for up to 85% of all cases of LC and is a serious health risk; notably, ~60% of these patients are diagnosed with locally advanced NSCLC and the current standard of care is radiotherapy-based combination therapy (2). The survival rate of patients following treatment with standard regimens has improved but still remains unsatisfactory (3). Immune checkpoint inhibitors (ICIs) are a relatively novel approach to the treatment of NSCLC. The increased use of immunotherapy has elevated 5-year survival rates in patients with NSCLC from 5 to 26% (4). Anti-programmed cell death protein-1 (PD-1) monotherapy is currently the most used immunotherapy for the treatment of malignant tumors (5). In addition, programmed death ligand-1 (PD-L1) is considered the best predictive biomarker for anti-PD-1 treatment (6,7). Nevertheless, PD-L1 assessments are associated with challenges that include equipment that may yield inconsistent findings, high fluctuation in detectable levels, tumor heterogeneity, puncture biopsy limitations and high testing costs (8).

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Abbreviations: PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; PD-1, programmed death protein-1; PD-L1, programmed death-ligand 1; ECOG, Eastern Cooperative Oncology Group; TMB, tumor mutation burden; TILs, tumor-infiltrating lymphocytes; ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; PFS, progression-free survival; OS, overall survival

Key words: NSCLC, immunotherapy, inflammatory indicators, PLR, NLR, PD-1, PD-L1

Tumor mutation burden (TMB) may predict immunotherapy outcomes (9). Results from phase III clinical trials that included patients with advanced NSCLC with high TMB revealed a better objective response rate (ORR; 47 vs. 28%) and median progression-free survival (PFS; 9.7 vs. 5.8 months) following treatment with nivolumab compared with after chemotherapy (10). In 2017, microsatellite instability and mismatch repair defects were proposed as immunomarkers associated with prognosis in colorectal and endometrial cancer; however, their value in NSCLC remains unclear due to their low expression levels in this disease (11). Tumor-infiltrating lymphocytes (TILs) at high density may recognize tumor cells and increase their sensitivity to checkpoint inhibition. In patients with advanced NSCLC (n=366) receiving nivolumab or pembrolizumab, mesenchymal TILs had the greatest impact on long-term survival and their levels were better predictors of outcomes than PD-L1 levels (12). An increase in TIL levels during treatment may help predict clinical and radiological response; however, more clinical studies are needed to confirm these findings. Patients with various genetic mutations respond differently to immunotherapy (13). It has been shown that patients with epidermal growth factor receptor (EGFR) mutations respond poorly to immunotherapy (14). However, patients with KRAS mutations tend to a have high (>50%) probability of PD-L1 expression, high density of active TILs and relatively high TMB values, which are associated with clinical benefit (15). Although the use of these immunomarkers is recommended by applicable clinical guidelines, they are cumbersome and expensive to obtain, suggesting a need for biomarkers that are straightforward and cost-effective, and which may help improve outcomes by allowing for accurate screening of patients most likely to benefit from a particular treatment.

Recently, new host-related biomarkers have gained attention, including lactic dehydrogenase levels (8), intestinal microecology profiles (16,17) and peripheral serological indicators (18), which may help prognosticate multisystem malignancies, including NSCLC, and help assess antitumor immune response. Peripheral serological indicators are novel tumor markers associated with prognosis in multiple malignant tumors, which have been used as biomarkers to predict the efficacy of ICIs in gastric cancer (19) and malignant melanoma (20). However, to the best of our knowledge, no studies have comprehensively investigated the role of serologically based inflammatory indicators in patients with stage IIIB-IV NSCLC undergoing PD-1 immunotherapy. Considering clinical applicability, only two inflammatory indexes, PLR and NLR, were examined in the present study.

Materials and methods

Patient selection. A total of 133 patients admitted to the Department of Respiratory Medicine and Oncology of The First Affiliated Hospital of Gannan Medical College (Ganzhou, China) between January 2019 and February 2021 were selected for the present study. Inclusion criteria were as follows: i) Histologically or cytologically confirmed diagnosis of NSCLC; ii) stage IIIB-IV NSCLC, with at least one measurable lesion, based on imaging findings and the 8th edition of the TNM staging criteria customized by the International Association for the Study of Lung Cancer (21); iii) treatment with a first-line PD-1 monoclonal antibody; iv) complete serological indicator data obtained within 1 week prior to receiving PD-1 monotherapy; v) receiving at least four cycles of PD-1 monotherapy; vi) age ≥18 years; vii) complete clinicopathological and follow-up information available. Patients with the following characteristics were excluded: i) Infectious or inflammatory disease within 4 weeks prior to admission; ii) recent history of antibiotic or hormone treatment; iii) autoimmune disease or hematologic cancer; iv) bone marrow suppression of grade II or higher 1 week prior to treatment with a PD-1 monoclonal antibody.

The Institutional Research Board of The First Affiliated Hospital of Gannan Medical College waived the requirement for informed consent for the present study because it involved only the analysis of an existing dataset and not the collection of data related to the intervention.

Clinical features. Data on the following characteristics were extracted from medical records: Sex, age, pathology type, disease stage, distant metastasis site, brain metastasis status, bone metastasis status, liver metastasis status, PD-L1 expression level, the Eastern Cooperative Oncology Group Performance (ECOG) score (22), driver gene mutation status, immunotherapy type, PLR values, NLR values, immunotherapy regimen (monotherapy or combination therapy) and immune-related adverse event (irAE) incidence. Data on serological indicators were obtained from routine blood tests performed within 1 week before the start of anti-PD-1 immunotherapy.

Efficacy evaluation. After four to six cycles of treatment, curative effect was evaluated by imaging examinations based on the Immune-Modified Response Evaluation Criteria In Solid Tumors (23). Complete remission (CR) was confirmed when all lesions disappeared, tumor markers returned to normal levels for 4 weeks and no new lesions appeared. Partial response (PR) was confirmed when the sum of the maximum diameter of the tumor was reduced by >30% from baseline and maintained at this value for 4 weeks, while some non-target lesions remained, and tumor markers did or did not return to normal levels. Immunity unconfirmed progressive disease (PD) was defined as an increase in the original lesion size of >20% or appearance of new lesions, and its efficacy needed to be evaluated after at least 4 weeks of treatment. Confirmed disease progression immunity confirmed PD was performed to confirm progress at least 4 weeks later. Patients who did not achieve PR and did not present with evidence indicative of PD were classified as having stable disease (SD). ORR was calculated as follows: ORR (%)=(CR + PR)/(CR +PR + SD + PD) x 100. Disease control rate (DCR) was calculated as follows: DCR (%)=(CR + PR + SD)/(CR +PR + SD + PD) x 100. PFS was measured from the start of drug administration to the point of any signs of disease progression, or death from any cause or the end of the observation period, whichever occurred first. Overall survival (OS) was measured from the start of immunotherapy to death or study end, whichever occurred first. Side effects were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0 grading scale (score 1-5) (24).

Statistical analysis. Comparison of qualitative information between the two groups was performed using the χ^2 test or Fisher's exact probability method. NLR and PLR values were used to draw receiver operating characteristic (ROC) curves and calculate the area under the curve (AUC) to evaluate the prognostic sensitivity and specificity of parameters. Univariate and multivariate analyses were performed using logistic regression models to identify independent factors associated with irAEs. The Kaplan-Meier method was used to evaluate any relationships between these parameters and PFS and OS rates, and the log-rank method was chosen to test for differences between groups. Univariate analysis was used to identify prognostic factors associated with outcomes. Variables that were statistically significant in univariate analyses were included in multivariate Cox regression models. Finally, nomograms were drawn based on the results of multivariate regression analysis, and the predictive accuracy of the model was evaluated. All analyses were performed in GraphPad Prism 8.0.1 (GraphPad Software, Inc.) and R v.3.0.2 (R Project for Statistical Computing; www.r-project.org). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The median follow-up time was 15.7 (range, 8.93-43.77) months. A total of 85.0% of the patients were male (overall mean age, 58.80±0.896 years). A total of 97.0% of the patients had an ECOG score of 0-1 points. The distribution of genetic mutations was as follows: 79.7, and 12.8 and 7.5% patients had no genetic mutations or lacked data on mutations, had EGFR mutations or had ALK/ROS1 mutations, respectively. In addition, 13.6% of the patients were positive for PD-L1 expression. Moreover, 81.2% of the patients had distant metastases, including liver (15.0%), brain (18.0%) and bone (44.4%) metastases (Table I).

ROC curves for PLR, NLR. PLR and NLR values were calculated. Cut-off values of 200.00 and 3.56 for PLR and NLR, respectively, were determined based on the median values. PLR, NLR, and combined PLR and NLR all revealed some prognostic value based on the ROC curve (Fig. 1). The AUC for NLR [0.77; 95% confidence interval (CI), 0.70-0.85; P<0.0001] was higher than that for PLR (0.68; 95% CI, 0.59-0.77; P=0.0004) and the combined PLR and NLR (0.71; 95% CI, 0.62-0.80; P<0.0001).

Relationship between PLR, NLR and recent outcomes. DCR values were 68.66 and 66.67% (P=0.76) and ORR values were 23.88 and 21.21% in the high-PLR (H-PLR) and low-PLR (L-PLR) groups, respectively (P=0.61). Disease control rates (P>0.99) and ORR (P=0.17) were comparable in the high-NLR (H-NLR) and low-NLR (L-NLR) groups (Table II). In conclusion, the levels of PLR and NLR did not correlate with DCR and ORR.

Clinicopathological factors associated with irAEs. During the treatment period, 16.5% of the patients experienced irAEs such as immune-associated pneumonia, hypoadrenocorticism, immune-associated pituitary inflammation, drug rash, immune-associated myocarditis and immune-related hepatitis. The results of univariate analysis showed P<0.1 for age, immunotherapy modality and PD-L1 expression, but were not significant. The results of the calibrated multifactorial analysis revealed a trend whereby outcomes were linked with age [adjusted OR (aOR), 0.327; 95% CI, 0.105-1.016; P=0.053] and immunotherapy modality (aOR, 0.348; 95% CI, 0.113-1.071; P=0.066) (Table III).

Relationship between PLR, NLR and long-term outcomes. The results of Kaplan-Meier survival analysis showed a significant advantage of the L-PLR group over the H-PLR group for both PFS and OS m[edian PFS (mPFS): 8.33 vs. 6.37 months, P=0.02; median OS (mOS): 26.33 vs. 13.47 months, P=0.02] (Fig. 2A and B). Similarly, PFS and OS differed between the L-NLR and H-NLR groups (mPFS: 9.17 vs. 5.73 months, P=0.004; mOS: 26.33 vs. 12.03 months, P<0.001) (Fig. 2C and D). Overall, lower PLR and NLR values at the start of immunotherapy were associated with improved outcomes in this patient group.

From the start of the study until October 31, 2021, a total of 101 patients experienced disease progression, and 64 patients died. The results of the univariate analyses suggested that an ECOG score of 0-1 [hazard ratio (HR), 0.194; 95% CI, 0.060-0.628; P=0.006], absence of driver mutations (HR, 0.536; 95% CI, 0.335-0.859; P=0.009), number of metastatic sites <3 (HR, 0.595; 95% CI, 0.401-0.883; P=0.010), L-PLR (HR, 0.632; 95% CI, 0.426-0.940; P=0.023) and L-NLR (HR, 0.565; 95% CI, 0.380-0.841; P=0.005) reduced the risk of near-term progression in the patients (Table IV). In univariate analysis, the ECOG score did not affect OS, but the absence of liver metastases (HR, 0.573; 95% CI, 0.310-1.059; P=0.076) reduced the risk of death in the patients, although this was not significant. Other protective factors for OS included negative driver mutations (HR, 0.479; 95% CI, 0.279-0.821; P=0.007), number of metastatic sites <3 (HR, 0.589; 95% CI, 0.360-0.964; P=0.035), L-PLR (HR, 0.550; 95% CI, 0.329-0.919; P=0.022) and L-NLR (HR, 0.336; 95% CI, 0.197-0.571; P<0.001) (Table V). A calibrated multifactorial analysis showed that the ECOG score (HR, 0.613; 95% CI, 0.376-0.999; P=0.049) and number of metastatic sites (HR, 0.627; 95% CI, 0.418-0.940; P=0.024) were associated with the estimated PFS (Table IV), whereas NLR was an independent prognostic factor for PFS (HR, 0.201; 95% CI, 0.060-0.670; P=0.009) and OS (HR, 0.413; 95% CI, 0.226-0.754; P=0.004) in patients with advanced NSCLC receiving immunotherapy (Tables IV and V).

Nomogram for OS. The present study used variables that exhibited a trend towards significant differences in the univariate analyses (P<0.1) to construct a nomogram model for predicting patient survival at 6, 12 and 18 months (Fig. 3). Nomograms can provide oncologists with a simple and effective tool to predict the prognosis of their patients. To use the column line plot, a straight line was plotted from the variables NLR (≤3.56), PLR (≤200), number of metastatic sites (≥3), driver gene mutation status (negative) and liver metastasis (positive) to obtain the corresponding points 0, 0, 25, 0 and 50. All values were then summed to obtain an overall score of 75. A patient survival rate of 85% was derived at 6 months, the 12-month survival rate was 68% and the 18-month survival rate was 55%. An

Table I. Baseline clinical characteristics of patients with NSCLC treated with PD-1 inhibitors.

Clinical characteristic	Overall number (%)	H-PLR, n (%)	L-PLR, n (%)	P-value	H-NLR, n (%)	L-NLR, n (%)	P-value
Total	133	67	66		65	68	
Sex				0.971			0.707
Male	113 (85.0)	57 (85.1)	56 (84.8)		56 (86.2)	57 (83.8)	
Female	20 (15.0)	10 (14.9)	10 (15.2)		9 (13.8)	11 (16.2)	
Age, years				0.925			0.528
≤60	72 (54.1)	36 (53.7)	36 (54.5)		37 (56.9)	35 (51.5)	
>60	61 (45.9)	31 (46.3)	30 (45.5)		28 (43.1)	33 (48.5)	
ECOG				>0.999			0.358
0-1	129 (97.0)	65 (97.0)	64 (97.0)		62 (95.4)	67 (98.5)	
2	4 (3.0)	2 (3.0)	2 (3.0)		3 (4.6)	1 (1.5)	
History				0.763			0.059
LUAD	72 (54.1)	36 (53.7)	36 (54.5)		38 (58.5)	34 (50.0)	
LUSC	57 (42.9)	28 (41.8)	29 (43.9)		25 (38.5)	32 (47.0)	
Others	4 (3.0)	3 (4.5)	1 (1.6)		2 (3.0)	2 (3.0)	
Stage				0.479			0.923
IIIB	25 (18.8)	11 (16.4)	14 (21.2)		12 (18.5)	13 (19.1)	
IV	108 (81.2)	56 (85.6)	52 (78.8)		53 (81.5)	55 (80.9)	
Genetic mutations				0.586			0.063
Negative/not tested	106 (79.7)	51 (76.1)	55 (83.3)		47 (72.3)	59 (86.8)	
EGFR(+)	17 (12.8)	10 (14.9)	7 (10.6)		10 (15.4)	7 (10.3)	
ALK/ROS1(+)	10 (7.5)	6 (9.0)	4 (6.1)		8 (12.3)	2 (2.9)	
Numbers of metastatic sites				0.939			0.020[a]
<3	75 (56.4)	38 (56.7)	37 (56.1)		30 (46.2)	45 (66.2)	
≥3	58 (43.6)	29 (43.3)	29 (43.9)		35 (53.8)	23 (33.8)	
Liver metastasis				0.602			0.913
No	113 (85.0)	58 (86.6)	55 (83.3)		55 (84.6)	58 (85.3)	
Yes	20 (15.0)	9 (13.4)	11 (16.7)		10 (15.4)	10 (14.7)	
CNS metastasis				0.682			0.140
No	109 (82.0)	54 (80.6)	55 (83.3)		50 (76.9)	59 (86.8)	
Yes	24 (18.0)	13 (19.4)	11 (16.7)		15 (23.1)	9 (13.2)	
Bone metastasis				0.426			0.071
No	74 (55.6)	35 (52.2)	39 (59.1)		31 (47.7)	43 (63.2)	
Yes	59 (44.4)	32 (47.8)	27 (40.9)		34 (52.3)	25 (36.8)	
Line of therapy				0.714			0.647
1	73 (54.8)	36 (53.7)	37 (56.1)		33 (50.8)	40 (58.8)	
2	30 (22.6)	17 (25.4)	13 (19.7)		16 (24.6)	14 (20.6)	
≥3	30 (22.6)	14 (20.9)	16 (24.2)		16 (24.6)	14 (20.6)	
PD-L1				0.072			0.564
Negative/not tested	115 (86.4)	55 (82.1)	60 (90.9)		55 (84.6)	60 (88.2)	
1-49%	9 (6.8)	4 (6.0)	5 (7.6)		4 (6.2)	5 (7.4)	
≥50%	9 (6.8)	8 (11.9)	1 (1.5)		6 (9.2)	3 (4.4)	
Regimen				0.800			0.727
Combination therapy	102 (76.7)	52 (77.6)	50 (75.8)		49 (75.4)	53 (77.9)	
Monotherapy	31 (23.3)	15 (22.4)	16 (24.2)		16 (24.6)	15 (22.1)	
Immunotherapy drug				0.265			0.874
Pembrolizumab	14 (10.5)	11 (16.4)	3 (4.6)		9 (13.8)	5 (7.4)	
Camrelizumab	27 (20.3)	14 (20.9)	13 (19.7)		13 (20.0)	14 (20.6)	
Sintilimab	63 (47.4)	27 (40.3)	36 (54.5)		29 (44.6)	34 (50.0)	

Table I. Continued.

Clinical characteristic	Overall number (%)	H-PLR, n (%)	L-PLR, n (%)	P-value	H-NLR, n (%)	L-NLR, n (%)	P-value
Tislelizumab	19 (14.2)	10 (14.9)	9 (13.6)		10 (15.4)	9 (13.2)	
Toripalimab	5 (3.8)	3 (4.5)	2 (3.0)		2 (3.1)	3 (4.4)	
Nivolumab	5 (3.8)	2 (3.0)	3 (4.6)		2 (3.1)	3 (4.4)	
irAEs				0.619			0.726
No	111 (83.5)	57 (85.1)	54 (81.8)		55 (84.6)	56 (82.4)	
Yes	22 (16.5)	10 (14.9)	12 (18.2)	0.096	10 (15.4)	12 (17.6)	0.565
Grade							
2-3	18 (81.8)	10 (14.9)	8 (12.1)		9 (13.8)	9 (13.2)	
4	4 (18.2)	0 (0.0)	4 (6.1)		1 (1.5)	3 (4.4)	

[a]P<0.05. NSCLC, non-small cell lung cancer; PD-1, programmed death 1; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; CNS, central nervous system; PD-L1, programmed death-ligand 1; irAEs, immune-related adverse events; NLR, neutrophil-lymphocyte ratio; PLR, platelet to lymphocyte ratio; H-, high; L-, low.

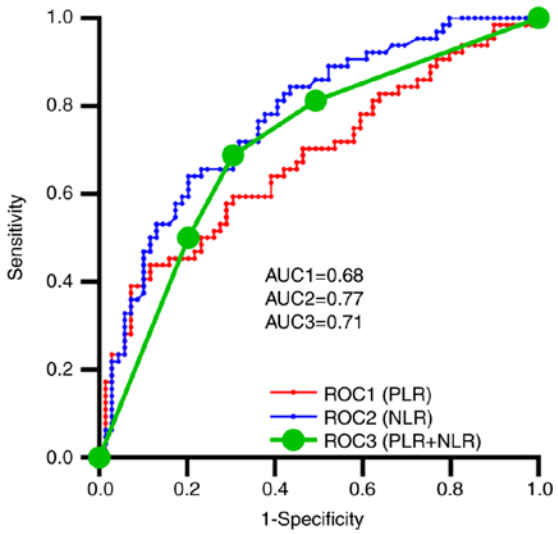

Figure 1. ROC curves for PLR, NLR, and PLR combined with NLR with AUC values of 0.68 (95% CI, 0.59-0.77; P=0.0004), 0.77 (95% CI, 0.70-0.85; P<0.0001) and 0.71 (95% CI, 0.62-0.80; P<0.0001), respectively. AUC, area under the curve; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ROC, receiver operating characteristic.

external calibration curve was then plotted, revealing the best agreement between the predicted and observed survival probabilities at 18 months (Fig. 4). The C-index value (Dxy/2 + 0.5 using R) was 0.696 (95% CI, 0.602-0.790), which indicated low predictive value of the model. Notably, when the actual incidence of OS at 18 months in patients was between 30 and 70%, the prediction model underestimated the probability of its occurrence; this is likely to result in lower patient survival without the use of immunotherapy.

Discussion

LC is the leading type of cancer in terms of global incidence and mortality (25). The cause of LC remains unclear, and has been related to factors such as smoking, air pollution, occupational carcinogenic factors, diet and genetics. Multidisciplinary treatment is advocated for LC. Between 30 and 40% of patients with NSCLC present with advanced disease at the time of diagnosis, and treatment mainly involves a combination of radiotherapy and chemotherapy (26). The decline in LC mortality in recent years may be linked to the decline in smoking rates and novel treatment options (27). Although molecular therapy has improved outcomes in this patient group, it has been associated with drug resistance. In 2015, the United States Food and Drug Administration approved the first PD-1 inhibitor, nivolumab, as a second-line treatment for patients with advanced NSCLC whose disease has progressed or who had previously received chemotherapy. Subsequently, treatment of NSCLC has shifted to immunotherapy, which has increased the 5-year survival rates of patients from 5 to 26% globally (28). However, challenges associated with immunotherapy remain, including effective screening of eligible patients, in a manner that reduces the risk of immunotherapy resistance, diagnosis and treatment of irAEs, and optimal timing of immunotherapy. Further studies are required to establish an evidence base that responds to these challenges.

PLR accounts for platelet and lymphocyte levels. Once tumor cells enter the bloodstream, platelets aggregate on the surface of tumor cells, forming platelet-tumor cell aggregates, thus protecting tumor cells from the immune cells in the body. Platelets also promote tumor endothelial cell blockage, protecting the circulating tumor cells from the effects of stress (29). Lymphocytes, as important immune cells, serve a role in the metastasis and infiltration of tumors. Asher *et al* (30) reported that PLR was an independent prognostic marker in patients with ovarian cancer and revealed that higher PLR values were associated with poorer prognosis. Qu *et al* (31) demonstrated that NLR and PLR could be used as predictors of near-term outcome in patients with advanced gastric cancer receiving immunotherapy. In addition, Song *et al* (32) evaluated 389 patients receiving concurrent radiotherapy, and revealed that higher NLR and PLR values were associated

Table II. Relationship between PLR, NLR and recent outcomes.

	PLR			NLR		
Groups	H-PLR	L-PLR	P-value	H-NLR	L-NLR	P-value
Efficacy evaluation			0.93			0.49
CR	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	
PR	16 (23.88)	14 (21.21)		12 (18.46)	18 (26.47)	
SD	30 (44.78)	30 (45.45)		32 (49.23)	28 (41.18)	
PD	21 (31.34)	22 (33.34)		21 (32.31)	22 (32.35)	
ORR (CR + PR)			0.61			0.17
Yes	16 (23.88)	14 (21.21)		12 (18.46)	18 (26.47)	
No	51 (76.12)	52 (78.79)		53 (81.46)	50 (73.53)	
DCR (CR + PR + SD)			0.76			>0.99
Yes	46 (68.66)	44 (66.67)		44 (67.69)	46 (67.65)	
No	21 (31.34)	22 (33.33)		21 (32.31)	22 (32.35)	

NLR, neutrophil-lymphocyte ratio; PLR, platelet to lymphocyte ratio; H-, high; L-, low CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

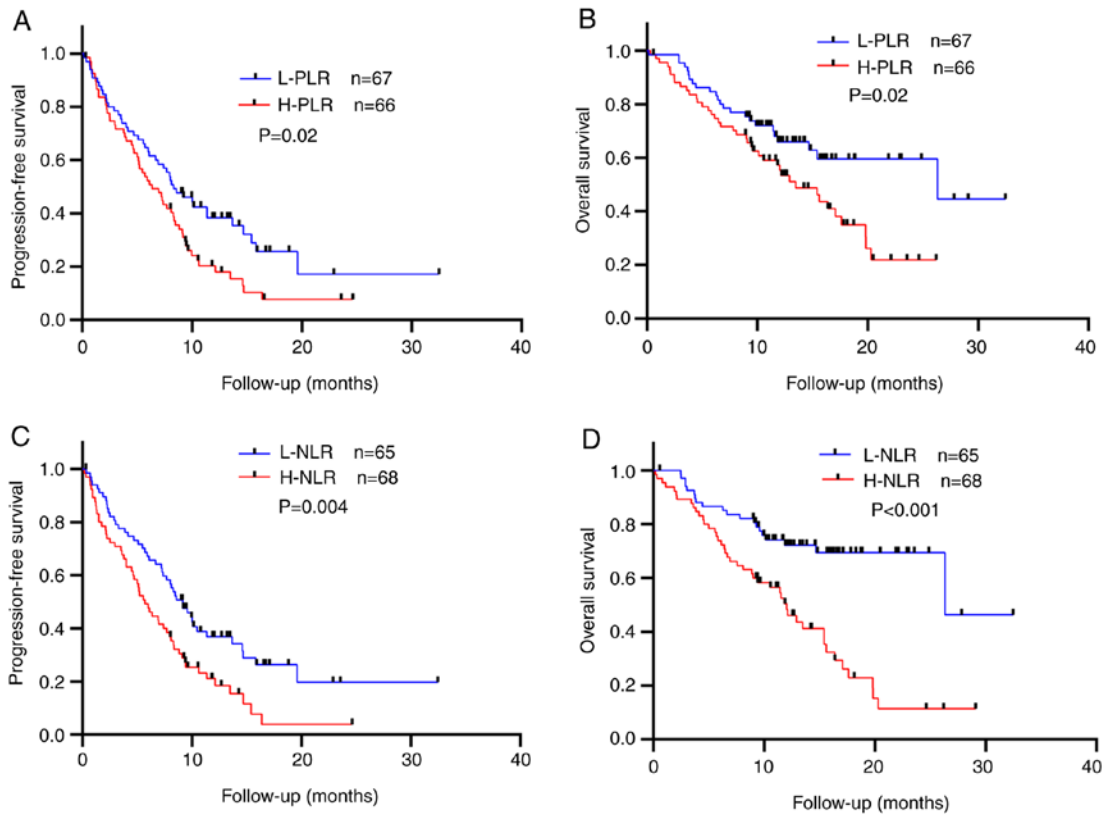

Figure 2. Kaplan-Meier analysis of PFS and OS. (A) Relationship between PLR and PFS in patients with NSCLC. (B) Relationship between PLR and OS in patients with NSCLC. (C) Relationship between NLR and PFS in patients with NSCLC. (D) Relationship between NLR and OS in patients with NSCLC. H-, high; L-, low; NLR, neutrophil-lymphocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PLR, platelet-lymphocyte ratio.

with poorer mOS estimates (NLR: 14.13 vs. 23.8 months, P<0.001; PLR: 15.49 vs. 22.04 months, P<0.001). The present study demonstrated that H-PLR values were associated with poorer PFS and OS estimates, with median values of 6.37 and 8.33 months, and 13.47 and 23.66 months in the H-PLR and L-PLR groups, respectively.

As determined by univariate analysis, PLR values were associated with PFS and OS estimates; however, these

Table III. Logistic analysis of clinical factors for immune-related adverse events in 133 patients with non-small cell lung cancer.

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Sex (male vs. female)	1.485 (0.314-7.020)	0.618		
Age (≤65 vs. >65 years)	0.276 (0.021-0.276)	0.021[a]	0.327 (0.105-1.016)	0.053[b]
Stage (IIIB-IIIC vs. IV)	0.845 (0.225-3.177)	0.804		
Genetic mutations (yes vs. no)	0.875 (0.263-2.909)	0.828		
PD-L1 (yes vs. no)	0.371 (0.123-1.117)	0.078[b]	0.395 (0.119-1.307)	0.128
Number of metastatic sites (<3 vs. ≥3)	2.223 (0.744-6.641)	0.153		
Liver metastasis (yes vs. no)	1.485 (0.314-7.020)	0.618		
CNS metastasis (yes vs. no)	4.250 (0.537-33.610)	0.170		
Bone metastasis (yes vs. no)	1.297 (0.469-3.584)	0.616		
Line of therapy (1 vs. ≥2)	1.770 (0.622-5.040)	0.285		
Regimen (combination therapy vs. monotherapy)	0.393 (0.137-1.125)	0.082[b]	0.348 (0.113-1.071)	0.066[b]
PLR (high vs. low)	1.018 (0.377-2.748)	0.973		
NLR (high vs. low)	1.228 (0.452-3.336)	0.686		

[a]P<0.05, [b]P<0.1. CNS, central nervous system; PD-L1, programmed death-ligand 1; OR, odds ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet to lymphocyte ratio; ORR, objective response rate.

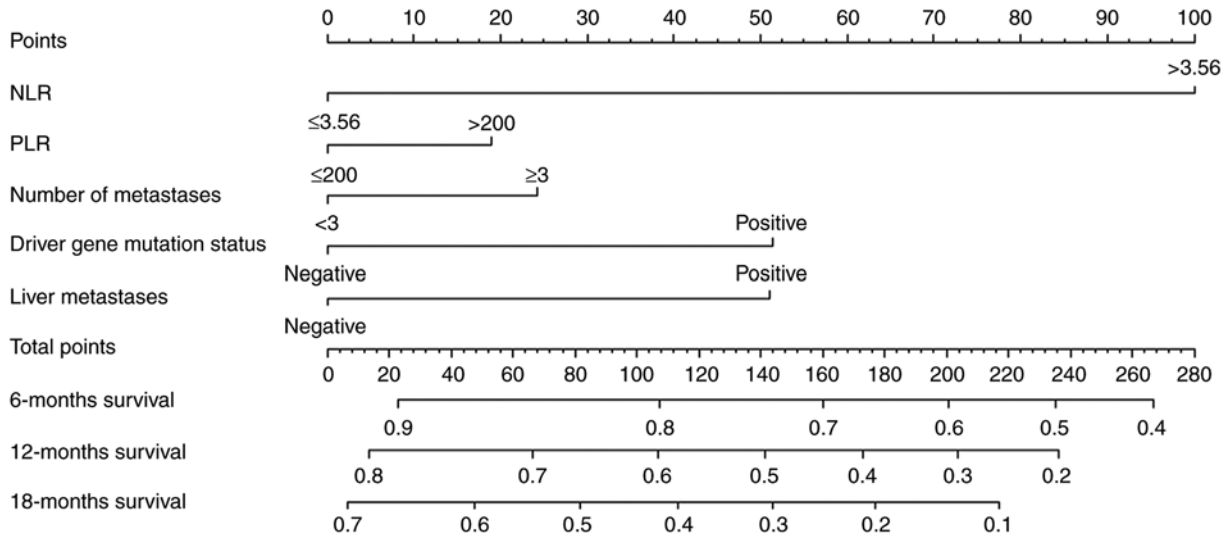

Figure 3. A nomogram for 6-, 12- and 18-month OS for patients with non-small cell lung cancer. Nomogram can be interpreted by adding up the points assigned to each variable according to line length. The total points score presented at the bottom scale represents the probability of 6-, 12- or 18-month OS. NLR, neutrophil-lymphocyte ratio; OS, overall survival; PLR, platelet-lymphocyte ratio.

associations were not observed in multivariate analysis; this finding is consistent with those of previous studies (30,32). Notably, Raungkaewmanee *et al* (33) showed no correlation between PLR values and ovarian cancer prognosis. Similarly, Zhao *et al* (34) identified no correlation between PLR values and OS estimates in ovarian cancer. These discrepancies among studies may be due to the different cut-off values used. The present study used the median to determine the cut-off value of PLR. Future studies should aim to standardize the approach to cut-off value determination when assessing the prognostic role of various inflammatory markers. Other factors that may account for among-study discrepancies include sample size, treatment regimen and tumor heterogeneity.

NLR accounts for neutrophil and lymphocyte levels. Circulating neutrophils promote tumor growth and metastasis through tumor inflammatory mediators (arginine and nitric oxide). NLR values have been shown to have prognostic relevance in various types of cancer, including NSCLC (35), esophageal cancer (32) and pelvic malignancies (36). In the present study, higher NLR values were associated with poorer PFS (mPFS, 5.73 vs. 9.17 months) and OS (mOS, 12.03 vs. 26.33 months) in the H-NLR group compared with in the L-NLR group. These estimates were higher than

Table IV. Univariate and multivariate analyses of progression-free survival in patients with non-small cell lung cancer treated with PD-1 inhibitors.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (male vs. female)	0.782 (0.458-1.337)	0.369		
Age (≤65 vs. >65 years)	1.265 (0.853-1.877)	0.243		
ECOG (0-1 vs. 2)	0.194 (0.060-0.628)	0.006[a]	0.613 (0.376-0.999)	0.049[a]
Stage (IIIB-IIIC vs. IV)	0.682 (0.404-1.151)	0.378		
Genetic mutations (yes vs. no)	0.536 (0.335-0.859)	0.009[a]	0.770 (0.0.487-1.216)	0.262
PD-L1 (yes vs. no)	1.159 (0.860-2.509)	0.159		
Number of metastatic sites (<3 vs. ≥3)	0.595 (0.401-0.883)	0.010[a]	0.627 (0.418-0.940)	0.024[a]
Liver metastasis (yes vs. no)	0.746 (0.436-1.275)	0.284		
CNS metastasis (yes vs. no)	0.890 (0.539-1.469)	0.649		
Bone metastasis (yes vs. no)	0.808 (0.545-1.198)	0.289		
Line of therapy (1 vs. ≥2)	0.947 (0.639-1.403)	0.786		
Regimen (combination therapy vs. monotherapy)	1.091 (0.683-1.744)	0.716		
irAEs (yes vs. no)	0.997 (0.599-1.661)	0.992		
PLR (high vs. low)	0.632 (0.426-0.940)	0.023[a]	0.781 (0.500-1.221)	0.279
NLR (high vs. low)	0.565 (0.380-0.841)	0.005[a]	0.201 (0.060-0.670)	0.009[a]

[a]P<0.05. PD-1, programmed death 1; CNS, central nervous system; PD-L1, programmed death-ligand 1; irAEs, immune-related adverse events; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

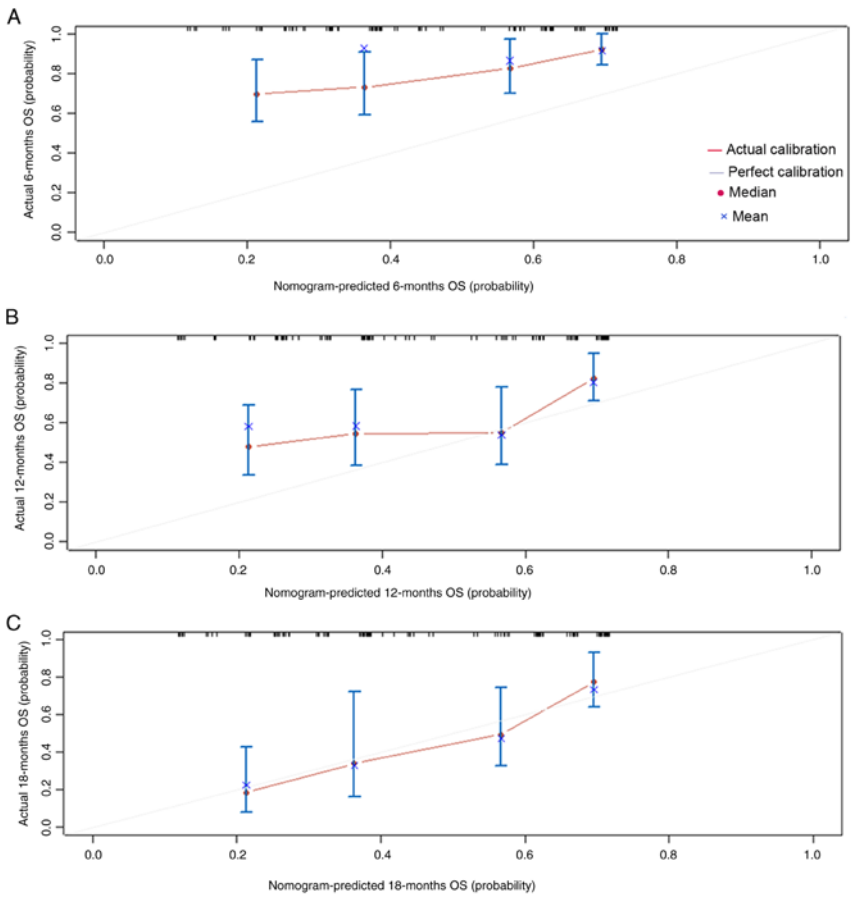

Figure 4. Calibration curves for (A) 6-, (B) 12- and (C) 18-month OS, as determined using the nomogram. The x-axis presents nomogram-predicted survival probability and y-axis presents observed survival probability. OS, overall survival.

Table V. Univariate and multivariate analyses of overall survival in patients with non-small cell lung cancer treated with PD-1 inhibitors.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex (male vs. female)	0.613 (0.332-1.131)	0.117		
Age (≤65 vs. >65 years)	1.298 (0.786-2.145)	0.308		
ECOG (0-1 vs. 2)	0.865 (0.119-6.269)	0.885		
Stage (IIIB-IIIC vs. IV)	0.559 (0.267-1.174)	0.124		
Genetic mutations (yes vs. no)	0.479 (0.279-0.821)	0.007[a]	0.635 (0.363-1.111)	0.112
PD-L1 (yes vs. no)	1.081 (0.563-2.075)	0.815		
Numbers of metastatic sites (<3 vs. ≥3)	0.589 (0.360-0.964)	0.035[a]	0.440 (0.467-1.392)	0.440
Liver metastasis (yes vs. no)	0.573 (0.310-1.059)	0.076[b]	0.638 (0.330-1.233)	0.182
CNS metastasis (yes vs. no)	0.946 (0.512-1.747)	0.859		
Bone metastasis (yes vs. no)	0.708 (0.433-1.157)	0.168		
Line of therapy (1 vs. ≥2)	0.693 (0.424-1.131)	0.142		
Regimen (combination therapy vs. monotherapy)	1.257 (0.689-2.294)	0.456		
irAEs (yes vs. no)	1.718 (0.842-3.507)	0.137		
PLR (high vs. low)	0.550 (0.329-0.919)	0.022[a]	0.566 (0.477-1.498)	0.566
NLR (high vs. low)	0.336 (0.197-0.571)	<0.001[a]	0.413 (0.226-0.754)	0.004[a]

[a]P<0.05, [b]P<0.1. PD-1, programmed death 1; CNS, central nervous system; PD-L1, programmed death-ligand 1; irAEs, immune-related adverse events; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; PLR, platelet to lymphocyte ratio.

those previously reported (37). These discrepancies may be accounted for by patient age, as in the present study, patients were younger than previous study patients (mean age, 58.80±0.89 years); the proportion of patients with an ECOG score of 0-1 points (97.0%); the proportion of patients that used immunotherapy as the first-line treatment (54.8%); and the proportion of patients treated with immune combination therapy (76.7%). Previous studies (38,39) have demonstrated that the use of immune combination therapies is associated with clinical benefits in patients with advanced NSCLC. Further evidence is required to determine optimum treatment selection and timing; however, in the present study, NLR values were independently associated with PFS (HR, 0.201; 95% CI, 0.060-0.670; P=0.009) and OS (HR, 0.413; 95% CI, 0.226-0.754; P=0.004) estimates.

Predictive reference values for PLR and NLR remain unclear. Yucel and Bilgin (14) proposed an NLR value of 3 in patients with advanced NSCLC and EGFR mutations. In a meta-analysis of 13 studies on ovarian cancer (n=3467), Zhao *et al* (34) proposed NLR values in the range of 2.6-5.03, and PLR values in the range of 200-300. These values were mostly determined by ROC curve analyses, as well as based on interquartile ranges, mean and median values, equivalents of fixed ratio scores, and other software-based methods that help identify cut-off values. In the present study, PLR and NLR cut-off values were determined using the median, yielding 200 and 3.56, respectively; these values are approximately equivalent to those previously reported.

In contrast to a previous study (35), the present univariate analysis suggested that number of metastases and mutation status were associated with PFS and OS estimates. In clinical practice, patients with multiple metastases tend to be in poor overall health, have advanced disease and poor previous treatment response, as well as high toxicity susceptibility.

In the present study on irAEs, a predictive value could not be found for serological indicators, in contrast to previous studies, which may be related to a retrospective bias (40). However, the present study revealed that patients aged <65 years and those receiving immune monotherapy were less likely to experience irAEs.

In the univariate analysis of factors associated with OS, the rates of liver metastases (HR, 0.573; 95% CI, 0.310-1.059; P=0.076) differed among the groups, although this difference was not statistically significant. Nevertheless, this finding suggested that liver metastases may affect prognosis. Notably, the results of the ATLANTIC study revealed that the presence of liver metastases was associated with poorer prognosis compared with the absence of these metastases, with the median OS of 5 and 10 months, respectively (HR, 1.83; 95% CI, 1.28-2.62; P<0.005) (41).

The liver has a metabolic function and is closely related to immune function. Non-parenchymal cells are present in the liver, including hepatic sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells and dendritic cells, which may be involved in the regulation of antigen expression, immune regulation and immune tolerance; therefore, the liver may be considered a part of a complex immune network (42). Nevertheless, the impact of liver metastases tends to be underestimated, specifically, relative to that of brain metastases. Furthermore, under hypoxic conditions, hepatocytes may upregulate the expression of several chemokines, such as CC

motif chemokine ligand (CCL)28 and CCL26, which recruit regulatory T cells to promote the expression of vascular endothelial growth factor (43). The results of the IMPOWER150 study showed that in a subgroup of patients with liver metastases, combination treatment with atezolizumab improved PFS (8.2 vs. 5.4 months) and OS (13.3 vs. 9.4 months) estimates (44). Consequently, combination therapy may improve outcomes in patients with liver metastases.

In the present study, the AUC values of PLR, NLR, and combined PLR and NLR were 0.68, 0.77 and 0.71, respectively, indicating good prognostic sensitivity and specificity of these parameters. The C-index was used to further evaluate the prognostic value of this model. In a study of 80 patients with NSCLC, Deng *et al* (45) revealed that fibrinogen, PLR and NLR were significantly more effective in diagnosing NSCLC than the individual indices. Further studies are required to identify the most relevant combination of these indices.

In the present study, nomograms were constructed for 133 patients at 6, 12 and 18 months, based on risk factors associated with OS estimates, including number of metastatic sites, liver metastases, driver gene mutation status, and PLR and NLR values. Survival rates observed at 18 months were in good agreement with the predicted survival rates. This finding was consistent with those of previous studies (46,47). However, the C-index of the model was 0.696, which was <0.7 (in general, 0.50-0.70 indicates low accuracy, 0.71-0.90 indicates moderate accuracy and >0.90 indicates high accuracy) (48), suggesting that the predictive value of this model was poor. This finding may be accounted for by the small sample size of the present study, and the NLR and PLR cut-off values used.

The present study had some limitations. First, it was a retrospective cohort study with a small and unrepresentative sample, which may have affected the presented findings. Retrospective studies are vulnerable to selection bias, which may yield inaccurate results, including adverse event rates. Second, the present study only included common inflammatory status indicators. Third, there is no established cut-off value for NLR and PLR. Fourth, the impact of unmeasured confounders could not be controlled; in addition, different treatment regimens may have affected the presented findings. Fifth, the follow-up period in the present study was short. Future large multicenter prospective cohort studies are required to validate the present findings.

Identifying biomarkers that are cost-effective and straightforward to obtain is required to achieve good outcomes with immunotherapy, specifically in the Chinese population, where lung cancer rates are high and access to treatment is inconsistent (49). Alongside PD-L1 expression, serological indicators should be evaluated in patients on ICIs to help predict outcomes. These serological parameters may be used in combination with established parameters, such as PD-L1, TMB and TILs.

In conclusion, in the present retrospective cohort study of patients with stage IIIB-IV NSCLC treated with ICIs, NLR values were associated with PFS and OS estimates. Our future work aims to validate these findings. The present findings suggested that the NLR indicator had good sensitivity and specificity; however, the calibrated results show a poor predictive performance. It is recommended that novel markers be used in combination with established markers to build highly accurate prognostic models.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

XL and HS designed the study, and wrote and edited the manuscript. JW performed statistical analyses with GraphPad Prism 8.0.1 and R-Studio. XL collected the data, including follow-up data. XL and HS wrote the manuscript, and JW and HS finalized the article. XL and HS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The informed consent requirement was waived by the Scientific Research Ethics Committee of the First Affiliated Hospital of Gannan Medical College due to the retrospective nature of the present study, which involved secondary analysis of an existing dataset.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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