

The Clinical And Prognostic Value of NLR, PDW, And PNI In Advanced Non-Small-Cell Lung Cancer Treated With Platinum-Based Chemotherapy

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Abstract

Objective: The purpose of this study was to investigate the relationship between the neutrophil-lymphocyte ratio (NLR), platelet distribution width (PDW) and prognostic nutrient index (PNI), and the prognosis of patients with advanced non-small-cell lung cancer (NSCLC) treated with platinum-based chemotherapy.

Methods: A total of 428 patients with advanced NSCLC treated with platinum-based chemotherapy between January 2015 and June 2019 were retrospectively analyzed. The patients were randomly divided into training set (n=300) and test set (n=128) in a ratio of 7:3, respectively. Clinical data and peripheral blood test results were collected within one week prior to the initiation of treatment to calculate PLR, PDW, and PNI. Receiver operating characteristic (ROC) curves were used to determine the optimal cut-off values of PLR, PDW, and PNI. Kaplan-Meier method and Cox regression analysis were used to evaluate the prognostic factors of advanced NSCLC treated with platinum-based chemotherapy. A Nomogram model was established for predicting the prognosis in advanced NSCLC treated with platinum-based chemotherapy. The test set was used for external validation of the prognostic model.

Results: There was no significant difference in the proportion of clinical features between the training set and the test set ($P \geq 0.05$). The ROC curve analysis determined the optimal cut-off values of PLR, PDW, and PNI to be 3.07, 16.81, and 52.025, respectively. Univariate and multivariate analyses indicated that tumor type ($P=0.038$), tumor differentiation ($P=0.014$), NLR ($P=0.001$), PDW ($P<0.001$), and PNI ($P=0.009$) were independent prognostic factors for PFS in patients with advanced NSCLC patients treated with platinum-based chemotherapy. Tumor type ($P=0.002$), tumor differentiation ($P=0.038$), EGFR status ($P=0.002$), NLR ($P=0.010$), PDW ($P=0.001$), and PNI ($P=0.002$) were independent prognostic factors for overall survival (OS) in advanced NSCLC patients treated with platinum-based chemotherapy. The established nomogram was validated internally and externally. The results showed a good agreement between the predicted value and the actual value of the calibration curve.

Conclusion: NLR, PDW, PNI, tumor type, and tumor differentiation are independent prognostic factors for PFS in advanced NSCLC patients treated with platinum-based chemotherapy. NLR, PDW, PNI, tumor type, tumor differentiation, and EGFR status are independent prognostic factors for OS in advanced NSCLC patients treated with platinum-based chemotherapy. The established model has an application value in predicting the prognosis of advanced NSCLC patients treated with platinum-based chemotherapy.

Background

Lung cancer is a leading cause of cancer-related deaths. There was an estimated 2.1 million new cases of lung cancer and more than 1.8 million deaths in 2018 [1]. In the United States, the 5-year survival rate for lung cancer is only about 18 percent, and NSCLC is the most common type of lung cancer, accounting for about 80 percent of all lung cancers. For patients with advanced NSCLC, platinum-based dual-drug chemotherapy is the standard treatment.

At present, the most recognized staging system for prognosis and treatment of cancer is the TNM staging system introduced and implemented by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [2]. Although the TNM staging system remains the strongest predictor of survival, tumor biology and survival outcomes vary widely at each stage. This suggests that factors affecting the prognosis of cancer patients remain unknown.

Inflammation plays an important role in the development and progression of tumors. Systemic inflammatory response promotes tumor cell growth, accelerates tumor cell metastasis, and suppresses tumor immunity [3]. Neutrophils and lymphocytes are important components of systemic inflammatory factors, and NLR is a commonly used inflammatory index. Recent studies have confirmed that NLR is associated with the prognosis of lung cancer [4], gastric cancer [5], colorectal cancer [6], and breast cancer [7]. In addition to inflammation, the long-term outcome of patients with malignancy is closely related to nutritional status. Albumin is a commonly used indicator of the nutritional status of the human body. PNI, which consists of peripheral blood neutrophils which reflects inflammation, and albumin which reflects nutritional status, is used to evaluate the prognosis of a variety of malignant tumors, such as rectal cancer [8], breast cancer [9], cervical cancer [10], etc. Studies [11, 12] indicate that platelets play an important role in the occurrence and development of tumors. Activation of platelets is related to inflammatory response and promotes tumor proliferation. Activated platelets are only a part of the platelet count, and the platelet count alone cannot fully reflect platelet activity. PDW is a blood analysis instrument that analyzes platelet distribution data to obtain the volume dispersion in platelet size. It is an indicator of platelet activity and reflects the heterogeneity of platelet volume. There are few studies on the relationship between PDW and tumor prognosis. Some studies believe that PDW is related to the prognosis of liver cancer [13], breast cancer [14], and gastric cancer [15].

Previous studies on prognostic factors for lung cancer mainly focus on the relationship between multiple parameters and prognosis. The purpose of this study was to analyze the clinical data of 428 patients with advanced NSCLC, investigate the relationship between NLR, PDW, PNI and the prognosis of patients with advanced non-small-cell lung cancer (NSCLC) treated with platinum-based chemotherapy, and to further identify prognostic markers for advanced NSCLC after platinum-based chemotherapy. The prognostic model was constructed based on the identified markers, and the clinical application value of the prognostic model evaluated.

Materials And Methods

2.1 Material

This retrospective study included patients with advanced NSCLC treated with platinum-based chemotherapy in the Department of Oncology of the First Affiliated Hospital of Nanjing Medical University between January 2015 and June 2019. The inclusion criterion were as follows: (1) Primary NSCLC diagnosed by fiberoptic bronchoscopy biopsy, percutaneous lung biopsy, lymph node or superficial tumor biopsy, and cytological examination of body cavity effusion. CT, MR, and X-ray results showed that the tumors had distant metastasis and could not be cured, and first-line platinum-based chemotherapy was suggested; (2) Had undergone routine blood and biochemical tests within the 1-week preceding treatment; (3) No history of acute infectious diseases was reported within 2 weeks before admission; (4) No previous history of other malignant tumors; (5) No previous diseases of the blood system, immune system or chronic liver and kidney insufficiency; (6) Complete follow-up data. The exclusion criterion were as follows: (1) had a history of acute infectious diseases within 2 weeks prior to initiation of treatment; (2) has used drugs affecting blood routine results, such as glucocorticoids, non-steroidal anti-inflammatory drugs, and recombinant human granulocyte colony-stimulating factor, within one month before treatment; (3) patients with other malignant tumors;(4) Patients with blood or immune system diseases; (5) A history of immunosuppressant or immunomodulators use, three months before treatment; (6) Patients with incomplete follow-up data.

2.2 Methods

In this study, general information such as gender, age, smoking status, KPS score, tumor type, tumor differentiation, EGFR status, and chemotherapy regimen were collected from NSCLC patients before treatment. Blood tests and biochemical indexes were collected within one week before treatment. NLR and PNI were calculated as follows; NLR was obtained by dividing the neutrophil count by the lymphocyte count, and PNI was obtained as serum albumin value (g/L) + 5×peripheral blood lymphocyte count ($\times 10^9/L$). The imaging baseline examination data of the subjects within two weeks before treatment and the imaging efficacy evaluation data of the platinum-based double-drug combined with chemotherapy were collected. All patients were treated according to the NCCN guidelines, followed up regularly, and treatment efficacy evaluated by RECIST standard. The endpoint of follow-up was June 30, 2020. PFS was defined as the time (months) from pathologic diagnosis to the time of tumor progression or death from any cause. OS was defined as the time (months) from patient pathological diagnosis to the time of death from any cause.

In this study, the hematological index value was considered as the variable and the short-term efficacy was considered as the outcome and used to draw the ROC curve and establish the optimal cut-off value of each index that could accurately predict the patient's prognosis. A total of 428 patients were randomly divided into a training set (n = 300) and a test set (n = 128) at a ratio of 7:3. Using the training set, univariate and multivariate analysis identified the independent prognostic factors of advanced NSCLC. A prognostic model was constructed based on the identified multi-parameter independent prognostic factors. The accuracy of the prediction model was determined by calculating the C-index and drawing the calibration curve for internal validation. The test set was used to externally validate the prediction efficiency of the prognostic model.

The survival rate was calculated using SPSS19 software. Enumeration data were compared using χ^2 test, Kaplan-Meier method was used to draw the survival curves, Log-rank univariate analysis and Cox proportional risk model were used to perform multivariate analysis, and $P < 0.05$ was considered to be statistically significant. Survival package and RMS in R3.5.2 software were used for mapping, and the C-index and its 95% confidence interval were calculated using Survcomp to determine the prediction ability of the model.

Results

428 cases were included in this study. We analyzed data obtained from patients with advanced NSCLC who received first-line platinum-based chemotherapy in the Department of Oncology, the First Affiliated Hospital of Nanjing Medical University between January 2015 and June 2019. The exclude patients included, 6 patients with a history of infection 2 weeks before treatment, 8 patients receiving drugs that affected the routine blood test results 1 month before treatment, 14 patients with a history of other tumor or immune diseases, 4

patients with a history of immunosuppressant/immunomodulator nearly 3 months before treatment, and 36 patients with incomplete follow-up data. The specific clinical features are shown in Table 1.

Table 1
 clinicopathological characteristics of 428 patients with advanced NSCLC treated with platinum-based chemotherapy

characteristics	training set	test set	P value
	n = 300	n = 128	
Gender			0.336
	Male	163(54.3%)	76(59.4%)
	Female	137(45.7%)	52(40.6%)
Age, years			0.211
	<60	98(32.7%)	34(26.6%)
	≥ 60	202(67.4%)	94(74.4%)
Smoking status			0.674
	Smoker	141(47.0%)	63(49.2%)
	Nonsmoker	159(53.0%)	65(50.8%)
KPS score			0.962
	<70	44(14.7%)	19(14.8%)
	≥ 70	256(85.3%)	109(85.2%)
Tumor type			0.856
	Squamous	120(40%)	50(39.1%)
	Adenocarcinoma	180(60%)	78(60.9%)
Tumor differentiation			0.959
	Poorly differentiated	71(23.7%)	30(23.4%)
	Moderate-well differentiated	229(76.3%)	98(76.6%)
EGFR status			0.678
	Mutation	83(27.7%)	40(31.3%)
	Without mutation	175(58.3%)	73(57.0%)
	Unknown	42(14.0%)	15(11.7%)
chemotherapy regimen			0.417
	With cisplatin	137(45.7%)	53(41.4%)
	With carboplatin	163(54.3%)	75(58.6%)

The NLR, PDW, and PNI in the training set samples were analyzed, and the ROC curves of the three parameters were established to predict the prognosis of advanced NSCLC patients treated with platinum-based chemotherapy. The areas under the ROC curve of NLR, PDW, and PNI to predicting the prognosis of advanced NSCLC patients treated with platinum-based chemotherapy were 0.717 (95%CI: 0.656–0.779, $P < 0.001$), 0.634 (95%CI: 0.568-0.700, $P < 0.001$) and 0.591 (95%CI: 0.524–0.658, $P = 0.010$), respectively. According to the principle of the Youden index, the optimal cut-off values of NLR, PDW, and PNI were determined to be 3.07, 16.81, and 52.025, respectively (Fig. 1).

Based on the optimal cut-off values of NLR, PDW, and PNI, the subjects were divided into the high NLR, PDW, and PNI groups and the low NLR, PDW, and PNI group. The differences in clinicopathological characteristics between the two groups were compared, and the results are shown in Table 2.

Table 2

Relationship between peripheral blood parameters and clinicopathological characteristics of 300 patients with advanced NSCLC treated with platinum-based chemotherapy

characteristics	NLR ≥ 3.07	NLR < 3.07	P value	PDW ≥ 40.1	PDW < 40.1	P value	PNI ≥ 52.025	PNI < 52.025	P value
	n = 107	n = 193		n = 51	n = 249		n = 194	n = 106	
Gender			0.783			0.598			0.042
Female	57(53.3%)	106(54.9%)		26(51.0%)	137(55.0%)		97(50.0%)	66(62.3%)	
Male	50(46.7%)	87(45.1%)		25(49.0%)	112(45.0%)		97(50.0%)	40(37.7%)	
Age, years			0.126			0.012			0.872
<60	29(27.1%)	69(35.8%)		9(17.6%)	89(35.7%)		64(33.0%)	34(32.1%)	
≥ 60	78(72.9%)	124(64.2%)		42(82.4%)	160(64.3%)		130(67.0%)	72(67.9%)	
Smoking status			0.755			0.066			0.660
Smoker	49(45.8%)	92(47.7%)		18(35.3%)	123(49.4%)		93(47.9%)	48(45.3%)	
Nonsmoker	58(54.2%)	101(52.3%)		33(64.7%)	126(50.6%)		101(52.1%)	58(54.7%)	
KPS score			0.142			0.274			0.128
<70	20(18.7%)	24(12.4%)		10(19.6%)	34(13.7%)		24(12.4%)	20(18.9%)	
≥ 70	87(81.3%)	169(87.6%)		41(80.4%)	215(86.3%)		170(87.6%)	86(81.1%)	
Tumor type			<0.001			0.017			0.009
Squamous	57(53.3%)	63(32.6%)		28(54.9%)	92(36.9%)		67(34.5%)	53(50.0%)	
Adenocarcinoma	50(46.7%)	130(67.4%)		23(45.1%)	157(63.1%)		127(65.5%)	53(50.0%)	
Tumor differentiation			<0.001			0.012			0.011
Poorly differentiated	40(37.4%)	31(16.1%)		19(37.3%)	52(20.9%)		37(19.1%)	34(32.1%)	
Moderate-well differentiated	67(62.6%)	162(83.9%)		32(62.7%)	197(79.1%)		157(80.9%)	72(67.9%)	
EGFR status			<0.001			0.411			0.009
Mutation	19(17.8%)	64(33.2%)		11(21.6%)	72(28.9%)		65(33.5%)	18(17.0%)	
Without mutation	80(74.8%)	95(49.2%)		34(66.7%)	141(56.6%)		103(53.1%)	72(67.9%)	
Unknown	8(7.5%)	34(17.6%)		6(11.8%)	36(14.5%)		26(13.4%)	16(15.1%)	
Chemotherapy regimen			0.652			0.078			0.529
With cisplatin	47(43.9%)	90(46.6%)		29(56.9%)	108(43.4%)		86(44.3%)	51(48.1%)	
With carboplatin	60(56.1%)	103(53.4%)		22(43.1%)	141(56.6%)		108(55.7%)	55(51.9%)	

Patients' clinicopathological characteristics were included in univariate analysis, and the results showed that KPS score ($P = 0.043$), tumor type ($P = 0.001$), tumor differentiation ($P < 0.001$), NLR ($P < 0.001$), PDW ($P < 0.001$), and PNI ($P < 0.001$) were associated with PFS in patients with advanced NSCLC (Fig. 2). These factors were substituted into the Cox proportional risk model, and further Cox multivariate analysis showed that tumor type ($P = 0.038$), tumor differentiation ($P = 0.014$), NLR ($P = 0.001$), PDW ($P < 0.001$), and PNI ($P = 0.009$) were independent prognostic factors for patients with NSCLC (Table 3).

Clinicopathological characteristics and single-factor analysis showed that age ($P = 0.008$), KPS score ($P = 0.012$), tumor type ($P < 0.001$), tumor differentiation ($P = 0.001$), EGFR status ($P < 0.001$), NLR ($P < 0.001$), PDW ($P < 0.001$), PNI ($P < 0.001$) were associated with OS in

patients with advanced NSCLC (Fig. 3). These factors were substituted in the Cox proportional risk model, and multivariate analysis showed that tumor type ($P = 0.002$), tumor differentiation ($P = 0.038$), EGFR status ($P = 0.002$), NLR ($P = 0.010$), PDW ($P = 0.001$), and PNI ($P = 0.002$) were independent prognostic factors affecting patients' OS (Table 4).

Table 3
Univariate and multivariate analyses of PFS in advanced NSCLC patients

variable	n	Univariate				multivariate			
		Mean of PFS(months)	95%CI	χ^2	P value	RR	95%CI	χ^2	P value
Gender				0.549	0.459				
Male	163	7.688	7.211–8.166						
Female	137	7.355	6.826–7.884						
Age, years				0.644	0.422				
<60	98	7.712	7.076–8.347						
≥ 60	202	7.449	7.022–7.876						
Smoking status				0.020	0.889				
Smoker	141	7.508	6.978–8.038						
Nonsmoker	159	7.553	7.078–8.027						
KPS score				4.078	0.043				
<70	44	6.523	5.576–7.469			Ref			
≥ 70	256	7.714	7.334–8.093			0.897	0.646–1.245	0.423	0.516
Tumor type				11.540	0.001				
Squamous	120	6.647	6.096–7.199			Ref			
Adenocarcinoma	180	8.111	7.675–8.547			0.771	0.604–0.985	4.326	0.038
Tumor differentiation				20.139	<0.001				
Poorly differentiated	71	5.877	4.835–7.165			Ref			
Moderate-well differentiated	229	8.028	7.591–8.409			0.696	0.521–0.929	6.040	0.014
EGFR status				0.861	0.650				
Mutation	83	7.410	6.797–8.022						
Without mutation	175	7.469	6.971–7.967						
Unknown	42	8.095	7.270–8.921						
Chemotherapy regimen				<0.001	0.993				
With cisplatin	137	7.547	7.032–8.061						
With carboplatin	163	7.530	7.040–8.021						

	Univariate			multivariate				
NLR				30.636	<0.001			
≥ 3.07	107	6.201	5.664– 6.738			Ref		
<3.07	193	8.279	7.847– 8.710			0.645	0.499– 0.834	11.171 0.001
PDW				37.742	<0.001			
≥ 16.81	51	5.314	4.603– 6.024			Ref		
<16.81	249	7.994	7.616– 8.372			0.494	0.358– 0.680	18.664 0.001
PNI				17.407	<0.001			
≥ 52.025	194	8.131	7.706– 8.556			Ref		
<52.025	106	6.420	5.853– 6.986			1.400	1.088– 1.802	6.826 0.009

Table 4
Univariate and multivariate analyses of OS in advanced NSCLC patients

variable	n	Univariate				multivariate			
		Mean of PFS(months)	95%CI	χ^2	P value	RR	95%CI	χ^2	P value
Gender				0.037	0.847				
Male	163	18.936	17.829–20.044						
Female	137	19.151	18.124–20.178						
Age, years				7.094	0.008				
<60	98	20.524	19.068–21.981			Ref			
≥ 60	202	18.320	17.442–19.198			1.258	0.925–1.711	2.140	0.144
Smoking status				0.107	0.743				
Smoker	141	19.266	18.097–20.435						
Nonsmoker	159	18.952	17.892–20.011						
KPS score				6.273	0.012				
<70	44	16.856	15.250–18.461			Ref			
≥ 70	256	19.383	18.535–20.230			0.641	0.424–0.970	4.438	0.035
Tumor type				31.807	<0.001				
Squamous	120	16.068	14.948–17.188			Ref			
Adenocarcinoma	180	20.411	19.493–21.330			0.596	0.426–0.834	9.147	0.002
Tumor differentiation				10.247	0.001				
Poorly differentiated	71	16.486	14.823–18.149			Ref			
Moderate-well differentiated	229	19.603	18.763–20.443			0.668	0.456–0.978	4.293	0.038
EGFR status				38.413	<0.001				
Mutation	83	22.653	21.274–24.032			0.495	0.314–0.781	9.159	0.002
Without mutation	175	17.013	16.107–17.918			Ref			
Unknown	42	18.411	16.940–19.882						
Chemotherapy regimen				0.726	0.394				
With cisplatin	137	19.533	18.400–20.667						
With carboplatin	163	18.683	17.629–19.737						

	Univariate			multivariate			
NLR				23.305	<0.001		
≥ 3.07	107	16.273	15.040- 17.505	Ref			
<3.07	193	20.254	19.354- 21.154	0.654	0.473- 0.904	6.604	0.010
PDW				17.179	<0.001		
≥ 16.81	51	15.209	13.867- 16.552	Ref			
<16.81	249	19.553	18.729- 20.377	0.488	0.315- 0.756	10.290	0.001
PNI				22.225	<0.001		
≥ 52.025	194	20.201	19.240- 21.163	Ref			
<52.025	106	16.509	15.450- 17.567	1.609	1.184- 2.186	9.250	0.002

In this study a nomogram was established to predict the prognosis and OS in patients with advanced NSCLC receiving platinum-based chemotherapy (Fig. 4). The probability of PFS at 3, 6, 9, and 12 months, and the probability of OS at 6, 12, 18, and 24 months were determined from the constructed model.

In the training set, after 1000 times of self-help sampling internal verification, we get the c-index of the nomogram of PFS prediction is 0.683(95%CI: 0.6444–0.723) and the c-index of the nomogram of OS prediction is 0.770 (95%CI: 0.738–0.803).The correction curves of both PFS and OS are close to 1, indicating that the nomogram has good predictive power (Fig. 5).

A total of 128 samples in the test set were used to validate the prognostic model. The c-index of nomogram for PFS was 0.686 (95% CI: 0.633–0.739) and OS was 0.782 (95% CI: 0.737–0.826). The calibration curves of PFS and OS were close to 1, indicating that the nomogram could accurately predict PFS and OS in patients with advanced NSCLC treated with platinum-based chemotherapy (Fig. 6).

Discussion

Platinum-based chemotherapy is a standard treatment for advanced NSCLC, however, drug resistance in chemotherapy remains a significant obstacle in cancer treatment [16, 17]. Clinical decision-making in the treatment of cancer patients requires appropriate prognostic indicators, which guide the prediction of the effectiveness of anti-cancer therapy. The findings indicated that NLR, PDW, and PNI are useful prognostic markers for advanced NSCLC patients receiving platinum-based chemotherapy. In addition to NLR, PDW, and PNI, KPS score, tumor type, tumor differentiation, and EGFR status were also found to be independent prognostic factors for advanced NSCLC patients treated with platinum-based chemotherapy.

NLR is an effective biomarker for detecting the inflammatory state of the immune system [18], and consist of two parameters: neutrophil count and lymphocyte count. Neutrophils contribute to the proliferation and survival of malignant cells, promote angiogenesis and metastasis [18], and disrupt T lymphocyte activation [19].By inducing cytotoxic cell's death, lymphocytes not only inhibit tumor cell proliferation, but also inhibit themigration of tumor cells, mediate the body's immune response to tumor cells, and play an important role in tumor defense and immune surveillance. Lymphocytes participate in autoimmunity and inhibit tumor progression by producing cytotoxic cell death ligands and cytokines that inhibit tumor cell proliferation and metastasis [20, 21]. Therefore, a high NLR reflects a higher degree of malignancy in NSCLC and poor immunity in the patient. In addition, to confirm that NLR reflects the body immune function, multivariate analysis was performed and indicated that high NLR is an independent prognostic factor of tumor malignancy, such as low KPS score and poor tumor differentiation, which are related factors for poor prognosis of NSCLC patients reported in previous studies. Yi et al. [22] reported similar findings, after retrospectively analyzing data from 68 patients with advanced NSCLC, and receiving first-line chemotherapy. Multivariate analysis showed that efficacy after 4 cycles of first-line chemotherapy (P = 0.022), second-line treatment status (P = 0.007), and NLR (P = 0.004) were independent prognostic factors for OS. Therefore, NLR can be considered as

a predictor of the efficacy and prognosis of first-line chemotherapy in advanced NSCLC, and a potential intervention target for the treatment of NSCLC.

Some scholars believe that in many tumors, the change in platelet count is sign of para-cancerous syndrome [23]. A high platelet count is closely associated with TNM staging, metastasis, and a high risk of recurrence [24, 25]. Platelets promote metastasis by interacting with malignant cells and directly affecting tumor progression [26]. Platelets act as chemical inducers to increase the migration of ovarian cancer cells. Larger platelets, however, store more particles and receptors, and bind more ligands than smaller platelets. Therefore, platelet activity is accurately expressed by their size [28]. Compared with the rapidly changing platelet count, PDW reflects the characteristics of activated platelets [29]. However, the underlying mechanism by which PDW affects tumor progression remains unclear. One possible explanation is that abnormal regulation of bone marrow cells is involved in PDW changes. Platelet volume is determined during megakaryogenesis and platelet formation. During megakaryocyte maturation, cytokines such as Interleukin-6(IL-6), macrophage colony-stimulating factor(M-CSF), and granulocyte colony-stimulating factor(G-CSF) play an important role in megakaryocyte maturation, platelet production, and platelet volume [30]. IL-6 promotes tumor angiogenesis, migration, and metabolism [31]. G-CSF stimulates megakaryocyte generation and inhibits tumor proliferation. M-CSF is an important factor in the tumor microenvironment and is involved in the interaction between infiltrating macrophages and tumor cells [32–34]. Cytokines G-CSF and M-CSF secreted by tumor cells stimulate the generation of tumor megakaryocytes and thrombopoietin (TPO) [35]. Therefore, PDW is an early indicator of platelet activation. Another possible mechanism is that platelets promote the hypercoagulant state of tumors. An increase in platelet number provides a microenvironment that promotes coagulation and aggregation with tumor cells, enabling platelets to guard tumor cells and eventually cause them to escape the host immune system [36]. Our results are inconsistent with those of Liu et al. [37], who analyzed 750 postoperative patients with NSCLC and found that low PDW was an independent adverse prognostic factor for DFS and OS. However, discrepancies have been observed in other studies. Two previous studies reported that decreased PDW predicts survival in patients with gastric cancer [15, 38]. Conversely, elevated PDW negatively affects the prognosis of melanoma [39], thyroid cancer [40], colorectal cancer [41], esophageal squamous cell carcinoma [12], and breast cancer [14]. The prognostic value of PDW in different studies is not consistent, which may be caused by the difference in tumor type, stage, treatment, study population, sample size, and other influencing factors. Therefore, it is important to further study the relationship between PDW and tumor prognosis.

Nutritional status is an important part of the immune status of cancer patients, which is of great significance for the survival of cancer patients including lung cancer. PNI is a cheap, reproducible and widely used blood test that reflects the immunotrophic status. When Smale et al. [42] first proposed the concept of PNI, it was mainly used to evaluate the risk of recurrence and death in patients undergoing surgery. At that time, its calculation method was complicated and not widely used. Until 1984, Onodera et al. [43] optimized the PNI calculation method and calculated the PNI value directly from the two parameters of serum albumin and lymphocyte count. The new PNI formula was mainly used to evaluate the nutritional and immune status of patients undergoing gastrointestinal surgery. In recent years, some scholars have studied the use of PNI to evaluate the prognosis of patients with various malignant tumors, including NSCLC [44–48]. PNI reflects the immune and nutritional status of cancer patients [49]. There are two important factors that contribute to malnutrition in cancer patients. One is an increase in metabolic rate, and a decrease in food intake due to cancer or treatment-related symptoms. Lack of serum albumin represents poor nutritional status and poor prognosis [50, 51]. As important immune cells, lymphocytes play an important role in immune surveillance by inhibiting the proliferation, invasion, and migration of tumor cells [49, 52]. Malnutrition and a compromised immune system jointly promote the development of tumors, while malnutrition increases the complications of tumor diseases and reduces tolerance to treatment [53, 54]. The optimal cut-off value of PNI is not known. Due to the heterogeneity of cases and the differences in sample size, this threshold differs in different studies. In our study, the optimal cut-off values of PNI calculated using the ROC curve was 52.025, and the OS of patients with $PNI \geq 52.025$ was significantly higher compared to that of patients with $PNI < 52.025$. The optimal cut-off value of PNI reported by Shimizu et al. [55] was 50, which was lower than 52.025 reported in our study. However, the value reported by Jin et al. [56] was 53.85, higher than the PNI value in this study. In addition, PNI was found to be an independent prognostic factor through multivariate analysis. These findings were consistent with those reported by Dai et al. [57]. Another study investigated the relationship between PNI and clinical features [58], and found that PNI was associated with gender and histology. The results showed that the incidence of low PNI status in women with lung cancer was lower than that in men, and low PNI was less common in patients with adenocarcinoma than in those with non-adenocarcinoma. What is interesting about this set of results is that the former is different from our results, while the latter is similar to our results. Considering the sample size of the study and the differences in the study subjects, these results need to be confirmed by further studies.

A nomogram is a complex mathematical formula represented by graphs [59]. A nomogram in medicine utilizes biological and clinical variables to build a prognostic model that generates the probability of a specific clinical event occurring in individual patients. The gold standard for predicting prognosis in oncology is the TNM staging system proposed in 1953 [60]. However, the TNM system has several

disadvantages. The first is the contradiction between anatomical disease progression and clinical survival. Patients within the same TNM stage are heterogeneous because their recurrence and death outcomes are often different. Second, TNM staging does not take into account primary tumor, regional lymph node metastases, and distant metastases as continuous variables. This makes it difficult to determine the prognosis with great accuracy. Third, the reference variables included in the TNM system are extremely limited. It does not introduce other prognostic variables into the prognostic judgment, such as genetic test results, immunological indicators, or histological types. Because of the limitations associated with TNM staging, a Nomogram is widely used in recent studies. One of the main advantages of the Nomogram is its ability to personalize risk assessment based on a patient's clinicopathological characteristics. Nomograms can also include continuous variables and related determinants of disease in the prognostic analysis [61]. Besides, Nomograms can be used in cancer diagnosis and treatment. Preoperative Nomograms can help surgeons assess the positive rate of surgical margin [62], determine the risk of lymph node metastasis [63], and screen outpatients who are likely to benefit from surgery. Nomogram of postoperative recurrence rate [64], tumor-specific survival time [65], overall survival time [66], efficacy of adjuvant therapy [67], and the impact of treatment on the patient's daily life [68] can help oncologists and patients to come up with a reasonable treatment plan. Although a Nomogram shows significant advancements in the development of methods for predicting patient outcomes, the correct clinical use of a Nomogram requires a thorough understanding of the specific problems, study population, construction methods, and results to assess its suitability for the clinical situation of a patient.

This study has several limitations. First, this study was a single-center study. Second, all peripheral blood test parameters were collected within the week preceding treatment, and the fluctuations in the test indicators during the entire treatment and follow-up were not fully recorded and analyzed. This is noteworthy because these data are likely to change over time and over the course of treatment. Third, due to the lack of data on chemotherapy side effects, these factors were not included in the evaluation. To further verify the effectiveness and accuracy of peripheral blood parameters in predicting the prognosis of advanced NSCLC patients treated with platinum-based chemotherapy, it is necessary to conduct multi-center studies with a large sample size in this regard.

Conclusion

NLR, PDW, PNI, tumor type, and tumor differentiation are independent prognostic markers for PFS in advanced NSCLC patients treated with platinum-based chemotherapy. NLR, PDW, PNI, KPS score, tumor type, tumor differentiation, and EGFR status were independent prognostic factors for OS in advanced NSCLC patients treated with platinum-based chemotherapy. Therefore, the established Nomogram of PFS and OS can guide accurate clinical prediction of individual prognosis in advanced NSCLC patients treated with platinum-based chemotherapy, and support individualized treatment.

Declarations

Ethics approval and consent to participate: Retrospective ethical approval was obtained. Informed consent to participate was obtained from family member or the patient themselves.

Consent for publication: Informed consent for publication was obtained from family member or the patient themselves.

Availability of data and material: Data are available from the corresponding author on reasonable request.

Competing interests: The authors declare no conflicts of interests.

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Authors' contribution: Lingxiang Liu and Jian Wang designed the study. Jian Wang and Yiqian Liu wrote the manuscript. Guoqing Wang, Mengting Shao, Xiaoguang Mi, Xingxing Yin, Teng Wang collected clinical data and contributed to data analyze.

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Figures

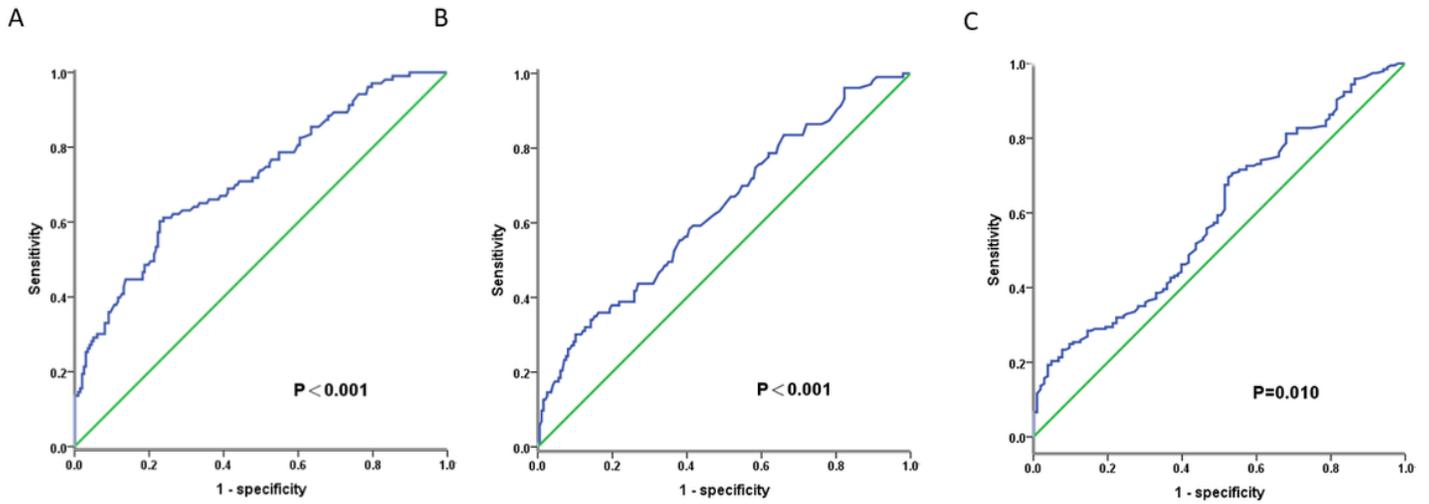


Figure 1

ROC curve of peripheral blood parameters predicting prognosis of patients with advanced NSCLC treated with platinum-based chemotherapy. A: ROC curve of NLR predicting patient prognosis ($P < 0.001$); B: ROC curve of PDW predicting patient prognosis ($P < 0.001$); C: ROC curve of PNI predicting patient prognosis ($P = 0.010$).

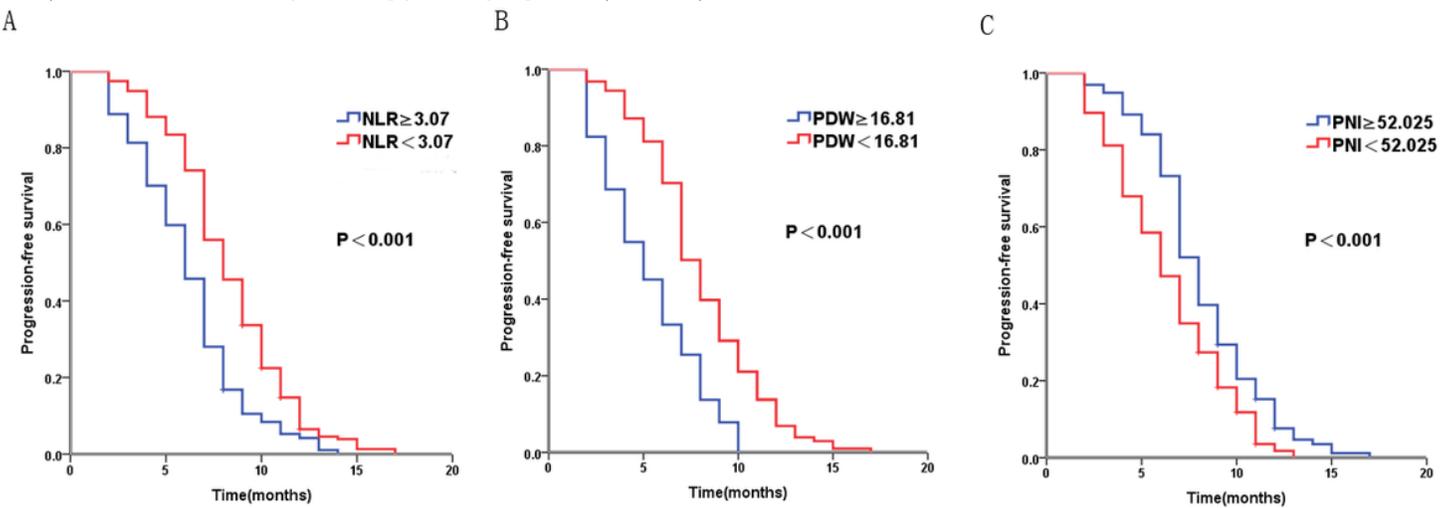


Figure 2

Kaplan-Meier survival curve analysis of the effect of clinical characteristics on PFS in patients with advanced NSCLC treated with platinum-based chemotherapy. A: The effect of NLR on PFS ($P < 0.001$); B: The effect of PDW on PFS ($P < 0.001$); C: The effect of PNI on PFS ($P < 0.001$).

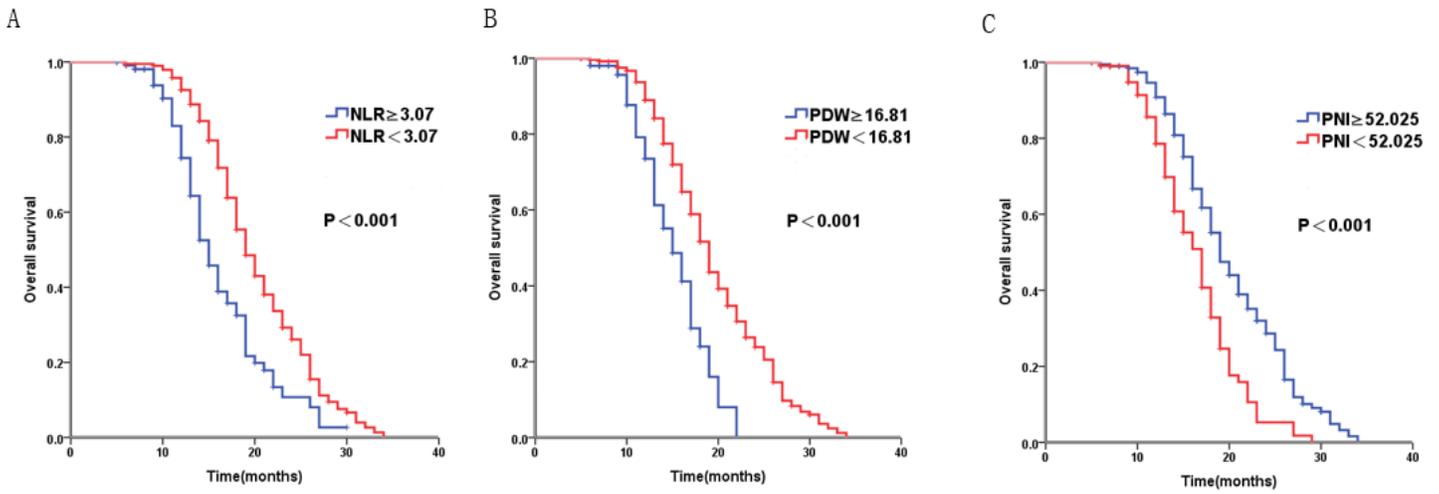


Figure 3

Kaplan-Meier survival curve analysis of the effect of clinical characteristics on OS in patients with advanced NSCLC treated with platinum-based chemotherapy. A: The effect of NLR on OS ($P < 0.001$); B: The effect of PDW on OS ($P < 0.001$); C: The effect of PNI on OS ($P < 0.001$).

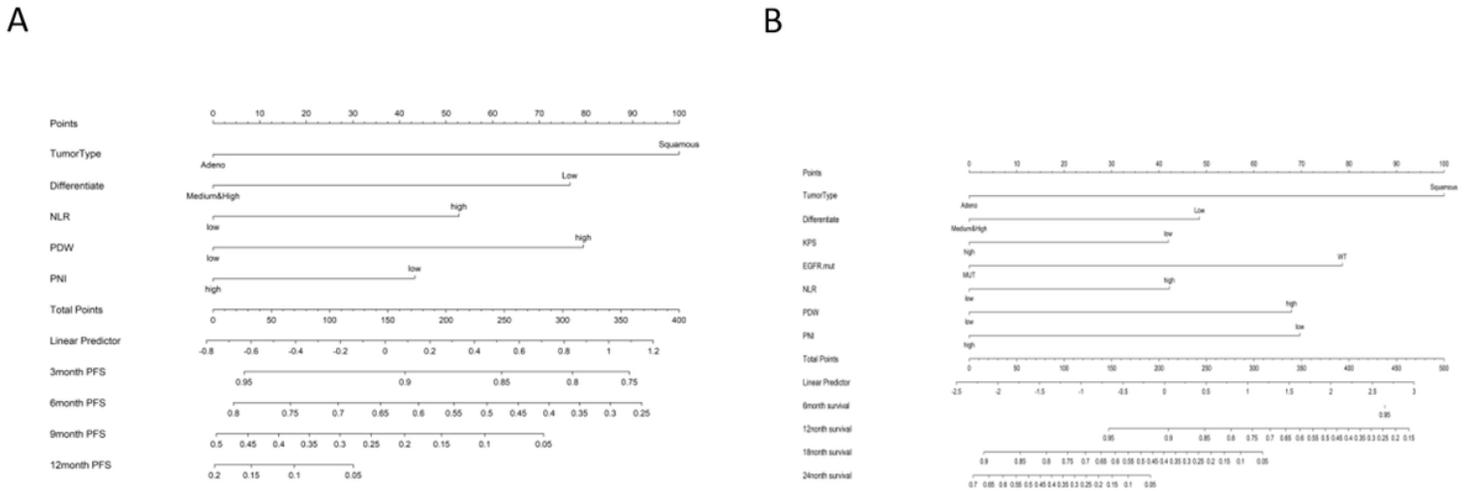


Figure 4

Nomogram for prediction in patients with advanced NSCLC treated with platinum-based chemotherapy. A: Nomogram for predicting PFS. B: Nomogram for predicting OS.

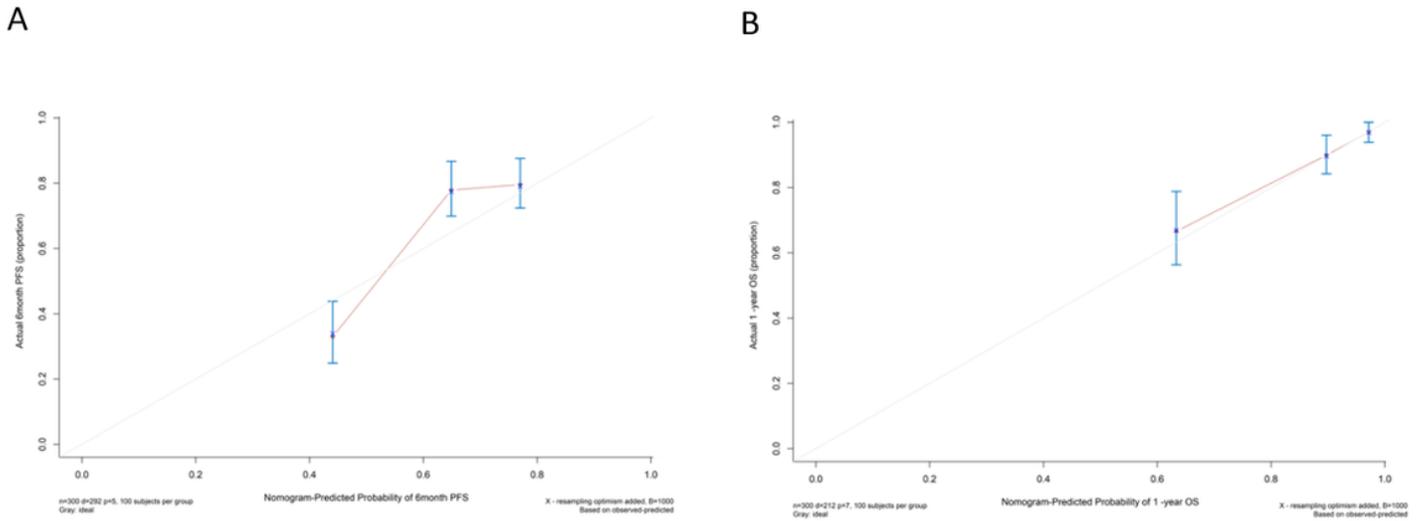


Figure 5

Correction curves for internal validation of the Nomogram in patients with advanced NSCLC treated with platinum-based chemotherapy. A: Correction curve of PFS at 6 months. B: Correction curve of OS at 12 months.

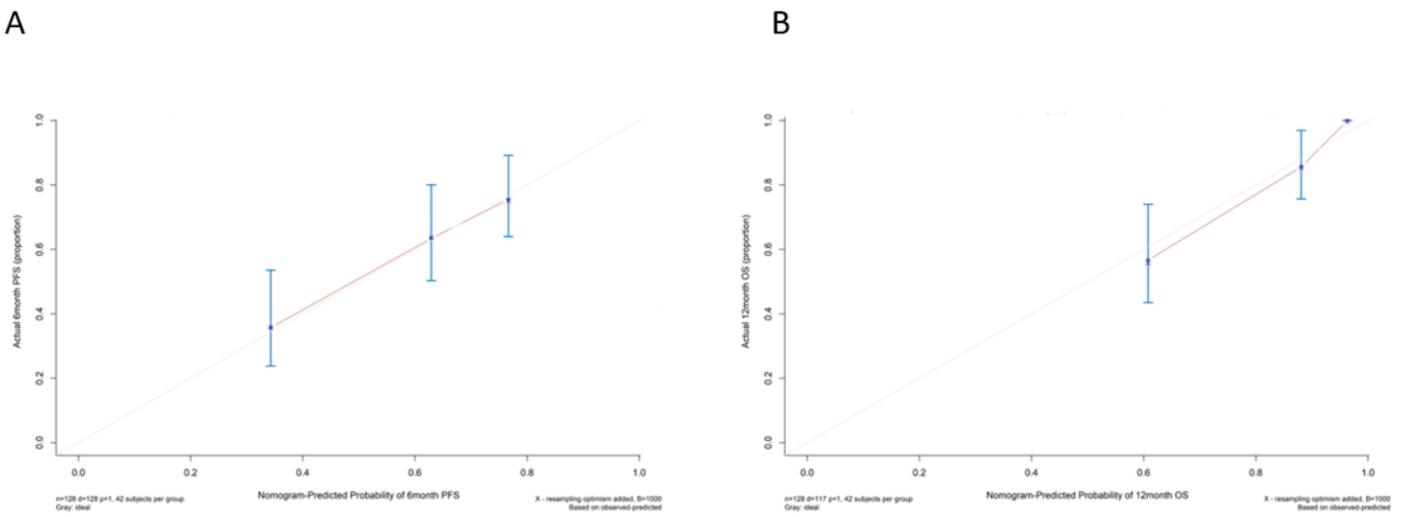


Figure 6

Correction curves for external validation of the Nomogram in patients with advanced NSCLC treated with platinum-based chemotherapy. A: Correction curve of PFS at 6 months. B: Correction curve of OS at 12 months.