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Preoperative platelet-lymphocyte ratio is a superior prognostic biomarker to other systemic inflammatory response markers in non-small cell lung cancer

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Abstract

Systemic inflammatory response markers are associated with poor survival in many types of malignances. This study aimed to evaluate the prognostic value of preoperative neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and C-reactive protein (CRP) in patients with non-small cell lung cancer (NSCLC).

We retrospectively evaluated 254 NSCLC patients who underwent radical surgery between January 2012 and April 2014 in the Sichuan Provincial Cancer Hospital. The cut-off values of NLR, PLR, LMR, and CRP were determined according to the receiver operating characteristic curve, and the correlation of NLR, PLR, LMR, and CRP with prognosis was analyzed based on the cut-off value.

The cut-off value for NLR, PLR, LMR, and CRP were 3.18, 122, 4.04, and 8.8, respectively. Univariate analysis showed that age ($P = .022$), tumor-node-metastasis (TNM) stage ($P < .001$), T stage ($P = .001$), and N stage ($P < .001$) were significantly correlated with disease-free survival (DFS), while age ($P = .011$), TNM stage ($P < .001$), T stage ($P = .008$), N stage ($P < .001$), and PLR ($P = .001$) were significantly correlated with overall survival (OS). In multivariate analysis, age (hazard ratio [HR]: 1.564, 95% confidence interval [CI]: 1.087–2.252, $P = .016$) and TNM stage (HR: 1.704, 95% CI: 1.061–2.735, $P = .027$) remained independent risk factors affecting DFS, while age (HR: 1.721, 95% CI: 1.153–2.567, $P = .008$), TNM stage (HR: 2.198, 95% CI: 1.263–3.824, $P = .005$), and PLR (HR: 1.850, 95% CI: 1.246–2.746, $P = .002$) were independent risk factors affecting OS.

The preoperative PLR is superior to NLR, LMR, and CRP as a biomarker for evaluating the prognosis of patients undergoing curative surgery for NSCLC.

Abbreviations: CIs = confidence intervals, CRI = cancer-related inflammation, CRP = C-reactive protein, DFS = disease-free survival, HRs = hazard ratios, LMR = lymphocyte-monocyte ratio, NLR = neutrophil-lymphocyte ratio, NSCLC = non-small cell lung cancer, OS = overall survival, PLR = platelet-lymphocyte ratio, ROC = receiver operating characteristic curve, VEGFR = vascular endothelial growth factor receptor.

Keywords: C-reactive protein, lymphocyte-monocyte ratio, neutrophil-lymphocyte ratio, non-small cell lung cancer, platelet-lymphocyte ratio, prognostic factor

1. Introduction

Lung cancer is the most prevalent cancer worldwide, and the most common type is non-small cell lung cancer (NSCLC), accounting for at least 85% of all lung cancer cases.[1] Surgery is the most important curative treatment modality for NSCLC, but the prognosis markedly differs between patients, with the 5-year survival rate after surgery varying between 36% and 82%.[2] Some studies have shown that preoperative performance status,

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smoking history, age, gender, histopathological type, tumor stage, surgical margin, and carcinoembryonic antigen are prognostic factors of NSCLC.[3–10] However, to date, NSCLC prognosis is evaluated mainly based on the tumor-node-metastasis (TNM) staging system. Patients with the same TNM stage could have different clinical outcomes and prognosis. Therefore, effective biomarkers should be applied to supplement TNM staging to ultimately achieve a more accurate pre-treatment risk stratification for individualized treatment of NSCLC patients.

Cancer-related inflammation (CRI) is associated with the development of cancer.[11,12] Inflammatory cells in the tumor microenvironment could induce tumor growth and metastasis by promoting tumor cell proliferation, angiogenesis, and DNA damage.[11,13,14] Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and C-reactive protein (CRP), which are evaluated based on the combination of inflammatory cells, are accurate indicators of the inflammatory state. Recent studies have shown that high NLR, PLR, and CRP levels[15–17] or low LMR[18] are significantly related to the poor prognosis of NSCLC. Further, studies have also shown that NLR has superior prognostic value than PLR.[19,20] However, a recent prospective study found that NSCLC prognosis is related to PLR, while its correlation with NLR was not significant.[21] Sakai et al found that NLR could not predict the prognosis of patients with lung adenocarcinoma undergoing radical resection.[22] In addition, some studies have shown that CRP is an independent risk factor of prognosis in NSCLC and colorectal cancer.[23–25] However, van der Stok et al found that the CRP level was not significantly correlated with cancer prognosis.[26]

Therefore, the prognostic value of inflammation indicators in NSCLC is still unclear, and thus they cannot be applied effectively in clinical practice. This study aimed to investigate the prognostic value of inflammatory markers in NSCLC to provide a basis for a more accurate risk stratification and treatment in the postoperative period.

2. Methods

2.1. Patients and data collection

We retrospectively evaluated patients with NSCLC who underwent radical surgery at Sichuan Cancer Hospital between January 2012 and April 2014. The inclusion criteria were:

(1) histopathologically confirmed NSCLC;
(2) complete preoperative blood test data;
(3) complete follow-up data.

Patients who

(1) received preoperative treatment such as chemotherapy and radiation therapy;
(2) had second primary malignancies;
(3) died within 3 months due to surgical or postoperative complications;
(4) had infection confirmed via preoperative microbiology or clinical evidence;
(5) had preoperative hematopoietic system, bone marrow hematopoietic system, and autoimmune diseases;
(6) were taking glucocorticoids, granulocyte colony-stimulating factors, and other drugs that stimulate the bone marrow hematopoietic system within 1 week before surgery were excluded.

In total, 254 patients were included in the study. Data on clinicodemographic parameters including gender, age, smoking history, type of surgery, histopathology, tumor diameter, differentiation, radiotherapy, and chemotherapy were collected from the Electronic Medical Record System. This study was approved by the Institutional Review Board of Sichuan Cancer Hospital and Research Institute and Written informed consent was obtained from each patient.

2.2. Inflammatory markers

Preoperative complete blood cell count (platelet, neutrophil, and lymphocyte counts) was evaluated using Sysmex XE-5000 Automated Hematology System (Shanghai, China). Preoperative CRP level was determined through BECKMAN ARRAY 360 (Brea) using turbidimetric inhibition immunoassay. NLR and PLR were calculated by dividing the absolute number of neutrophils or platelets, respectively, by the absolute number of lymphocytes. LMR was calculated as the absolute lymphocyte count divided by the absolute monocyte count. Postoperative TNM staging was according to the seventh edition of the Lung Cancer Staging Guide set by the American Joint Committee on Cancer and the Union for International Cancer Control.

2.3. Follow-up

The primary endpoint of this study was overall survival (OS), while the secondary endpoint was disease-free survival (DFS). OS was defined as the time from the date of surgery to the date of death by any cause or the last follow-up, while DFS was defined as the time from the date of surgery to the date of recurrence. All patients were followed up every 3 months for the first 2 years, every 6 months for 2 to 5 years, and once a year after 5 years. The follow-up deadline for all patients was December 31, 2017. At each visit, the patients were assessed using clinical assessments, tumor marker test, and imaging examinations including computed tomography, magnetic resonance imaging, and ultrasonography.

2.4. Statistical analysis

Receiver operating characteristic curve (ROC) curves of the NLR, PLR, LMR, and CRP were plotted to determine the cut-off value that yielded the optimal sensitivity and specificity based on the maximum value of the Youden index. The $\chi 2$ test was used to compare categorical variables, and Fisher exact probability test was used for between-group comparisons. Survival curves were plotted using the Kaplan–Meier method compared using log-rank test. Univariate and multivariate analyses were performed using the Cox regression proportional hazard model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to quantify the intensity of correlation between the predictors and prognosis. All statistical analyses were performed using the SPSS statistical package (SPSS statistics 17.0) and Medcalc statistical software. A *P*-value less than .05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Among the 254 patients, 186 (73.2%) were male and 68 (26.8%) were female. The mean patient age was 60.2 ± 9.5 years (range

30–82 years), and 150 (59.1%) patients had a history of smoking. A total of 134 patients (52.8%) had adenocarcinoma; 112 patients (44.1%), squamous cell carcinoma; 6 patients (2.4%), adenosquamous carcinoma; and 2 patients (0.8%), large cell carcinoma. There were 138 (54.3.7%) patients who underwent postoperative adjuvant chemotherapy, and 18 (7.1%) underwent postoperative adjuvant chemotherapy. With respect to TNM stage, 102 (40.2%) patients had stage I disease; 59 (23.2%), stage II; and 93 (36.6%), stage III. The patients' clinicodemographic characteristics and levels of inflammatory response markers are shown in Table 1.

Table 1

Clinical data and levels of inflammatory response markers of the patients (n = 254).

Variable	N (%)/median (range)
Gender	
Male	186 (73.2%)
Female	68 (26.8%)
Age, yr	
≥60	141 (55.5%)
<60	113 (44.5%)
Smoking history	
Smoker	150 (59.1%)
Nonsmoker	104 (40.9%)
Type of surgery	
Lobectomy	207 (81.5%)
Bilobectomy	27 (10.6%)
Pneumonectomy	20 (7.9%)
Histopathology	
Adenocarcinoma	134 (52.8%)
Squamous cell	112 (44.1%)
adenosquamous	6 (2.4%)
Large cell	2 (0.8%)
TNM stage	
I	102 (40.2%)
II	59 (23.2%)
III	93 (36.6%)
T stage	
1	78 (30.7%)
2	117 (46.1%)
3	36 (14.2%)
4	23 (9.1%)
N stage	
0	140 (55.1%)
1	40 (15.7%)
2	65 (25.6%)
3	9 (3.5%)
Tumor diameter, cm	
≤5 cm	155 (61.0%)
>5 cm	99 (39%)
Differentiation	
Poor	121 (47.6%)
Moderate	53 (20.9%)
Well	22 (8.7%)
Unknown	58 (22.8%)
Chemotherapy	
Yes	138 (54.3%)
No	116 (45.7%)
Radiotherapy	
Yes	18 (7.1%)
No	236 (92.9%)
Neutrophil, 10^9/L	4.25 (1.32–15.81)
Platelet, 10^9/L	186 (60–615)
Lymphocyte, 10^9/L	1.55 (0.47–3.55)
CRP, mg/L	4.99 (0.12–221.10)
NLR	2.86 (0.20–19.00)
PLR	122 (31–651)
LMR	3.94 (0.47–19.29)

CRP = C-reactive protein, LMR = lymphocyte-monocyte ratio, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, TNM = tumor-node-metastasis.

3.2. Cut-off value for inflammatory response markers

We performed ROC curve analysis to evaluate the predictive capability of these inflammatory response markers for OS (Fig. 1). The optimal cut-off values of NLR, PLR, LMR, and CRP were 3.18, 122, 4.04, and 8.8, respectively based on the maximum principle of the Youden index. The area under the curve for PLR was 0.653 (95% CI: 0.591–0.711, $P = .0001$); LMR, 0.623; NLR, 0.592; and CRP, 0.508 (Table 2). This shows that PLR had the most significant correlation with NSCLC prognosis.

3.3. Relationship between inflammatory response markers and clinicopathological characteristics

Patients were grouped according to the cut-off values of the inflammatory response markers, and the relationship between each inflammatory index and clinicopathological features was evaluated. The results showed that the NLR was associated with gender, age, pathological type, TNM stage, T stage, and tumor diameter ($P < .05$), while PLR was only associated with tumor diameter ($P = .029$) (Table 3). In addition, LMR was significantly associated with gender, age, pathological type, T stage, and tumor diameter ($P < .05$). CRP had significant differences in gender, smoking history, pathological type, TNM stage, T stage, tumor diameter, and pathological grade ($P < .05$) (Table 4).

3.4. Prognostic analysis

The median follow-up time was 48.0 months (range, 3–72 months), and the average follow-up for 43 months. In

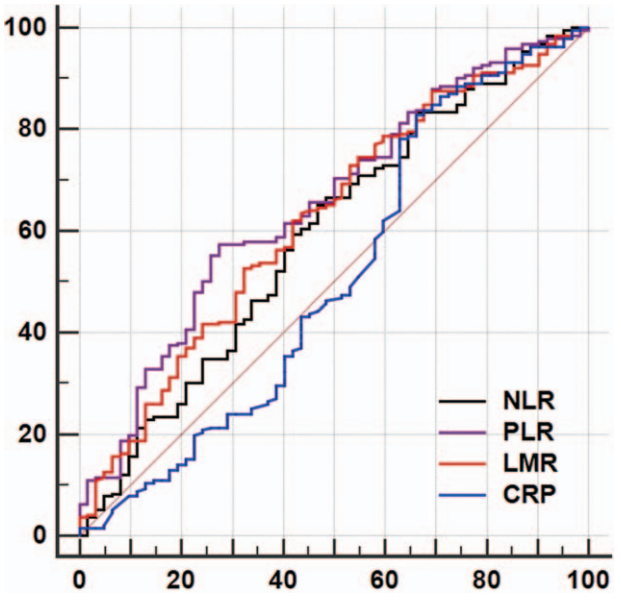

Figure 1. ROC curve of the preoperative inflammation markers for OS. OS = overall survival, ROC = receiver operating characteristic.

Table 2

Cut-off values of the preoperative inflammation markers.

Variable	Cut-off level	AUC	Sensitivity	Specificity	95% CI	*P*
NLR	3.18	0.592	0.651	0.532	0.529–0.653	.03
PLR	122	0.653	0.573	0.726	0.591–0.711	.0001
LMR	4.04	0.623	0.526	0.677	0.560–0.683	.002
CRP	8.8	0.508	0.828	0.338	0.444–0.571	.872

AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, LMR = lymphocyte-monocyte ratio, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio.

total, 108 patients (42.5%) died of progressive disease, and the median OS had not been reached at the time of that analysis. There were 127 patients (50%) who developed tumor recurrence, and the median DFS was 51.0 months. The 5-year OS and DFS were 54% and 40%, respectively. In univariate analysis, the factors significantly correlated with DFS were age (HR: 1.524; 95% CI: 1.064–2.184, $P = .022$), TNM stage (HR: 1.753; 95% CI: 1.095–2.807, $P = .019$), T stage (HR: 1.958; 95% CI: 1.252–3.063, $P = .003$), and N stage (HR: 2.588; 95% CI: 1.722–3.890, $P < .001$) (Table 5). Meanwhile, they were age (HR: 1.670; 95% CI: 1.125–2.479, $P = .011$), TNM stage (HR: 2.347; 95% CI: 1.351–4.077, $P = .002$), T stage (HR: 1.787; 95% CI: 1.085–2.944, $P = .023$), N stage (HR: 3.203; 95% CI: 2.077–4.939, $P < .001$), and PLR (HR: 1.936; 95% CI: 1.312–2.858, $P = .001$) for OS (Table 5). In multivariate analysis using the Cox proportional hazards model, TNM stage (HR: 1.704, 95% CI: 1.061–2.735, $P = .027$) was an independent prognostic factor for DFS (Table 6), while age (HR: 1.721; 95% CI: 1.153–2.567, $P = .008$), TNM stage (HR: 2.198, 95% CI: 1.263–3.824, $P = .005$), and PLR (HR: 1.850, 95% CI: 1.246–2.746, $P = .002$) were independent prognostic factors for OS (Table 6).

Kaplan–Meier survival curves were plotted to illustrate survival differences between the high and the low preoperative

Table 3

Clinicopathological features of the high and the low NLR groups and the high and the low PLR group.

Variable	NLR <3.18	NLR ≥3.18	*P*	PLR <122	PLR ≥122	*P*
Gender			.04			.888
Male	105 (41.3%)	81 (31.9%)		91 (35.8%)	95 (37.4%)	
Female	48 (18.9%)	20 (7.9%)		34 (13.4%)	34 (13.4%)	
Age, yr			.014			
<60	78 (30.7%)	35 (13.8%)		63 (24.8%)	50 (19.7%)	.077
≥60	75 (29.5%)	66 (26.0%)		62 (24.4%)	79 ((31.1%)	
Smoking			.193			.899
Yes	85 (33.5%)	65 (25.6%)		73 (28.7%)	77 (30.3%)	
No	68 (26.8%)	36 (14.2%)		52 (20.5%)	52 (20.5%)	
Histopathology			.000			.852
Adenocarcinoma	96 (37.8%)	38 (15.0%)		68 (26.8%)	66 (26.0%)	
Squamous cell	53 (20.9%)	59 (23.2%)		54 (21.3%)	58 (22.8%)	
Adenosquamous	4 (1.6%)	2 (0.8%)		2 (0.8%)	4 (1.6%)	
Large cell	0 (0.0%)	2 (0.8%)		1 (0.4%)	1 (0.4%)	
TNM stage			.045			.553
I	72 (28.3%)	30 (11.8%)		54 (21.3%)	48 (18.9%)	
II	29 (11.4%)	30 (11.8%)		26 (10.2%)	33 (13.0%)	
III	52 (20.5%)	41 (16.1%)		45 (17.7%)	48 (18.9%)	
T stage			.01			.082
1	67 (22.4%)	21 (8.3%)		41 (16.1%)	37 (14.6%)	
2	67 (26.4%)	50 (19.7%)		59 (23.2%)	58 (22.8%)	
3	15 (5.9%)	21 (8.3%)		11 (4.3%)	25 (9.8%)	
4	14 (5.5%)	9 (3.5%)		14 (5.5%)	9 (3.5%)	
N stage			.954			.513
0	85 (33.5%)	55 (21.7%)		67 (26.4%)	73 (28.7%)	
1	25 (9.8%)	15 (5.9%)		24 (9.4%)	16 (6.3%)	
2	38 (15.0%)	27 (10.6%)		30 (11.8%)	35 (13.8%)	
3	5 (2.0%)	4 (1.6%)		4 (1.6%)	5 (2.0%)	
Tumor diameter, cm			.000			.029
<5 cm	108 (42.5%)	47 (18.5%)		85 (33.5%)	70 (27.6%)	
≥5 cm	45 (17.7%)	54 (21.3%)		40 (15.7%)	59 (23.2%)	
Differentiation			.051			.284
Poor	64 (25.2%)	57 (22.4%)		58 (22.8%)	63 (24.8%)	
Moderate	31 (12.2%)	22 (8.7%)		28 (11.0%)	25 (9.8%)	
Well	16 (6.3%)	6 (2.4%)		7 (2.8%)	15 (5.9%)	
Unknown	42 (16.5%)	16 (6.3%)		32 (12.6%)	26 (10.2%)	

NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, TNM = tumor-node-metastasis.

Table 4

Clinicopathological features of the high and the low LMR groups and the high and the low CRP groups.

Variable	LMR <4.04	LMR ≥4.04	P	CRP <8.8	CRP ≥8.8	P
Gender			.01			.002
Male	106 (41.7%)	80 (31.5%)		137 (53.9%)	49 (19.3%)	
Female	26 (10.2%)	42 (16.5%)		62 (24.4%)	6 (2.4%)	
Age, yr			.000			
<60	44 (17.3%)	69 (27.2%)		94 (37.0%)	19 (7.5%)	.125
≥60	88 (34.6%)	53 (20.9%)		105 (41.3%)	36 (14.2%)	
Smoking			.447			.003
Yes	81 (31.9%)	69 (27.2%)		108 (42.5%)	42 (16.5%)	
No	51 (20.1%)	53 (20.9%)		91 (35.8%)	13 (5.1%)	
Histopathology			.001			.000
Adenocarcinoma	55 (21.7%)	79 (31.1%)		122 (48.0%)	12 (4.7%)	
Squamous cell	72 (28.3%)	40 (15.7%)		70 (27.6%)	42 (16.5%)	
Adenosquamous	3 (1.2%)	3 (1.2%)		5 (2.0%)	1 (0.4%)	
Large cell	2 (0.8%)	0 (0.0%)		2 (0.8%)	0 (0.0%)	
TNM stage			.754			.020
I	53 (20.9%)	49 (19.3%)		87 (34.3%)	15 (5.9%)	
II	33 (13.0%)	26 (10.2%)		39 (15.4%)	20 (7.9%)	
III	46 (18.1%)	47 (18.5%)		73 (28.7%)	20 (7.9%)	
T stage			.027			.002
1	31 (12.2%)	47 (18.5%)		70 (27.6%)	8 (3.1%)	
2	68 (26.8%)	49 (19.3%)		90 (35.4%)	27 (10.6%)	
3	23 (9.1%)	13 (5.1%)		21 (8.3%)	15 (5.9%)	
4	10 (3.9%)	13 (5.1%)		18 (7.1%)	5 (2.0%)	
N stage			.096			.549
0	81 (31.9%)	59 (23.2%)		111 (43.7%)	29 (11.4)	
1	18 (7.1%)	22 (8.7%)		28 (11.0%)	12 (4.7%)	
2	27 (10.6%)	38 (15.0%)		52 (20.5%)	13 (5.1%)	
3	6 (2.4%)	3 (1.2%)		8 (3.1%)	1 (0.4%)	
Tumor diameter, cm			.000			.000
<5 cm	66 (26.0%)	89 (35%)		134 (52.8%)	21 (8.3%)	
≥5 cm	66 (26.0%)	33 (13.0%)		65 (25.6%)	34 (13.4%)	
Differentiation			.49			.009
Poor	68 (26.8%)	53 (20.9%)		88 (34.6%)	33 (13.0%)	
Moderate	28 (11.0%)	25 (9.8%)		40 (15.7%)	13 (5.1%)	
Well	10 (3.9%)	12 (4.7%)		17 (6.7%)	5 (2.0%)	
Unknown	26 (10.2%)	32 (12.6%)		54 (21.3%)	4 (1.6%)	

CRP = C-reactive protein, LMR = lymphocyte-monocyte ratio, TNM = tumor-node-metastasis.

PLR groups. Patients with PLR ≥122.22 had significantly worse OS compared to those with PLR <122.22 ($P = .001$) (Fig. 2A). Subgroup analysis based on TNM stage and pathology showed that among patients with stage I and stage II disease, those with a PLR >122.22 had slightly worse OS compared with those with a PLR ≤122.22 (Fig. 2B and C), but the difference was not statistically significant (P for stage I and II = .103 and .166, respectively). Meanwhile, among patients with stage III disease, those with PLR ≥122.22 had significantly poorer survival outcomes compared with those with PLR <122.22 ($P = .004$, Fig. 2D). In the subgroup analysis according to pathological types, the low PLR group had better prognosis than the high PLR group in both adenocarcinoma and squamous cell carcinoma patients ($P = .025$ and .003, respectively; Fig. 2E and F).

4. Discussion

Several studies have indicated that inflammatory markers including NLR, PLR, CRP, and LMR could effectively predict the prognosis of patients with NSCLC,[15–18] and this has been confirmed by 2 high-quality meta-analyses.[15,16] However, recent studies have questioned the value of inflammatory markers in the prognosis of cancer. Sakai et al showed that NLR could not predict postoperative recurrence of lung adenocarcinoma.[22] Meniawy et al also reported that NLR could not predict the prognosis of malignant pleural mesothelioma.[27] Dutta et al indicated that there was no significant correlation between preoperative PLR and prognosis of gastric cancer.[28] In addition, 1 study demonstrated that PLR, but not PLR, was an independent risk factor for the prognosis of NSCLC patients.[29] Therefore, the significance of these inflammatory markers in the prognosis of NSCLC is unclear and needs further investigation. In our study, the ROC curve was used to evaluate the correlation between inflammatory markers and prognosis. The area under the ROC curve of each inflammatory marker was compared and we found that PLR > LMR > NLR > CRP, showing that PLR is more significantly correlated with prognosis than other inflammation markers. Our study showed that preoperative PLR was an independent prognostic factor for NSCLC, while NLR, LMR, and CRP were not, consistent with the results of Lan et al[21] Dilek et al[29] and van der Stok et al.[26] To the best of our knowledge, our study was the first to demonstrate that preoperative PLR has superior prognostic value to other inflammatory markers for NSCLC patients who have undergone

Table 5

Univariate analysis of prognostic factors of DFS and OS.

Variable	DFS			OS		
	HR	95 CI%	*P*	HR	95% CI	*P*
Gender						
Female	1			1		
Male	1.080	0.732–1.595	.697	1.254	0.806–1.949	.315
Age, yr						
<60	1			1		
≥60	1.524	1.064–2.184	.022	1.670	1.125–2.479	.011
Smoking						
No	1			1		
Yes	1.010	0.710–1.436	.957	1.269	0.859–1.876	.232
Histopathology						
Squamous cell	1			1		
Adenocarcinoma	1.264	0.885–1.805	.198	1.140	0.775–1.675	.506
Adenosquamous	0.387	0.053–2.802	.347	0.911	0.221–3.755	.897
TNM stage						
I	1			1		
II	1.753	1.095–2.807	.019	2.347	1.351–4.077	.002
III	2.826	1.868–4.274	.000	3.780	2.325–6.145	.000
T stage						
1	1			1		
2	1.958	1.252–3.063	.003	1.787	1.085–2.944	.023
3	2.156	1.224–3.800	.008	2.552	1.402–4.643	.002
4	3.444	1.856–6.390	.000	2.607	1.312–5.178	.006
N stage						
0	1			1		
1	1.520	0.937–2.465	.09	1.622	0.932–2.825	.087
2	2.588	1.722–3.890	.000	3.203	2.077–4.939	.000
3	4.061	1.743–9.461	.001	5.021	2.242–11.245	.000
Differentiation						
Poor	1			1		
Moderate	1.005	0.643–1.571	.984	0.864	0.515–1.447	.578
Well	0.754	0.387–1.472	.408	1.034	0.525–2.035	.923
Unknown	0.941	0.598–1.479	.791	1.049	0.655–1.680	.842
Tumor diameter, cm						
<5 cm	1			1		
≥5 cm	1.412	0.994–2.007	.054	1.333	0.912–1.948	.138
Adjuvant chemotherapy						
No	1			1		
Yes	1.331	0.935–1.895	.112	1.067	0.730–1.560	.739
NLR						
<3.18	1			1		
≥3.18	1.352	0.951–1.921	.093	1.409	0.963–2.060	.077
PLR						
<122	1			1		
≥122	1.329	0.937–1.886	.110	1.936	1.312–2.858	.001
LMR						
<4.04	1			1		
≥4.04	0.831	0.587–1.178	.299	0.739	0.505–1.081	.119
CRP						
<8.8	1			1		
≥8.8	1.221	0.806–1.848	.346	1.391	0.899–2.151	.138

CI = confidence interval, CRP = C-reactive protein, DFS = disease-free survival, HR = hazard ratio, LMR = lymphocyte-monocyte ratio, NLR = neutrophil-lymphocyte ratio, OS = overall survival, PLR = platelet-lymphocyte ratio, TNM = tumor-node-metastasis.

surgical resection, and thus it can be used as a biomarker to evaluate patient prognosis.

The standard optimal cut-off value for these markers is yet to be established; some studies choose the median of each inflammatory marker as the cut-off value, while others determine the cut-off value based on previous studies. Kacan et al determined the cutoff value of NLR as 2.5, 3, 4, and 5, with NLR >5 being an independent prognostic factor for NSCLC.[30] However, Tomita demonstrated that high preoperative NLR (≥2.5 vs <2.5, $P = .039$) was significantly associated with poor OS.[31] Meanwhile, the PLR cut-off in the study by Lan et al was 148.6,[21] whereas it was 119.50 in the study by Wu et al.[32] Hu defined the cut-off values of LMR as 3.68 based on the ROC curve of LMR and prognosis correlation.[18] In 1 study, the upper limit of normal CRP value (≤3 mg/L) was found as the cut-off value, and the study reported that high levels of pretreatment

Table 6

Multivariate analysis of prognostic factors of DFS and OS.

Variable	DFS HR	DFS 95 CI%	DFS *P*	OS HR	OS 95% CI	OS *P*
Age, yr						
<60	1			1		
≥60	1.564	1.087–2.252	.016	1.721	1.153–2.567	.008
TNM stage						
I	1			1		
II	1.704	1.061–2.735	.027	2.198	1.263–3.824	.005
III	2.951	1.948–4.470	.000	4.041	2.481–6.582	.000
PLR						
<122.22	1			1		
≥122.22	1.283	0.897–1.834	.172	1.850	1.246–2.746	.002

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, PLR = platelet-lymphocyte ratio, TNM = tumor-node-metastasis.

serum CRP was a poor prognostic factor.[17] In our study, a ROC curve was constructed to determine the optimal cut-off value based on the correlation between the inflammatory marker and patient prognosis and the sensitivity and specificity. The cut-off value of NLR and PLR were 3.18 and 122, respectively, consistent with previous studies. Meanwhile, the cut-off value of LMR and CRP were different from that in previous studies, which could be due to the difference in patient characteristics. Further large-scale studies are needed to confirm these cut-offs.

The potential mechanism by which inflammation influences cancer prognosis is yet to be determined, but it could be related to systemic inflammatory response and changes in tumor microenvironment. The neutrophil and platelet counts are important indices of systemic inflammation, with the increase in neutrophil and platelet count indicating patient response to CRI. Neutrophils could secrete cytokines that promote tumor growth, inhibit lymphocyte activity, alter the tumor microenvironment, promote invasion and metastasis, including vascular endothelial growth

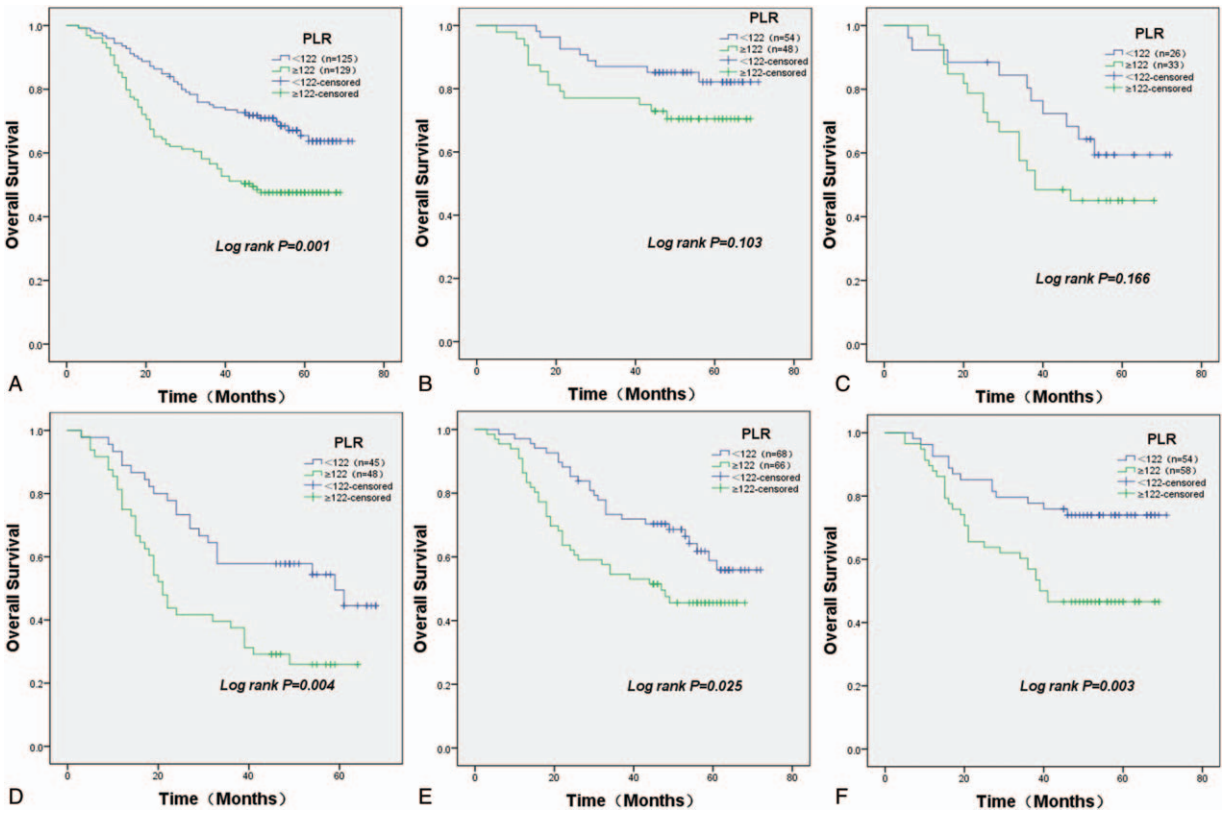

Figure 2. Relationship between preoperative PLR level and survival of NSCLC patients. (A) In the overall population, patient with PLR ≥122 had significantly poorer overall survival compared to those with PLR <122 (P = 0.001). (B, C) In stage I and II patients, those with PLR ≥122 had shorter OS than those with PLR <122, but the difference was not statistically significant (P = .103 and.166, respectively). (D) In stage III patients, those with PLR ≥122 had worse prognosis than those with PLR <122 (P = .004). (E, F) In adenocarcinoma and squamous cell carcinoma patients, those with PLR ≥122 also had significantly poorer overall survival compared to those with PLR <122 (P = .025 and .003, respectively). OS = overall survival, NSCLC = non-small cell lung cancer, PLR = platelet-lymphocyte ratio.

factor receptor (VEGFR), interleukin-6, and interleukin-8.[33] Platelets not only participate in hemostasis and coagulation, but also in inflammation and tumor development. They could secrete cytokines that stimulate the proliferation of tumor cells and adhere to other cells, including platelet-derived growth factor, platelet factor 4, transforming growth factor-β, VEGFR, and thrombospondin-1.[34,35] As an immune monitoring cell, lymphocytes secrete cytokines to kill or induce apoptosis of tumor cells. Some studies have shown that the decrease of lymphocyte indicates poor prognosis.[36] In general, CRI increases neutrophil and platelet counts, decrease lymphocyte counts, and ultimately promote tumor growth and metastasis by secreting regulatory T cells and activating chemokines.

The results of this study are different from those in previous reports owing to different inclusion criteria and different clinical characteristics of patients. Previous studies included many patients with advanced stage, while our study excluded advanced patients, which could account for poor prognosis in patients with high NLR. Further, NLR, LMR, and CRP could vary significantly over times, while PLR vary are relatively insignificant, which may have influenced research results. In previous studies, researchers were excessively enthusiastic about the positive results of inflammatory markers, but this was common in the study of biomarkers. A meta-analysis of articles on cancer prognostic biomarkers found that 95% studies reported positive results.[37] In addition, most of the current studies on inflammatory markers are retrospective observational studies, and few prospective studies have investigated the prognostic value of inflammatory markers.[21,38] Therefore, the value of inflammatory markers in cancer prognosis needs to be further verified by large-scale prospective studies.

This study has some limitations. First, this was a single-center retrospective study with a median follow-up of only 49 months, which could be insufficient for early NSCLC patients. Second, the sample size was small (only 254 patients), and thus the possibility of a type II error could not be ruled out. NLR, LMR, and CRP may also be related to the prognosis of NSCLC, but this was impossible to identify because of the small sample size. In addition, patients were diagnosed by different pathologists and treated by different thoracic surgeons, and this could also lead to different prognosis.

5. Conclusions

Our study demonstrates that PLR is superior to other systemic inflammatory response markers as a prognostic biomarker of NSCLC. It is a simple and easily available biomarker that can effectively evaluate the prognosis of NSCLC patients undergoing complete surgical resection. Thus, PLR can be useful as a clinical biological marker for risk stratification of patients after surgery and to guide individualized treatment.

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