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ORIGINAL RESEARCH

Total lymphocyte count, neutrophil–lymphocyte ratio, and platelet–lymphocyte ratio as prognostic factors in advanced non–small cell lung cancer with chemoradiotherapy

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Objective: The objective of this study was to investigate the prognostic significance and the efficacy evaluation of total lymphocyte count (TLC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in advanced non–small cell lung cancer (NSCLC) patients treated with chemoradiotherapy.

Patients and methods: A total of 389 advanced NSCLC patients who received chemoradiotherapy from 2011 to 2016 were enrolled in this retrospective study. TLC, NLR, and PLR were analyzed with overall survival (OS). Survival data were identified with the Kaplan–Meier method and optimal cutoff values with receiver operating characteristic curves.

Results: The median OS for all patients was 18.37 months. Pretreatment and median baseline TLC was $2.47\times10^3/\mu L$ (±0.78); NLR, 3.15 (±3.96); and PLR, 143.82 (±91.77); corresponding cutoffs were 2.4, 3.4, and 136.1. Higher TLC was associated with superior median OS (21.78 vs 15.66 months, $P<0.001$), and higher NLR and PLR with worse median OS (NLR: 14.13 vs 23.8 months, $P<0.001$; PLR: 15.49 vs 22.04 months, $P<0.001$).

Conclusion: The lymphopenia indicators (TLC, NLR, and PLR) were significant prognostic indicators of survival in advanced NSCLC patients treated with chemoradiotherapy.

Keywords: TLC, NLR, PLR, advanced NSCLC, chemoradiotherapy

Introduction

Lung cancer is a malignant tumor with the highest incidence worldwide, and non–small cell lung cancer (NSCLC) accounts for ~85% of all new lung cancer cases.[1] Although surgical techniques and medical treatment have been advanced by leaps and bounds, the prognosis for lung cancer remains poor, with a 5-year survival rate <15%.[2] For inoperable locally advanced patients, radiotherapy and chemotherapy are now the main treatment methods, but there is a lack of precise biomarkers for efficacy and prognosis. Therefore, sensitive and prognostic factors are needed to guide clinical practice.

An increasing number of studies have been devoted to explore the relationship between the occurrence and development of cancer and inflammation. The malignant transformation of inflammation as a very complex biological process often requires pathogens, cells, genes, and other factors involved jointly. In March 2011, two professors published an updated review which briefly describes the hot spots and progresses in oncology in the last 10 years and adds four new features on the basis of the original six features. "Tumor Promotion Inflammation" as one of the tumor cell features was

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known to us.[3–7] Peripheral blood total lymphocyte count (TLC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are signs of systemic inflammatory response, and they are closely related to prognosis of multiple malignant tumors.[8] As TLC, NLR, and PLR can be calculated by using only blood routine results, they have the advantages of being cheaper, more stable, and repeatable. At present, some studies have confirmed their correlation with the prognosis of various tumors, such as gastric cancer,[9,10] colorectal cancer,[11,12] liver cancer, cholangio carcinoma,[13] breast cancer,[14] and so on. But there are relatively few studies on the correlation of prognosis of patients with advanced NSCLC alone, especially for unresectable patients. So the aims of this study were to identify the prognostic value of TLC, NLR, and PLR in advanced NSCLC patients treated with chemoradiotherapy and whether they could be better prognostic indicators.

Patients and methods

Patient selection

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Committee Board of Shandong Cancer Hospital (Jinan, China). Written informed consent was obtained from all patients. We retrospectively collected patients with advanced NSCLC from 2011 to 2016. The inclusion criteria were: 1) patients were diagnosed as NSCLC by pathologic examination (histology and/or cytology examination); 2) according to the TNM criteria of NSCLC (Union for International Cancer Control, eighth edition), patients were diagnosed with stage IIIA or IIIB; 3) the whole course of radiotherapy was conducted in our hospital; and 4) availability of laboratory data obtained at the same institution before initiation of any curative treatment (radiotherapy, chemotherapy, or both). The exclusion criteria were: 1) had upfront surgery in the past three years; 2) did not complete radiation therapy. All the enrolled patients received standard treatment in our institution, including chemotherapy followed by concurrent chemoradiotherapy, upfront concurrent chemoradiotherapy followed by adjuvant chemotherapy, induction chemotherapy followed by sequential radiotherapy, or concurrent chemoradiotherapy alone. The standard chemotherapies were platinum-based regimens. Finally, 389 advanced NSCLC patients were included in this study. Patients were generally followed up every 3 months for the first 2 years, every 6 months from 3 to 5 years, and every year thereafter. Thoracic computed tomography (CT) and positron emission tomography-CT scans were performed at each follow-up visit, magnetic resonance imaging (MRI) studies or CT scans of the brain were also obtained at every follow-up visit or on the appearance of any neurologic symptoms. The compliance of making CT was satisfactory, but other examinations were not performed in time unless patients have symptoms.

Data collection

Patient characteristics and hematologic data were obtained from electronic medical records from Shandong Cancer Hospital. Targeted variables included age, gender, Karnofsky Performance Status (KPS) score, smoking status, and laboratory values from pretreatment data of complete blood count (CBC). The most recent CBC data before the initial point of definitive treatment (radiotherapy, chemotherapy, or both) were used. Treatment variables included chemotherapy regimen and dose, radiation technique and dose, receipt of prophylactic cranial irradiation, and receipt of induction or concurrent chemotherapy. Tumor-specific variables included T status, N status, and TNM stage. Variables from CBC included TLC, NLR, and PLR. All the CBC variables were obtained within 3 months before the initial time they received definitive treatment.

Statistical analysis

Overall survival (OS) was measured from the date of definitive therapy to the date of death from any cause or the date on which the patients were last known to be alive. In order to determine the independent prognostic factors, a multivariate analysis was performed using Cox proportional hazard model. The optimal cutoff value of TLC, NLR, and PLR were determined by a running log-rank test. The two category comparisons were performed by χ^2 test or Fisher's exact test. The comparison of continuous variables was performed by *t* test. *P*-values reported were bidirectional, and the significant level was at <0.05. All analyses were performed using SPSS statistics 19.0.

Ethics approval and consent to participate

Due to the retrospective nature of the study, informed consent was waived. The study was approved by the committee of our hospital.

Results

A total of 389 patients were treated with definitive therapy for unresectable advanced NSCLC in this study; 345 of these patients had neutrophil, lymphocyte, and platelet counts within 1 month before the initiation of definitive therapy,

but only 310 had biopsy-proven stage IIIA or IIIB NSCLC. Of these patients, 43 were excluded from this study, 29 for having been initially treated at other hospital or institution, eight for not receiving integrated course of treatment, and six for having had upfront surgery in the last three years. Finally, 267 patients were enrolled in this study; 170 patients had adenocarcinoma, 89 had squamous cell carcinoma, and eight were not specified further than NSCLC. Patient characteristics and hematologic data are shown in Table 1. The median follow-up for all patients was 28 months.

Table 1 Patient characteristics

		Pretreatment lymphocyte count		
		Value or no. of patients (%)		
Characteristic	**All patients**	**TLC <2.4×10³/μL**	**TLC ≥2.4×10³/μL**	***P*-value**
	(n=267)	(n=132)	(n=135)	
Demographics				
Gender				
Male	146	74	72	0.654
Female	121	58	63	
Age				
Median (IQR), years	62(58–71)	63(59–70)	62(60–71)	0.851
KPS score				
60–80	234	113	121	0.283
≥80	33	19	14	
Smoking status				
Current	92	43	49	0.088
Former	151	72	79	
Never	24	17	7	
Treatment				
Radiation technique				
3D-CRT	101	49	52	0.814
IMRT	166	83	83	
Chemotherapy				
No induction chemo	157	77	80	0.879
Induction chemo	110	55	55	
No concurrent chemo	70	36	34	0.698
Concurrent chemo	197	96	101	
T status				
T1	31	15	16	0.494
T2	72	34	38	
T3	70	37	33	
T4	88	45	43	
Tx	9	4	5	
N status				
N0	50	23	27	0.905
N1	38	19	19	
N2	100	52	48	
N3	79	38	41	
Disease stage				
IIIA	58	27	31	0.641
IIIB	209	105	104	
Pretreatment laboratory findings				
Hb, median (IQR), g/dL	12.9 (12.0–14.4)	12.9 (12.1–14.4)	12.9 (12.0–14.3)	0.047
WBC, median				
(IQR), ×10³/μL	7.6 (6.3–8.9)	6.8 (5.5–8.3)	8.4 (7.5–9.6)	<0.001
Neutrophils, median				
(IQR), ×10³/μL	4.8 (3.7–5.9)	4.4 (3.4–5.9)	5.1 (4.2–6.1)	0.063
Platelets, median				
(IQR), ×10³/μL	249 (201–316)	245 (197–304)	262 (217–334)	0.189

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; Hb, hemoglobin; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; KPS, Karnofsky Performance Status; TLC, total lymphocyte count; WBC, white blood cells.

The median time to obtain the indicators of hematology before treatment was 8 days (interquartile range [IQR], 1–12 days). Median baseline value of TLC was 2.47×10^3/μL (±0.78), NLR was 3.15 (±3.96), and PLR was 143.82 (±91.77). According to receiver operating characteristic (ROC) analysis, the cutoff values of TLC was 2.4 (sensitivity 43%, specificity 56%), NLR was 3.4 (sensitivity 54%, specificity 73%), and PLR was 136.1 (sensitivity 54%, specificity 73%). According to these different cutoff values, patients were divided into two groups for OS analysis.

The median OS time for all patients was 18.37 months (IQR 10.3–48.2). In univariate analysis, KPS score ≥70, TNM stage IIIB, higher TLC (≥2.4× 10^3/μL), lower NLR (<3.4), and lower PLR (<136.1) were all associated with better survival (P<0.05) (Table 2).

From the Kaplan–Meier plots of OS, we can see that patients with higher pretreatment TLC (≥2.4×10^3/μL) had better OS than patients with lower TLC (<2.4×10 /μL) (21.78 vs 15.66 months, P<0.001) (Figure 1). Inversely, patients with higher pretreatment NLR (≥3.4) and PLR (≥136.1) had worse median OS times than patients with lower NLR (<3.4) and PLR (<136.1) (NLR: 14.13 vs 23.8 months, P<0.001; PLR: 15.49 vs 22.04 months, P<0.001) (Figures 2 and 3). Because TLC, NLR, and PLR have strong collinearity, these factors cannot be tested simultaneously, so they will be tested separately in multivariate analysis.

The final multivariate Cox regression analysis was adjusted for age, KPS score, disease stage, and the CBC values (Table 3). Results indicate that along with the positive effect of KPS score on OS, higher TLC (≥2.4×10^3/μL) was associated with superior OS (HR 0.49, 95% CI 0.33–0.95, P=0.041). Conversely, higher baseline NLR (≥3.4) and higher PLR (≥136.1) were associated with inferior OS (NLR: HR

Table 2 Univariate analysis of factors potentially associated with overall survival

Characteristics	HR	95% CI	*P*-value
Age ≥65 years	1.32	0.91–2.46	0.085
Male	0.95	0.74–2.60	0.228
KPS score ≥70	2.32	1.51–4.12	0.009
TNM stage IIIB	1.24	0.87–1.94	0.013
Current smoker	0.84	0.51–1.85	0.182
Receipt of induction chemotherapy	0.73	0.32–1.54	0.797
Receipt of concurrent chemotherapy	0.88	0.45–1.84	0.791
Pretreatment TLC ≥2.4×10^3/μL	0.46	0.39–0.91	0.035
Pretreatment NLR ≥3.4	1.87	1.19–2.63	0.010
Pretreatment PLR ≥136.1	1.78	1.16–2.56	0.025

Abbreviations: HR, hazard ratio; KPS, Karnofsky Performance Status; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TLC, total lymphocyte count.

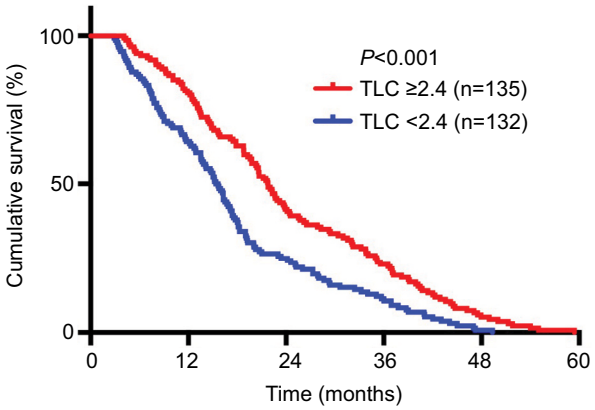

Figure 1 Kaplan–Meier plots of overall survival among patients who received chemoradiotherapy for advanced NSCLC stratified by baseline TLC.
Abbreviations: NSCLC, non–small cell lung cancer; TLC, total lymphocyte count.

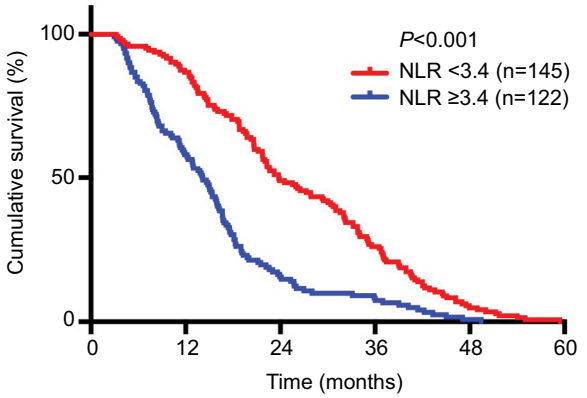

Figure 2 Kaplan–Meier plots of overall survival among patients who received chemoradiotherapy for advanced NSCLC stratified by baseline NLR.
Abbreviations: NSCLC, non–small cell lung cancer; NLR, neutrophil-to-lymphocyte ratio.

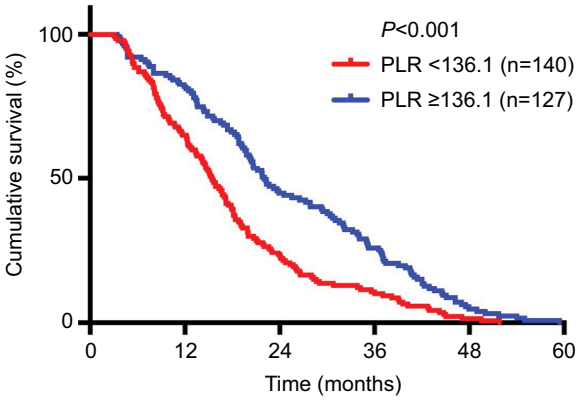

Figure 3 Kaplan–Meier plots of overall survival among patients who received chemoradiotherapy for advanced NSCLC stratified by baseline PLR.
Abbreviations: NSCLC, non–small cell lung cancer; PLR, platelet-to-lymphocyte ratio.

Table 3 Multivariate analysis of factors potentially associated with overall survival

	Model 1 (TLC included)			Model 2 (NLR included)			Model 3 (PLR included)		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Characteristics									
Age ≥65 years	1.51	0.88–2.41	0.185	1.43	0.87–2.35	0.176	1.43	0.89–2.35	0.175
KPS score ≥70	1.68	1.04–3.63	0.041	1.53	1.13–3.24	0.032	1.52	1.1–3.23	0.033
TNM stage IIIB	1.32	0.44–2.43	0.162	1.84	0.71–2.82	0.148	1.82	0.74–2.85	0.143
Pretreatment TLC ≥2.4×10^3/μL	0.49	0.33–0.95	0.041						
Pretreatment NLR ≥3.4				1.66	1.05–2.79	0.041			
Pretreatment PLR ≥136.1							1.67	1.09–2.78	0.038

Abbreviations: HR, hazard ratio; KPS, Karnofsky Performance Status; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TLC, total lymphocyte count.

1.66, 95% CI 1.05–2.79, *P*=0.041; PLR: HR 1.67, 95% CI 1.09–2.78, *P*=0.038).

Discussion

In recent years, studies have shown that systemic inflammatory response and the body's immune system are correlated with tumor progression and prognosis. Inflammatory response may promote tumor metastasis by upregulating cytokines, producing inflammatory mediators, inhibiting cell apoptosis, promoting angiogenesis, and inducing DNA mutations. The invasiveness of cells is not only related to the essential characteristics of tumor cells, but also depends on the microenvironment. Inflammatory cells secrete inflammatory mediators, cytokines, and so on to stimulate the body to produce a series of stress reaction, then excessive inflammatory cells gathered themselves together and ultimately lead to cell oxidative damage and other negative biological effects, which influence the microenvironment of the body. In the end, normal cells are transformed into tumor cells, and the changed microenvironment could accelerate tumor growth, invasion and metastasis process.[15] As for the immune system, under normal circumstances, the body relies on a complete immune mechanism to effectively monitor and reject cancerous cells, so the vast majority of individuals do not develop tumors. If cancer cells proliferate to a certain extent because they evade immune surveillance and rejection for some reason, the occurrence of tumors is inevitable.

Lymphocytes are an important part of the immune system and play a key role in immune response to cancer. TLC is closely related to the immune ability of the body and a low lymphocyte count indicates that the body is immunosuppressed.[16] Hasenclever and Diehl first detected that lymphocyte reduction was an adverse prognostic factor for advanced Hodgkin's lymphoma treated with combination chemotherapy, with or without adjuvant radiotherapy. And patients with peripheral blood lymphocyte count of <0.6×10^9/L had a worse prognosis.[17] Ray-Coquard et al reported a prospective multicenter study, peripheral blood lymphocyte count was an independent prognostic factor of OS and progression-free survival (PFS) in patients with metastatic breast adenocarcinoma treated with chemotherapy, and in patients with diffuse large B-cell lymphoma.[18]

NLR represents the state of balance between neutrophils and lymphocytes. The higher NLR is, the more obvious the imbalance state is, that is, the more severe the inflammatory response and the stronger the immune suppression. The mechanism may be that neutrophils and lymphocytes participate in the escape of the tumor's own immune system, thus promoting the occurrence and diffusion of the tumor.[19] Elevated NLR indicates a decrease in T-lymphocyte-mediated anti-tumor response, and the release of inflammatory cytokines by neutrophils can help stimulate the tumor microenvironment and promote tumor metastasis.[20] Ietomi first proposed in 1990 that the progression of malignant tumors was accompanied by increased neutrophils and decreased lymphocytes, and for the first time suggested that NLR may be associated with the prognosis of tumors.[21] And recent studies confirmed that PFS and OS of patients with high NLR were significantly inferior to those with low NLR in patients with advanced NSCLC receiving first-line targeted therapy or chemotherapy.[22,23]

Most studies suggest that PLR has the similar effect with NLR in predicting the prognosis of cancer patients. The mechanism of poor prognosis caused by elevated PLR may be related to tumor metastasis or lymphocyte reduction associated with increased platelet count in cancer patients. During the immune process, platelets are activated and release a certain amount of growth factors, which are involved in the proliferation and adhesion of tumor cells and thereby promote the occurrence and invasion of tumors.[24] Qiang et al conducted a meta-analysis on the relationship between PLR and lung cancer prognosis. The research showed that high PLR predicted shorter OS and PFS, which were independent risk factors influencing the prognosis of NSCLC patients.[25]

In our study we found that in advanced NSCLC patients treated with chemoradiotherapy, higher pretreatment TLC (≥2.4×10^3/μL) had better OS than patients with lower pretreatment TLC (<2.4×10^3/μL). Inversely, patients with higher pretreatment NLR (≥3.4) and PLR (≥136.1) had worse median OS times than patients with lower pretreatment NLR (<3.4) and PLR (<136.1). It can be seen that in advanced NSCLC, patients with high TLC and low NLR and PLR can obtain relatively good treatment effect and prognosis, which was consistent with previous research on other tumors by others. Therefore, the detection of TLC, NLR, and PLR before treatment is of certain value in the evaluation of prognosis of patients with advanced NSCLC.

However, there are still some limitations in this study. First, this study is a single-center clinical study with only 267 advanced NSCLC patients included. Therefore, a large sample multicenter clinical study is needed to verify the conclusions of this study. Second, this study did not take into account the mutation of EGFR and ALK in patients with advanced NSCLC, because the prognosis of patients receiving targeted therapy was significantly better than that of patients receiving radiotherapy and chemotherapy, which to some extent affected our evaluation of the value of TLC, NLR, and PLR in the prognosis of advanced NSCLC. In subsequent studies, the genetic status of patients should be further examined to exclude the effect of gene or targeted therapy on this result. Finally, the survival time of patients with advanced NSCLC is affected by a variety of factors, the influence of those factors on the survival time should be excluded as far as possible in subsequent studies.

Conclusion

Advanced NSCLC patients with high TLC and low NLR and PLR can obtain relatively good treatment effect and prognosis. The lymphopenia indicators (TLC, NLR, and PLR) were significant prognostic indicators of survival in advanced NSCLC patients treated with chemoradiotherapy.

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Disclosure

The authors report no conflicts of interest in this work.

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