

# Preoperative Neutrophil to Lymphocyte Ratio as a Prognostic Predictor after Curative Resection for Non-small Cell Lung Cancer

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**Abstract.** *Background: The prognostic impact of neutrophil to lymphocyte ratio (NLR) in non-small cell lung cancer (NSCLC) was examined using patients with a follow-up period more than 5 years. Patients and Methods: Two hundred and eighty four consecutive resected NSCLC patients were reviewed retrospectively. In this study, patients who were treated with a follow-up period less than 5 years were omitted, Results: The mean value of NLR was  $2.44 \pm 2.22$  (range: 0.56-29.44). The 5-year survival of the patients with a high NLR ( $\geq 2.5$ ) was significantly worse than that of the patients with a low NLR (47.06% vs. 67.84%,  $p < 0.0001$ ). Univariate analysis of the clinicopathological factors affecting survival revealed that age, gender, histology, pT status, pN status, high serum CEA level, positive findings of pleural lavage cytology and high NLR were significant risk factors for reduced survival. On multivariate analysis, a high NLR was an independent risk factor for reduced survival. Conclusion: A high preoperative NLR may be a convenient biomarker to identify patients with a poor prognosis after resection for NSCLC.*

It is generally agreed that inflammatory cells in the tumour microenvironment have significant effects on tumour development (1,2). The neutrophil count or neutrophil to lymphocyte ratio (NLR) has been documented as a simple index of systemic inflammatory response in critically ill patients with malignancy (3-14). These previous studies except for one (14) also showed that a high pretreatment NLR was associated with poor survival in patients with various malignancies (3-13). The European Lung Cancer

Working Group (15) and The Japan Multinational Trial Organisation (16) found that the high neutrophil count was an independent prognostic factor for poor survival in patients with non-small cell lung cancer (NSCLC). Tibaldi *et al.* (17) also reported similar results. Unfortunately their results were not applicable to surgical patients because patients examined in these studies were unresectable advanced NSCLC (Stage IIIB and IV). Ferrigno *et al.* (18) also found that the neutrophil count was of prognostic value in newly diagnosed patients with lung cancer, however they included 771/1201 (64.2%) patients with distant metastasis and 134/1201 (11.1%) patients with small cell lung cancer. To our knowledge, only one study has examined the prognostic significance of NLR for patients with completely resected NSCLC (19) and reported that an increasing preoperative NLR was associated with higher stage, but remained an independent predictor of survival after complete resection. However, this study included relatively many patients with Stage III and IV disease (27.68%) and only 14% of Stage IA disease. Furthermore, the cumulative survival rate was occasionally confounded due patients with short follow-up period. In the present study, the prognostic impact of the NLR was retrospectively investigated for completely resected NSCLC patients with a follow-up period more than 5 years.

## Patients and Methods

The present retrospective study was conducted from 2000 through 2005 and included 284 patients with NSCLC, who had received complete resection which consisted of either a lobectomy or a pneumonectomy together with regional lymph nodes dissection. All the patients also received intraoperative pleural lavage cytology (PLC), any patients who did not receive PLC were excluded. Any patients treated with a follow-up period less than 5 years before the study commenced were also excluded. This study included 178 men and 106 women, with ages ranging from 26 to 85 years, with an average of 67 years. The overall follow-up periods ranged from 60.7 to 131.7 months. The baseline characteristics are summarized in Table I. The NLR was calculated as neutrophil count divided by lymphocyte count from the full blood count routinely performed before surgery and no patient had clinical signs of sepsis at the time

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**Key Words:** Neutrophil-lymphocyte ratio, non-small cell lung cancer, survival.

Table I. Clinicopathological characteristics.

		Number of patients
Age	65<	104
	65≥	180
Gender	Male	178
	Female	106
Histology	Adenocarcinoma	208
	Others	76
pStage	I	189
	II	41
	III	54
pT status	pT1	153
	pT2-4	131
pN status	pN0	210
	pN1-2	74
PLC	Negative	260
	Positive	24
CEA	Normal	169
	High	115

CEA: Carcinoembryonic antigen, PLC: pleural lavage cytology.

of blood sampling for NLR. Pathological (p) TNM staging was recorded in all the patients. Follow-up information, including cause of death, was ascertained through a review of clinic notes and direct or family contact. Survival curves were obtained according to the Kaplan-Meier method. Comparison of survival curves was carried out using the log-rank test. Statistical calculations were conducted with JMP (SAS Institute Inc. Cary, NC, USA) and values of *p* less than 0.05 were accepted as significant.

### Results

The mean value of NLR was 2.44±2.22 (range: 0.56-29.44). Based on this mean value, the cut-off value of NLR was set as 2.5 (9,10). Using this discriminatory value, 199 patients had NLR less than 2.5 and 85 patients had NLR equal to or greater than 2.5. The survival curve based on NLR is shown in Figure 1 and the 5-year survival of the patients with low or high NLR was 67.84% or 47.06%, respectively (*p*<0.0001). The results of univariate analysis are summarized in Table II. The age, gender, histology, pT status, pN status, serum CEA level, PLC findings and NLR were related to patient prognosis. The results of multivariate analysis including all the variables for which *p*<0.05 on univariate analysis are summarized in Table III. Out of the variables that were included in the multivariate analysis, age, histology, pT status, pN status, positive PLC findings and NLR were independent prognostic determinants.

### Discussion

In the present study, NSCLC patients diagnosed after 2006 were omitted so that the follow-up period of all the patients could be more than 5 years. High NLR was an independent

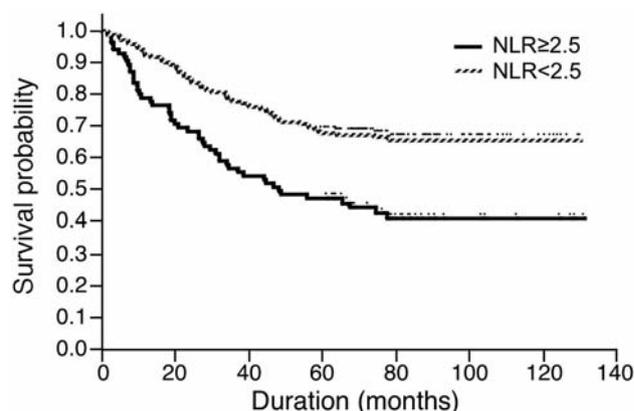


Figure 1. Survival of patients based on NLR.

prognostic factor for poor survival in these patients with resected NSCLC. The association between high NLR and poor prognosis is probably complex and largely unclear, however, several possible explanations exist. Inflammation has been shown to play an important role in the pathogenesis and progression of NSCLC (20, 21). The host's immune response to the tumour is lymphocyte dependent. Several studies have demonstrated that patients with high densities of lymphocytes in the stroma are independent positive prognostic indicators for resected NSCLC patients (20, 21). Patients with a high NLR have relative lymphocytopenia, and, as a result may exhibit a poorer lymphocyte mediated immune response to malignancy, thereby worsening their prognosis and increasing the potential for the tumour aggressiveness. Furthermore, one obvious cause of neutrophilia might be regarded as a paraneoplastic phenomenon. Such patients may be considered to have tumour-related neutrophilia, which is caused mainly by the unregulated production of haematopoietic cytokines, such as granulocyte-colony stimulating factor. Circulating neutrophils have been shown to contain and secrete the vast majority of circulating vascular endothelial growth factor, a pro-angiogenic factor that is thought to play an integral role in tumour development (22). Many previous studies used the cut-off value of 5.0 (3-7), while other studies used cut-off values varying from 2.2 to 4.0 (8-14). Using the present discriminatory value of 2.5, it was possible to differentiate clearly between two prognostic groups. However, it is possible that other useful discriminatory values exist and they should be investigated in future studies. The present series had only 18/284 (6.33%) patients with NLR>5.0 giving a frequency of NLR>5.0 lower than that in previous studies for other malignancies (27.08-42.69%) (3-9). This difference in the frequency of NLR>5.0 might be due to the differences in primary organs at least in part. Furthermore, it

Table II. *Univariate analysis.*

Factors	Risk ratio	95% CI	p-Value
Age	1.2437	1.0217-1.5319	0.0293
Gender	1.4605	1.1912-1.1817	0.0002
Histology	1.6551	1.4549-2.1437	<0.0001
pT	1.7589	1.4549-2.1457	<0.0001
pN	1.8733	1.5545-2.2513	<0.0001
CEA	1.3283	1.1056-1.5961	0.0025
PLC	2.0336	1.5761-2.5662	0.0001
NLR	1.4630	1.2137-1.7572	0.0001

CI: Confidence interval, CEA: carcinoembryonic antigen, PLC: pleural lavage cytology, NLR: neutrophil to lymphocyte ratio.

Table III. *Multivariate analysis.*

Factors	Risk ratio	95% CI	p-Value
Age	1.3149	1.0560-1.6598	0.0138
Gender	1.1218	0.8947-1.4358	0.3253
Histology	1.6216	1.3123-1.9989	<0.0001
pT	1.3379	1.0851-1.6618	0.0062
pN	1.7148	1.3816-2.2107	<0.0001
CEA	1.1695	0.9957-1.4303	0.1262
PLC	1.6378	1.2555-2.0939	0.0005
NLR	1.2863	1.0462-1.5738	0.0173

CI: Confidence interval, CEA: carcinoembryonic antigen, PLC: pleural lavage cytology, NLR: neutrophil to lymphocyte ratio.

has been reported that increasing NLR is associated with higher stage (19) and thus high NLR might be more common among patients with advanced stage disease. Previous studies (3-9) included many patients with advanced stage, while the number of patients with advanced stage in the present series was small, which might account for the difference in the frequency of high NLR. The measurement of NLR is an inexpensive and routinely available method. Preoperative prediction of recurrence and outcome using an inflammation-based score has potentially valuable implications with regard to directing both pre- and postoperative therapies to improve outcomes. From the present results, induction and/or adjuvant chemotherapies may have a significant role to play in NSCLC patients with high NLR. Therefore, the subgroup of NSCLC patients with high NLR could represent a reasonable study population for an induction and/or adjuvant therapy trial. Further prospective studies in this area are warranted.

In conclusion, because a peripheral blood cell count is a quick and easy assay to perform, measurement of the NLR may be useful as a clinical biological marker to predict prognosis in patients with NSCLC.

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