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Does neutrophil-to-lymphocyte ratio have a role among the other prognostic factors of nonsmall cell lung cancer?

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Abstract:

INTRODUCTION: Neutrophil-to-lymphocyte ratio (NLR), an index of systemic inflammation, has been associated with poor survival for many cancers. The aim of this study was to investigate the clinical significance of blood NLR in nonsmall cell lung cancer (NSCLC) as a prognostic factor.

METHODS: We retrospectively reviewed medical records of patients with NSCLC and collected data from December 2009 to September 2013. NLRs were calculated at the time of diagnosis before any type of treatment. Data about NLR, age, sex, smoking, histopathology, Eastern Cooperative Oncology Group (ECOG) performance score, disease stage, serum albumin, and treatment modalities were investigated. These parameters were tested for its association with the 1-year, 2-year, and overall survival (OS); OS was calculated by the Kaplan–Meier analysis.

RESULTS: A total of 121 patients with a median age of 61.9 (range 34–84), 14 (11.6%) female, and 107 (88.4%) males were included in the study. Majority of the patients were at local or advanced stage (Stage IIIA: 14.9%, Stage IIIB 14.9%, and Stage IV: 48.8%). Most common histological tumor type was squamous cell carcinoma (56.2%). Median neutrophil (N) count was 6.400 μl/ml, median lymphocyte (L) count was 1.570 μl/ml, while median NLR was 3.7. In univariate analysis, survival rates of patients did not have any differences according to gender, age, tumor histology, albumin level, and treatment modality (surgery and chemoradiotherapy). 1-year and 2-year survival rates of patients with ECOG 0 were higher than ECOG 1, 2, 3 patients ($P = 0.034$). Survival rates of Stage 1 patients ($P < 0.001$) and Stage 2 patients ($P = 0.035$) were longer, and survival rates of Stage 4 patients were lower than all other stages ($P < 0.001$). We divided the patients into 2 groups according to median NLR value of study group as NLR ≤3.7 and NLR >3.7. The percentage of patients who survived at the 1-year and 2-year were higher in the NLR <3.7 group ($P = 0.043$). The results showed that there was no significant difference regarding the patient's age, smoking history, tumor histology between 2 groups of high-level and low-level NLR. However, more male patients had higher NLR level ($P = 0.036$), and NSCLC patients with ECOG 2–3 ($P = 0.002$) and advanced disease stages ($P < 0.001$) were significantly associated with high-level NLR. Kaplan–Meier survival analysis revealed that there was a significant survival difference between NLR ≤3.7 and NLR >3.7 groups (14 vs. 9 months, $P = 0.036$). The multivariate Cox regression analysis revealed that the independent predictive factors for longer OS were low ECOG performance score (hazard ratio [HR] 0.786, 95% confidence interval [CI]: 0.799–0.931, $P = 0.001$), early disease stage (HR 1.517, 95% CI: 0.527–0.886, $P < 0.001$), and low NLR (HR 0.573, 95% CI: 0.440–0.962, $P = 0.036$).

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CONCLUSIONS: In our study, the increased NLR is an estimator of shorter survival in patients with NSCLC. NLR is an easy-to-measure, reproducible test that can be considered as a routine practice in patients with NSCLC.

Keywords:

Neutrophil-to-lymphocyte ratio, non-small cell lung cancer, prognosis

Introduction

Lung cancer is a rapidly spreading, aggressive tumor, and it is still one of the leading causes of death among all cancer types.[1] Approximately 85% of all lung cancer cases are nonsmall cell lung cancer (NSCLC), and the majority of patients with NSCLC have advanced disease stage at the time of diagnosis.[2] Although there have been recent advances in the diagnosis and treatment of NSCLC, their contributions to the early diagnosis and prediction of prognosis of the disease remain unsatisfactory, and the 5-year survival rate of NSCLC could reach to 15-33.9% even after radical resection of cancer.[3,4] Therefore, it is necessary to determine the prognostic factors to predict the rapid progression of NSCLC. The prognostic markers for lung cancer that have been studied and accepted so far are the patient's age,[5] gender,[6] smoking status,[7] and tumor stage tumor/node/metastasis (TNM).[8] However, even in patients with same TNM stage and same clinical and demographic characteristics, the tumor course could be different.[9]

Prognostic biomarkers such as carcinoembryonic antigen, cytokeratin-19 fragments, squamous cell carcinoma (SCC) antigen, progastrin-secreting peptide, tumor M2-pyruvate kinase, and C-reactive protein[9] have been investigated so far, but these have not been found to be used in routine practice because of their costs. Hemogram measurement is a cheap and easy method which is used in followed up of almost all patients. Leukocyte, neutrophil, lymphocyte counts, and neutrophil-to-lymphocyte ratio (NLR) are indicators of systemic inflammation, which are known to play a major role in cell-mediated destruction of cancer cells.[10] Studies conducted so far suggest that NLR can be used to predict disease progression and prognosis in different cancer types. It is proposed that patients with higher systemic inflammation at diagnosis might have more aggressive disease and should be treated promptly and potently, while an increasing NLR during treatment might be a precursor of disease progression and treatment failure.[11,12] In recent studies, NLR has been investigated and proposed to be a promising biomarker in NSCLC patients.[13-16] The aim of the our study was to evaluate the prognostic significance of pretreatment NLR levels in NSCLC patients among other prognostic factors.

Methods

Medical records of the NSCLC patients who were diagnosed and treated at the thoracic oncology unit of Gazi University Faculty of Medicine, Department of Pulmonary Medicine between December 2009 and September 2013 were retrospectively reviewed. Clinicopathological information, patient age, gender, smoking habits, performance status (Eastern Cooperative Oncology Group [ECOG]: the scale was developed by the Eastern Cooperative Oncology Group), hemogram parameters (total white blood cell [WBC] count, neutrophil count, lymphocyte count, NLR), serum albumin level at initial diagnosis, the date of diagnosis, pathological diagnosis, tumor stage, treatment, last visit date, and Exitus data were collected from patients' records. 1-year, 2-year, and overall survival (OS) were examined.

TNM stages of the patients were performed radiologically with ^{18}FDG-PET/BT, cranial magnetic resonance imaging, and clinically according to the 7th American Joint Committee on Cancer classification.[13] Tumor histology was classified as SCC, adenocarcinoma, and undetermined NSCLC.[14]

All early stage patients (Stage IA-2B) were treated with curative surgery. After surgery, patients received platinum-based adjuvant chemotherapy in accordance with their disease stage. Stage IIIA patients did not undergo surgery. All advanced stage (Stage IIIA-IV) patients received first-line platinum-based chemotherapy and received appropriate medical treatment according to their disease situation.

Statistical analysis

We used statistical software package (SPSS, version 21.0; SPSS, Inc., Chicago, IL, USA) for data analysis. Data were expressed with frequency distribution and percentages. Chi-squared statistics or Fisher's exact test The Mann–Whitney U-tests were used for comparing the differences between the groups. Survival curves were compared with the log-rank test, and Kaplan–Meier survival curves were drawn. To determine risk factors for mortality, multivariate logistic regression analysis was performed using the maximum likelihood method and backward stepwise selection. Odds ratios were calculated from the coefficients in the logistic regression model, and 95% confidence intervals (CIs) were calculated for all variables.

Results

A total of 121 patients (14 [11.6%] female, 107 [88.4%] male) with a median age of 61.9 (34–84) were included

in the study. Majority of the patients were at local or advanced stage (Stage IIIA: 14.9%, Stage IIIB 14.9%, and IV: 48.8%). Most common histological tumor type was SCC (56.2%). Median neutrophil (N) count was 6.400 µl/ml, median lymphocyte (L) count was 1.570 µl/ml, while median NLR was 3.68 (2.63–6.02). The demographics, disease characteristics, and blood biochemical parameters at the time of NSCLC diagnosis of the patients are shown in Table 1.

We subsequently investigated the association between clinical factors of NSCLC patients and 1-year survival, 2-year survival, and OS in the univariate analysis. In univariate analysis, survival rates of patients did not have any differences according to gender, age, tumor histology, albumin level, and treatment modality (surgery and chemoradiotherapy). 1-year and 2-year survival rates of patients with ECOG 0 were higher than ECOG 1, 2, 3 patients (P = 0.034). Survival rates of Stage 1 patients (P < 0.001) and Stage 2 patients (P = 0.035) were longer, and survival rates of Stage 4 patients were lower than all other stages (P < 0.001). The percentage of patients who survived at the 1-year and 2-year were higher in the NLR <3.7 group (P = 0.043) [Table 2].

Table 1: General characteristics of study population (*n*=121)

	n (%)
Gender	
Male	107 (88.4)
Female	14 (11.6)
Age, mean±SD (range)	61.9±9.5 (34-84)
<65 years	73 (60.3)
≥65 years	48 (39.7)
Smoking (package/year), mean±SD (range)	49.7±33.8 (0-160)
Smoking habit	
Never smoked	9 (7.4)
Active smoker	57 (47.1)
Ex-smoker	55 (45.5)
ECOG performance score	
ECOG 0	79 (65.3)
ECOG 1	26 (21.5)
ECOG 2	11 (9.1)
ECOG 3	5 (4.1)
Disease stage	
Stage 1A	6 (5.0)
Stage 1B	6 (5.0)
Stage 2A	4 (3.3)
Stage 2B	10 (8.3)
Stage 3A	18 (14.9)
Stage 3B	18 (14.9)
Stage 4	59 (48.8)
Tumor histopathology	
SCC	68 (56.2)
Adenocarcinoma	40 (33.0)
Adenosquamous	2 (1.7)
Undifferentiated	11 (9.1)
WBC (median) (25-75)	9.340 (7.600-11.425)
Neutrophils (median) (25-75)	6.400 9 (5.100-8.520)
Lymphocytes (median) (25-75)	1.570 (1.275-2.200)
NLR (median) (25-75)	3.68 (2.63-6.02)
Surgery	
Yes	26 (21.6)
No	95 (78.4)
Chemotherapy	
Yes	88 (72.7)
No	33 (27.3)

SD: Standard deviation, ECOG: Eastern Cooperation Oncology Group, WBC: White blood cells, NLR: Neutrophil-to-lymphocyte ratio, SCC: Squamous cell carcinoma

We divided the patients into 2 groups according to median NLR value of study group as NLR ≤3.7 and NLR >3.7. The results showed that there was no significant difference regarding the patient's age, smoking history, tumor histology between 2 groups of high-level and low-level NLR. However, more male patients had higher NLR level (P = 0.036), and NSCLC patients with ECOG 2–3 (P = 0.002) and advanced disease stages (p<0.001) were significantly associated with high-level NLR. The baseline characteristics of the NSCLC patients according to the NLR are listed in Table 3.

Kaplan–Meier survival analysis revealed that there was a significant survival difference between NLR ≤3.7 and NLR >3.7 groups (14 vs. 9 months, P = 0.036) [Figure 1].

The multivariate Cox regression analysis revealed that the independent predictive factors for longer OS were low ECOG performance score (hazard ratio [HR] 0.786, 95% CI: 0.799–0.931, P = 0.001), early disease stage (HR 1.517, 95% CI: 0.527–0.886, P < 0.001), and low NLR (HR 0.573, 95% CI: 0.440–0.962, P = 0.036) [Table 4].

Discussion

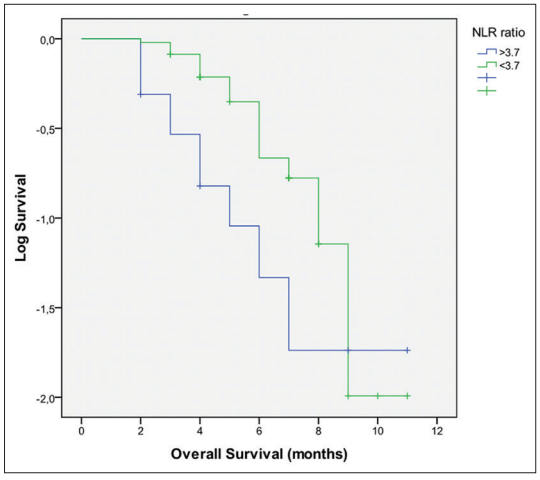

Figure 1: Kaplan–Meier curve of patients according to NLR >3.7 and NLR ≤3.7

Table 2: Survival rates of patients

Characteristics	1 year survival (%)	2 year survival (%)	*P*	OS, month (median) (25-75)
Gender				
Male (*n*=107)	49 (45.8)	26 (24.3)	0.705	10 (5-23)
Female (*n*=14)	5 (35.7)	2 (14.3)		10.5 (8.8-19.3)
Age				
<65 years (*n*=73)	31 (42.5)	20 (27.4)	0.689	10 (5.5-29.5)
≥65 years (*n*=48)	23 (47.9)	8 (16.7)		10.5 (4-19)
Smoking habits				
Never smoked (*n*=66)	31 (47)	17 (25.8)	0.858	11 (5.8-24.3)
Active/ex-smoker (*n*=55)	23 (41.8)	11 (20)		10 (4-21)
ECOG				
ECOG 0 (*n*=79)	39 (49.4)	24 (30.4)	0.034	11 (6-23)
ECOG 1 (*n*=26)	9 (34.6)	4 (15.4)	0.893	7.5 (3-15.8)
ECOG 2 (*n*=11)	4 (36.4)	0 (0)	0.981	10 (5-16)
ECOG 3 (*n*=5)	2 (40)	0 (0)	<0.001	5 (2-22.5)
Tumor histology				
SCC (*n*=68)	32 (47.1)	19 (27.9)	0.725	10 (4-25)
Adenocarcinoma (*n*=42)	18 (42.9)	7 (16.7)	0.565	11 (5-19.3)
Undifferentiated (*n*=11)	4 (36.4)	2 (18.2)	0.099	8 (7-18)
Disease Stage				
Stage 1 (*n*=12)	11 (91.7)	9 (75)	<0.001	49 (23.5-60)
Stage 2 (*n*=14)	8 (57.1)	6 (42.9)	0.035	22 (5.3-40.3)
Stage 3 (*n*=36)	19 (52.8)	11 (30.6)	0.074	15 (6-33.8)
Stage 4 (*n*=59)	16 (27.1)	2 (3.4)	<0.001	9 (4-13)
Surgery				
No (*n*=95)	32 (34.8)	9 (9.8)		9 (4-15.8)
Yes (*n*=26)	22 (75.9)	19 (65.5)		37 (13.5-51.5)
Chemotherapy				
No (*n*=33)	11 (33.3)	5 (15.2)	0.203	6 (4-13)
Yes (*n*=88)	43 (48.9)	22 (26.1)		11 (9-17)
Albumin level (g/dl)				
<25 (*n*=25)	8 (32)	5 (20)	0.250	5 (3-20.5)
≥25 (*n*=96)	46 (47.9)	23 (24)		11 (6-21.8)
NLR ratio				
≤3.7 (*n*=27)	12 (70.6)	5 (29.4)	0.043	13 (10-26.5)
>3.7 (*n*=94)	45 (43.3)	24 (23.1)		10 (4.3-21)

ECOG: Eastern Cooperation Oncology Group, NLR: Neutrophil/lymphocyte ratio, SCC: Squamous cell carcinoma

In this retrospective study, we investigated the prognostic values of inflammatory parameters (WBC, neutrophil, lymphocyte, and NLR) from complete blood count and other clinicopathological factors (age, sex, smoking, ECOG performance status, histopathological types, and disease stage) in NSCLC patients. Our results indicate that early disease stage, good ECOG performance status, and low NLR ratio were the independent prognostic factors for OS. Our results demonstrated that decreased NLR was significantly associated with longer survival.

Studies have shown that inflammatory cells, which are the basic components of microenvironment, have an important role in the progression of the tumor. Several recent studies evaluating the relationship between the immune system and tumors showed that the immune system plays important roles in killing tumor cells and preventing tumor growth while is also providing an inflammatory microenvironment that fosters tumor growth via a process called immunoediting.[11,12] It has been reported that the immune response profile and inflammatory signature in several cancers may provide useful information on patient prognosis and treatment.

It has been shown that the tumor microenvironment (TME) orchestrates tumorigenesis and malignant progression. The TME significantly influences both tumor therapeutic response and its efficacy.[17] In addition, tumor-associated neutrophils, tumor-infiltrating lymphocytes, and tumor-associated macrophages are important components of the TME and regulate the inflammatory response. These cells have also been identified as prognostic factors in malignant tumors including NSCLC.[15,16]

For almost half a century, Coussens and Werb[18] reported that chronic inflammatory response mediated the formation and development of tumors. Inflammatory

Table 3: The associations between neutrophil/lymphocyte ratio and clinical features

Characteristics	*n* (%)	NLR ≤3.7	NLR >3.7	*P*
Gender				
Male	107	23 (21.5)	84 (78.5)	0.036
Female	14	4 (28.6)	10 (71.4)	
Age (years)				
<65	73	20 (27.4)	53 (72.6)	0.452
≥65	48	7 (14.6)	41 (85.4)	
Smoking history				
Never smoked	66	10 (15.2)	56 (84.8)	
Active/ex-smoker	55	17 (30.9)	38 (69.1)	
ECOG performance score				
ECOG 0-1	105	20 (19.0)	85 (81.0)	0.002
ECOG 2-3	16	1 (6.3)	15 (93.8)	
Tumor histology				
Adenocarcinoma	42	17 (40.5)	25 (59.5)	0.623
SCC	68	8 (11.8)	60 (88.2)	
Others	11	2 (18.2)	9 (81.8)	
Disease stage				
Early stage (1-2)	26	1 (3.8)	25 (96.2)	<0.001
Locally advanced stage (3-4)	95	26 (27.4)	69 (72.6)	
Treatment modality				
Surgery	26	10 (38.5)	16 (61.5)	0.126
CT-RT	95	17 (17.9)	78 (82.1)	
Hypoalbuminemia (<2.5 g/dl)				
No	96	23 (24.0)	73 (76.0)	0.362
Yes	25	4 (16.0)	21 (84.0)	

ECOG: Eastern Cooperation Oncology Group, CT-RT: Chemotherapy-radiotherapy, NLR: Neutrophil/Lymphocyte ratio, SCC: Squamous cell carcinoma

Table 4: Multivariate cox regression analysis to reveal independent risk factors for survival

Characteristics	OS		
	HR	%95 CI	*P*
Age (≤65 vs. >65)	1.131	0.996-1.044	0.182
Gender (female vs. male)	0.657	0.956-1.218	0.196
Smoking (yes vs. no)	0.523	0.356-1.039	0.282
Histology (adenocarcinoma vs. squamous)	1.259	0.688-1.858	0.691
ECOG PS (0-1 vs. 2-3)	0.786	0.799-0.931	0.001
Stage (early stage vs. advanced stage)	5.617	3.527-17.886	<0.001
NLR (≤3.7 vs. >3.7)	0.573	0.440-0.962	0.036

HR: Hazard ratio, CI: Confidence interval, ECOG PS: Eastern Cooperation Oncology Group performance score, NLR: Neutrophil/lymphocyte ratio

reactions in the progression of tumors occur with a number of inflammatory cells, including lymphocytes, monocytes, platelets, and various signaling molecules in the cellular immune system.

In the previous study, a high pretreatment NLR was reported to be associated with a poor outcome for various types of cancers.[19] Some thresholds of NLR for patients with NSCLC have been proposed and commonly used one has been 5.[17,20-22] NLR is an inexpensive, reproducible, and widely available blood test. In previous studies, it has been shown that high neutrophil count and NLR in patients before treatment is associated with a poor prognosis.[23] Recently, an increasing neutrophil count has also been identified as an independent predictor of death in patients with lung cancer NSCLC and in advanced NSCLC[24,25] been associated with poor prognosis in stage 4 NSCLC patients.[22] In our study, we included both surgically resected early stage patients and advanced stage patients. The advanced stage, we investigated all the patient group according to NLR threshold 3.7.

Yu *et al*.[23] performed a meta-analysis to evaluate the relationship between NLR and lung cancer outcome, and it was recently published. They evaluated the relationship between NLR and OS and/or progression-free survival (PFS) in 7219 patients with lung cancer in 18 studies. They found that pretreatment high NLR predicts poor OS (HR = 1.46, 95% CI: 1.30–1.64) and poor PFS (HR = 1.42, 95% CI: 1.15461.75). Their subgroup analysis showed that the prognostic value of NLR was higher in patients undergoing surgery (HR = 1.50, 95% CI: 1.21–1.84) or higher in patients with early stage disease (HR = 1.64, 95% CI: 1.37–1.97). If the NLR cutoff value was ≥4, it was significantly predictive of poor OS (HR = 1.56, 95% CI: 1.31–1.1.85) and PFS (HR = 1.54, 95% CI: 1.13–1.82), especially in small cell lung cancer patients. An NLR cutoff value of ≥4 significantly predicted poor OS (HR = 1.56, 95% CI: 1.31–1.85) and PFS (HR = 1.54, 95% CI: 1.13–1.82), particularly in the cases of small-cell lung cancer.[23]

Limitations of this study can be considered to be that it was retrospective, single center, and there was an inequality in the early-stage and advanced-stage patient numbers. Therefore it seems to be difficult to generalize our results to all NSCLC patients.

Conclusions

Our study revealed that NLR before treatment is an independent prognostic factor of OS in patients with all stage (early and advanced stage) NSCLC. However, NLR can be greatly influenced by patient's condition and treatment. Larger prospective studies are required to confirm our findings.

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Conflicts of interest
There are no conflicts of interest.

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