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Research Article

Prognostic Significance of C-Reactive Protein and Neutrophil- Lymphocyte Ratio in Lung Adenocarcinoma Patients

Akin Ozturk,[1] Ozlem Oruc,[2] Merve Hormet Igde,[2] Ozgur Bilgin Topcuoglu,[3] Murat Kavas,[2] Cansel Atinkaya Baydemir,[4] Mahmut Gumus[5]

[1]Department of Oncology, Süreyyapaşa Chest Dieseases and Thorax Surgery Training and Research Hospital, İstanbul, Türkiye
[2]Department of Chest Diseases, Süreyyapaşa Chest Dieseases and Thorax Surgery Training and Research Hospital, İstanbul, Türkiye
[3]Department of Neurology, Atlas University, İstanbul, Türkiye
[4]Department of Thorax Surgery, Süreyyapaşa Chest Dieseases and Thorax Surgery Training and Research Hospital, İstanbul, Türkiye
[5]Department of Oncology, Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye

Abstract

Objectives: Lung adenocarcinoma (LAC) is the most common subtype of lung cancers. The prognostic value of C-Reactive Protein (CRP) and Neutrophil-Lymphocyte Ratio (NLR) in different types of cancer were reported. There is no clear information about the prognosis in association with the markers, and there are few studies for prognosis in lung cancer. For this reason we investigated CRP and NLR for prognosis in the patients with LAC.

Methods: Medical records of 294 pre-treatment LAC patients without any signs or symptoms of an infection who were admitted to the Oncology Outpatient Clinic between 2016-2019, were retrospectively analyzed. Patients were divided into three groups; local, locally advanced, metastatic considering disease course. CRP and NLR values were scanned. The relationship between disease stage, metastases, age, gender, comorbidities, smoking and family history of cancer with survival were evaluated.

Results: Deceased patients in all three groups had significantly higher CRP and NLR values ($p<0.01$). Prognosis and survival in LAC patients may be predicted via both CRP and NLR measurements.

Conclusion: We conclude that both of the two markers are reliable with significant distinction of CRP.

Keywords: Lung Adeno Carcinoma, CRP, NLR, NSCLC.

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Lung adenocarcinoma (LAC) is the most common subtype of lung cancers observed in non-smokers.[1] Familial cancer history and occupational reasons (silica, asbestosis, radon, heavy metals) are observed among detectable causes in the etiology.[1] Gene relationship and chronic inflammation relationship, p53 gene mutation have been detected in 52% of NSCLC, and p53 mutation dominance is observed in individuals with adenocarcinoma.[2]

Recent studies have also shown that tumor-related systemic inflammatory states may be a prognostic factor in cancer patients. It has been already shown in former studies that tumor cells can recruit neutrophils in the tumor stroma via

Address for correspondence: Akin Ozturk, MD. Department of Oncology, Süreyyapaşa Chest Dieseases and Thorax Surgery Training and Research Hospital, İstanbul, Türkiye
Phone: +90 216 421 42 00 **E-mail:** onkoakin@gmail.com

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specific chemokines.[3] Also, neutrophils exert pro-tumorigenic effects by increasing apoptosis inhibition, angiogenesis, and metastasis.[4,5]

In prognostic studies with NSCLC, it has been emphasized that age, gender, weight loss, smoking status, performance status and TNM Staging are independent parameters which are related to survival, although there is no consensus, yet. Just as the prognostic value of CRP in different types of cancer.[6] NLR has also been shown to be a diagnostic factor in patients with breast cancer, renal cell cancer, stomach cancer, hepatocellular cancer, metastatic melanoma, esophageal cancer, colorectal cancer, pancreatic cancer, metastatic castration-resistant prostate cancer, diffuse large B-cell lymphoma and NSCLC.[7] Neutrophil-to-lymphocyte ratio (NLR) reflects tumor-associated systemic inflammatory states; high ratios are associated with poor prognosis in multiple cancers.

We aimed to investigate the relationship of survival and prognosis with CRP and NLR in the patients with lung adenocarcinoma.

Methods

436 patients diagnosed with LAC who were referred to the medical oncology outpatient clinic of Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital between January 2016 and December 2019 were enrolled in the study. All medical records and files were meticulously examined. Patients who were older than 18 years of age with pathologically and radiologically confirmed diagnosis of LAD, who had pre-treatment CRP and NLR values without any signs or symptoms of an infection and whose further treatments and follow-ups were completed in our hospital were included in the study. 82 patients who were already under treatment, 29 patients who had certain infections and 31 patients who switched to another oncology clinic during follow-up were excluded. Overall, the current study was conducted with 294 patients. Demographic characteristics of the patients according to age, gender, comorbidities, smoking status were examined. Patients who smoked less than 100 cigarettes in their lifetime were considered non-smokers while patients who quitted smoking one year ago were considered ex-smokers.

Patients were classified according to TNM 8th staging. Same treatment plans were applied for the same stage patients. Patients in Stage I and II were evaluated for operation. According to age, comorbidities, organ functions and ECOG performance status Cisplatin and Vinorelbin were applied as postoperative adjuvant chemotherapy. Patients in Stage III were given neo-adjuvant chemo-radiotherapy and discussed in multidiciplinary oncology council to be surgery candidates after chemotherapy treatment. Operable patients went under surgery while non-operable patients were given complementary definitive radiotherapy. As first line treatment of stage IVB patients with driver mutations, patients were given mutation targeted treatment while mutation negative patients were given Cisplatin+ Pemetrexed combination. In case of disease progression in stage IV patients after first-line treatment follows-ups, patients were given single agent Dosetaxel as second line treatment.

Patients were divided into three groups according to disease course; local, locally advanced, metastatic. Predictive value of survival with CRP and NLR values were evaluated in each individual group. The relationship between disease stage, metastases, age, gender, comorbidities, smoking and family history of cancer with survival were evaluated. The results of the three groups were compared accordingly.

The follow-up durations of the patients varied between 0.27 to 58 months (14.6±12.6).

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) was used for statistical analysis. While evaluating the study data, besides descriptive statistical methods (mean, standard deviation, median, frequency, ratio), Student's t-test was used for comparing the parameters showing normal distribution between groups; Mann-Whitney U test was used for intergroup comparisons of parameters not showing normal distribution. In the comparison of qualitative data, the Pearson's Chi-Squared test and ROC analysis and diagnostic screening tests were used to determine cut-off values for CRP and NLR. Kaplan-Meier analysis was used for survival analysis. Significance was set at the $p<0.05$ level.

Ethical Considerations

The study was conducted under the Declaration of Helsinki by obtaining the approval of our hospital Ethics Committee.

Results

Of the 294 patients included in the study, 24% (n=70) were female, 76% (n=224) were male. The ages of the patients varied between 27 to 85 years, with a median value of 61.2±10 years (Table 1).

The pathological stage of 13% (n=39) of the patients were determined as Stage 1; 11% (n=32) Stage 2; 22% (n=65) Stage 3 and 54% (n=158) Stage 4. The patients were 23% (n=67) were local stage, 24% (n=69) were locally advanced, 54% (n=158) were metastatic.

Table 1. Demographic Features of Patients

	n (%)
Age (years)	
Min-Max (Median)	27-85 (61)
Gender	
Female	70 (23.8)
Male	224 (76)
Weight Loss	244 (86.5)
Smoking	
Non-smoker	55 (18.7)
Ex-smoker	83 (28)
Smoker	156 (53)
Comorbid Disease	142 (48)
Familial History of Cancer	135 (46)
Follow-up Duration (months)	0.27-58 (10.6)

Exitus were observed that 72.8% (n=214) of the patients during follow-up.

CRP levels of the patients ranged from 2 mg/L to 330 mg/L, with a mean of 42.7±53.9 mg/L. Neutrophil levels were between 0,38 κ/mm^3 and 28,4 κ/mm^3, with a mean of 7.24±4.40 κ/mm^3. Lymphocyte measurements were between 0,3 κ/mm^3 to 23,1 κ/mm^3 with a mean of 2±1.8 κ/mm^3 and the N/L ratio ranged from 0,26 to 51,82, with a mean of 4.8±4.7 (Table 2).

The death rate was found to be significantly lower in non-smokers than ex-smokers while no significant difference was observed between the surviving and deceased individuals in terms of age, gender, presence of weight loss, presence of comorbid diseases, and the frequency of cancer history in the family (p<0.005).

CRP and NLR values of the deceased patients were found to be significantly higher than those who were alive (p=0.001, p=0.001, respectively). Further analysis of CRP and NLR values in each of the three subgroups according to the the disease course (local, locally advanced, metastatic) revealed significantly higher results in deceased patients when compared to alive patients (Table 2). Evalatuation of CRP values among deceased patients showed no significant difference between the three groups (p=0.135; p>0.05). This finding shows that although CRP is higher in the metastatic group, it is a variable which predicts mortality in all three groups.

The cut-off value obtained for CRP was determined as 18.4 mg/L while cut-off value for NLR was considered as 2.77 (Table 3, Fig. 1).

The evaluation of survival rates of all patients according to CRP cut-off value by Log Rank test showed significant difference in 4 year-survival rates (p=0.001; p>0,01).

Patients who had higher CRP values had lower survival rates. Same analysis with Log Rank test in local, locally advanced and metastatic subgroups showed significant difference in survival rates (p=0.001; p=0.014; p=0.006 respectively) (Table 3).

Discussion

Inflammatory cells affect the tumor microenvironment and activate tumorigenesis.[8] In our study, a significant relationship was found between mortality and high CRP levels in patients with LAC. Hong et al. emphasized that a high CRP level is associated with poor prognosis in patients with NSCLC.[9] A high CRP level is one of the poor prognostic factors of NSCLC in a meta-analysis.[10] Although the reason why high CRP is a poor prognostic factor is still not clear, chronic inflammation (such as weight loss, decreased performance, increased fatigue) might be responsible.[11]

Neutrophil/Lymphocyte Ratio (NLR) is a current parameter that has been included in numerous publications examining cancer pathogenesis. NLR is thought to be a parameter associated with inflammation12. Although its prognostic significance is more clearly stated, publications on the predictive value for mortality are limited. In our study, the

Table 2. Comparative CRP and NLR values in different stages of the LAC

Variables (Medin±SD)	Alive (n=80)	Ex (n=214)	p
CRP	2-148 (6.78)	3.02-330 (32)	0.001
CRP values to the stage			
Local (n=67)	2-148 (5.99)	3.02-162 (25.5)	0.001
Locally Advanced (n=69)	3.02-83.5 (5.21)	3.03-175 (30.1)	0.001
Metastatic (n=158)	3.02-97.7 (10.79)	3.02-330 (34.9)	0.001
NLR	0.26-51.82 (2.59)	0.27-23 (3.98)	0.001
NLR values to the stage			
Local (n=67)	0.26-11.56 (2.20)	1.09-20.3 (3.47)	0.017
Locally Advanced (n=69)	0.52-7.87 (1.63)	0.27-11.3 (3.45)	0.016
Metastatic (n=158)	1.5-51.82 (5.20)	0.30-23 (4.72)	0.479

Table 3. Survival Analysis According to CRP cut-off point

	CRP	n	Ex	Alive	Survival Rate (%)	Mean Survival Period (month)	p
All patients							
	Normal	133	71	62	46.6	25.91±22.64	0.001**
	High (≥18.4)	161	143	18	11.2	12.77±1.17	
Local (n=67)							
	Normal	47	11	36	76.6	38.03±2.22	0.001**
	High (≥18.4)	20	16	4	20.0	17.54±2.47	
Locally Advanced (n=69)							
	Normal	31	19	12	38.7	25.56±2.92	0.014*
	High (≥18.4)	38	32	6	15.8	16.34±2.05	
Metastatic (n=158)							
	Normal	55	41	14	25.5	15.23±2.14	0.006**
	High (≥18.4)	103	95	8	7.8	9.53±1.19	

Kaplan-Meier Analysis; *p<0,05; **p<0,01.

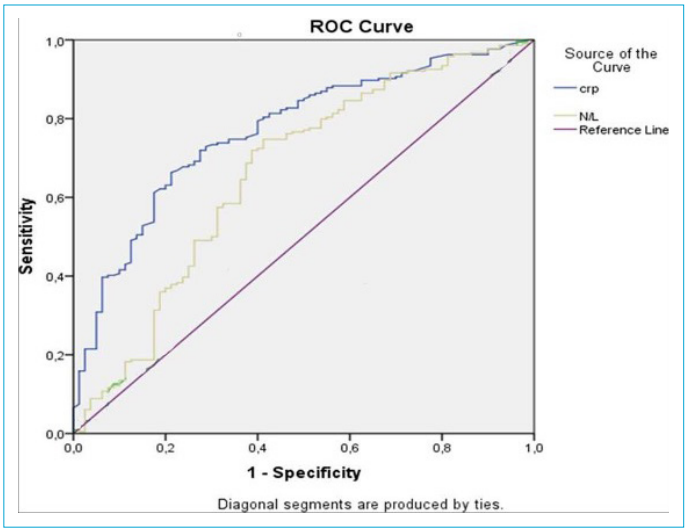

Figure 1. CRP by Mortality, ROC Curve Plot for NLR.

predictive value of NLR for mortality was found to be 2.77. Similarly Deng et al. found the predictive value of NLR to be 2.65.[12] Fourteen studies were examined in a meta-analysis on the diagnostic importance of NLR in cases with NSCLC7. The cut-off values in these studies ranged from 2,5 to 5. In a meta-analysis have shown that increased NLR is associated with decreased overall survival.[7] NLR had a negative relationship with total survival was found in operated NSCLC patients.[13] Consistently, we showed the negative effect of increased NLR on total survival.

We investigated the role of two inflamatory biomarkers in determining mortality in LAC, which is a subgroup of NSCLC, constitutes the strength of our study. The biomarkers may be potential markers for guiding the treatment response by predicting mortality in targeted therapies in the future.

Limitations in our study are retrospectively and performing it in a single-center.

It has been observed that CRP and NLR are biomarkers that can predict poor prognosis in LAC patient. Both tests can be performed easily and at low costs.

Disclosures

Ethics Committee Approval: The study was initiated after the approval of the Ethics Committee with the decision number Süreyyapaşa E.A.H. EK 116.2017.123.

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