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The role of neutrophil albumin ratio in predicting the stage of non-small cell lung cancer

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Abstract. – OBJECTIVE: Inflammation forms the basis of cancer development and progression. It causes changes in complete blood count parameters, such as neutrophil counts. Low albumin levels are associated with poor prognosis in cancer patients. We aimed to investigate the association between neutrophil to albumin ratio (NAR) and the stage of non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS: 257 NSCLC patients (24 females and 198 males) were included in the study. Patients were divided into two groups. Group 1 (n=61) included patients with early stage cancer (stage 1 and 2), while group 2 (n=196) included those with advanced stage cancer (stage 3 and 4). Demographic data, neutrophil, lymphocyte, platelet, white blood cell counts (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin and albumin levels at the time of diagnosis were recorded. The NAR of 2 groups were compared.

RESULTS: There were no significant differences between the lymphocyte count (2.0 *vs.* 2.0 $10^3/mm^3$) and platelet count (291 *vs.* 311 $10^3/mm^3$) of the two groups ($p > 0.05$). ESR (38.8 *vs.* 57.5 mm/h), CRP (158 *vs.* 57 mg/l), ferritin (85 *vs.* 261 ng/ml), WBC count (8.6 *vs.* 10.6 $10^3/mm^3$), neutrophil count (5.6 *vs.* 7.5 $10^3/mm^3$), albumin values (2.9 *vs.* 3.7 gr/dl), and ($p < 0.05$) NAR levels (1.6 *vs.* 2.3) ($p < 0.05$) were significantly higher in group 2.

CONCLUSIONS: NAR can be used in predicting the stage of NSCLC.

Key Words:
Neutrophil albumin ratio, NSCLC, Stage.

Introduction

Although there have been ground-breaking developments in the diagnosis and treatment, the incidence of lung cancer is still high all over the world. Based on the obtained results from cancer recordings in 2018, 18,078,957 cases (197.9 per 100,000) have been reported in both sexes, of which 9,456,418 (218.6 per 100,000) in men and 8,622,539 (182.6 per 100,000) in women. The number of deaths due to cancer in 2018 was 9,555,027 (101.1 per 100,000), which was estimated to be 5,385,640 in men (122.7 per 100,000) and 4,169,387 in women (83.1 per 100,000). The results showed that lung cancer has the highest incidence and mortality rates in the world with 20,938,676 new cases (with 12.22 per 100,000) and 1,761,007 deaths (19.78 per 100,000)[3]. NSCLC account for more than 80% of lung cancer cases. Most of these patients are diagnosed at an advanced stage, which complicates their treatment[3].

Inflammation forms the basis of cancer development and progression. Previous scholars[4] have shown the role of inflammatory markers in determining cancer progression and survival. Complete blood count is one of the most common tests performed in clinical work-up. Neutrophil, lymphocyte, monocyte and platelets can reflect the immune status and have important predictive value for the prognosis of tumors.

Albumin is the major protein of human serum. It plays an important role in inflammation and reflects the nutritional status of the patients. Many studies[5-9] have demonstrated the relationship between serum albumin levels and survival in several malignancies, such as colorectal cancer, breast cancer, ovarian cancer, gastric cancer and lung cancer.

NAR is a new marker indicating systemic inflammation and severity of the disease which can be calculated using complete blood count parameters. It is a cheap and easy method to predict the stage of cancer in patients with NSCLC.

The current study aimed to investigate the association between NAR and the stage of NSCLC.

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Patients and Methods

A total of 257 NSCLC patients (26 females and 231 males), who were diagnosed at the Medical Oncology Clinics of Sakarya University Medicine Faculty between January 2019 and December 2021, were enrolled in the study. All patients were diagnosed by pathologic assessment and classified according to the International Association for the Study of Lung Cancer (IASLC) Tumor, Lymph node and metastasis eighth edition (TNM) staging.

Hospital records (demographic, clinical) of patients above 18 years of age were retrospectively reviewed. Neutrophil, lymphocyte, platelet, WBC, CRP, ESR and albumin values of all patients were analyzed, and the NAR values were calculated.

Hematological parameters were analyzed by using a hematology analyzer (Abbott CELL DYN 3700 System, Ramsey, MN, USA) within 30 minutes after blood withdrawal. Serum albumin levels were analyzed by using the kinetic alkaline picrate method with the Architect C 16000, IL, USA (Abbott) device at the biochemistry laboratory of the hospital.

Patients were divided into two groups according to their stage of disease. Group 1 (n=61) included early-stage cancers; 24 (9.3%) patients with stage 1 and 37 (14.4%) patients with stage 2. Group 2 (n=196) included advanced stage cancers; stage 3 in 98 (38.1%) patients and stage 4 in 98 (38.1%) patients, according to International Association for the Study of Lung Cancer (IASLC) TNM staging.

The study was approved by Sakarya University Medicine Faculty Ethics Committee and performed in accordance with the Helsinki Declaration (28.05.2021-71522473-050.01.04-32198-315).

Statistical Analysis

Data analysis was performed by using SPSS-22 for Windows (Statistical Package for Social Science, SPSS® Corp., Armonk, NY, USA). The variables were analyzed in terms of normality distribution using Kolmogorov-Simirnov test. Depending on the normality of the distribution, continuous variables were reported as mean and standard deviation or median and interquartile range. Categorical variables were expressed using frequency tables. The Mann-Whitney U test was used to compare non-normally distributed variables, while Student's *t*-test was used to compare normally distributed variables. A suitable Chi-square test was used to analyze categorical traits and relationships between groups. The "Receiver Operating Properties (ROC)" curve analysis was used to assess the ability of neutrophil to albumin ratio factors to predict mortality. Sensitivity and specificity ratios of significant threshold values were calculated according to the ROC analysis results. A 5% type-1 error level was utilized to accept a statistically significant predictive value of the test variables while evaluating the area under the curve. The statistically significant two tailed *p*-value was considered as <0.05.

Results

A total of 257 NSCLC patients were included in the study. Histologic types were adenocarcinoma in 120 patients, squamous-cell carcinoma in 100 patients, large-cell carcinoma in 6 patients, and other histologic types in 31 patients. The mean age of the patients was 64.3 ± 9.3 years and 89.9% (n=231) were male. At the time of diagnosis, according the TNM stage classification 24 patients were stage 1, 37 patients were stage 2, 98 patients were stage 3, and 98 patients were stage 4. 196 (76.2%) patients were either stage 3 or 4, and 95 (37.0%) had distant metastases at the time of diagnosis. The most common tumor location was the right upper lobe (n=112), while the least location (n=15) was the right middle lobe (Table I).

Inflammation-related laboratory parameters, including white blood cell count, absolute neutrophil count, absolute lymphocyte count, platelet count, sedimentation, CRP, and albumin were compared between group 1 and group 2. There was a significant difference between all the parameters other than absolute lymphocyte count and platelet count (Table II). Neutrophil-albumin ratios were significantly higher in group 2 (2.3 ± 1.8) compared to group 1 (1.6 ± 1.1) (p <0.001) (Figure 1).

The value of NAR level in predicting the presence of advanced stages of lung cancer was evaluated by ROC analysis. It was found that a NAR cut-off value of 1.40 was significantly predicting the presence of advanced stages (AUC = 0.681 [95%CI=0.594-0.769], $p < 0.001$), with *a* sensitivity of 76% and specificity of 64% (Figure 2).

WBC counts were significantly higher in group 1 [8.6 ± 3.2 $10^3/mm^3$ (2.7-21.3)] compared to group 2 [10.6 ± 5.8 $10^3/mm^3$ (2.3-72.3)] (p=

Table I. Baseline characteristics of non-small-cell lung carcinoma (NSCLC) patients.

	Results (n = 257)
Age, years	64.3 ± 9.3
Gender, male (%)	231 (89.9)
Smoking, n (%)	240 (93.4)
Histological subtypes, n (%)	
Adenocarcinoma	120 (46.7)
Squamous-cell carcinoma	100 (38.9)
Large-cell carcinoma	6 (2.3)
Others	31 (12.1)
Stage at diagnosis, n (%)	
Stage 1	24 (9.3)
Stage 2	37 (14.4)
Stage 3	98 (38.1)
Stage 4	98 (38.1)
Tumor location	
Right upper lobe	112 (43.6)
Right middle lobe	15 (5.8)
Right lower lobe	30 (11.7)
Right hiler	19 (7.4)
Left upper lobe	40 (15.6)
Left lower lobe	20 (7.8)
Left hiler	21 (8.2)
Metastasis, n (%)	95 (37.0)

0.012). Neutrophil counts were significantly higher in group 1 (5.6 ± 2.8 10^3/mm^3 (0.8-16.7) compared to group 2 [7.5 ± 5.3 10^3/mm^3 (1.3-63)] (p= 0.009). Lymphocyte counts were 2.0 ± 0.6 10^3/mm^3 (0.4-3.4) in group 1 and 2.0 ± 0.8 10^3/mm^3 (0.4-5.6) in group 2 (p= 0.777). Platelet counts were 291 ± 108 10^3/mm^3 (91-630) in group 1 and 311 ± 114 10^3/mm^3 (52-897) in group 2 (p= 0.239) (Table II).

Albumin values were significantly higher in group 1 [3.7 ± 0.6 gr/l (2.1-4.6)] compared to group 2 [2.9 ± 0.6 (1.9-4.4)] (p= 0.009). ESR values were 38.8 ± 24.7 mm/h (3-92) in group 1 and 57.5 ± 35.3 mm/h (4-150) in group 2 (p= 0.002). Ferritin levels were 85 ng/ml (4.6-1976) in group 1 and 261 ng/ml (6.3-2857) in group 2 (p= 0.001). CRP levels were 34.0 mg/l (3-236) in group 1 and 57.0 mg/l (2-458) in group 2 (p= 0.001) (Table II).

We also compared inflammation-related laboratory parameters between stage 3 and 4. WBC counts were 9.7 ± 3.1 10^3/mm^3 (4.7-21) in stage 3 and 11.5 ± 7.5 10^3/mm^3 (2.32-72.3) in stage 4 (p=0.012), Neutrophil counts were 6.5 ± 2.7 10^3/mm^3 (2.3-17.3) in stage 3 and 8.6 ± 6.9 10^3/mm^3 (1.33-63) in stage 4 (p=0.007), CRP levels were 22 mg/l (9-81.5) in stage 3 and 65.8 mg/l (17.7-131) in stage 4 (p=0.006). Ferritin levels were 200 ng/ml (103-329) in stage 3 and 415 ng/ml (176-1146) in stage 4 (p=0.002), NAR values were 1.8±0.9 in stage 3 and 2.8±2.4 in stage 4 (p= 0.001). All these parameters were significantly higher in stage 4. Albumin values were 3.6 ± 0.5 gr/l (2.1-4.5) in stage 3 and 3.3 ± 0.5 gr/l (1.9-4.4) in stage 4 and significantly lower in stage 4 (p= 0.001) (Table III).

Discussion

In the current study, we found high WBC, neutrophil and NAR levels and low albumin values in patients with advanced stage of NSCLC. High NAR levels were associated with advanced stage NSCLC and poor prognosis.

The inflammatory response has an important role in different stages of tumoral development by inhibiting apoptosis and accelerating angiogenesis. Neutrophils release chemokines and cytokines. These released cytokines and chemokines stimulate angiogenesis, cytogenesis, antiviral defense, and help in the regulation of immune response[10]. Neutrophils play a key role in tumor

Table II. Comparison of indicators of inflammation between patients with early stage and locally-advanced/metastatic disease.

	Stage I-II (n = 61)	Stage III-IV (n = 196)	p-value
White blood cell count, 10^3/mm^3	8.6 ± 3.2	10.6 ± 5.8	0.012
Absolute neutrophil count, 10^3/mm^3	5.6 ± 2.8	7.5 ± 5.3	0.009
Absolute lymphocyte count, 10^3/mm^3	2.0 ± 0.6	2.0 ± 0.8	0.777
Platelet count, 110^3/mm^3	291 ± 108	311 ± 114	0.239
Sedimentation, mm/h	38.8 ± 24.7	57.5 ± 35.3	0.002
C-reactive protein, mg/l	34 (19-57)	57 (31-84)	0.001
Albumin, gr/l	3.7 ± 0.6	2.9 ± 0.6	0.008
Ferritin, ng/ml	85 (25-190)	261 (140-547)	< 0.001
Neutrophil/Albumin Ratio	1.6 ± 1.1	2.3 ± 1.8	< 0.001

Note: Descriptive results for continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution.

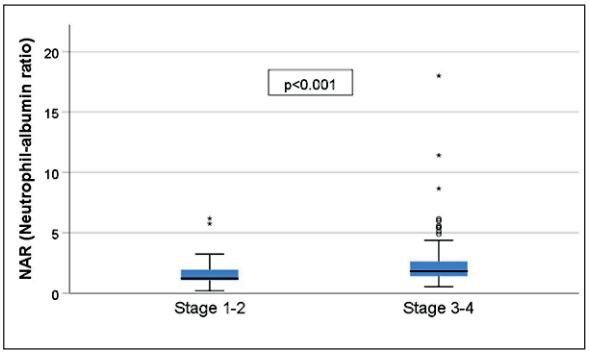

Figure 1. Comparison of NAR results of stage 1-2 and stage 3-4 patients.

progression as they trigger genetic instability, increase tumor growth, angiogenesis, and support the invasive behavior of cancer cells[11].

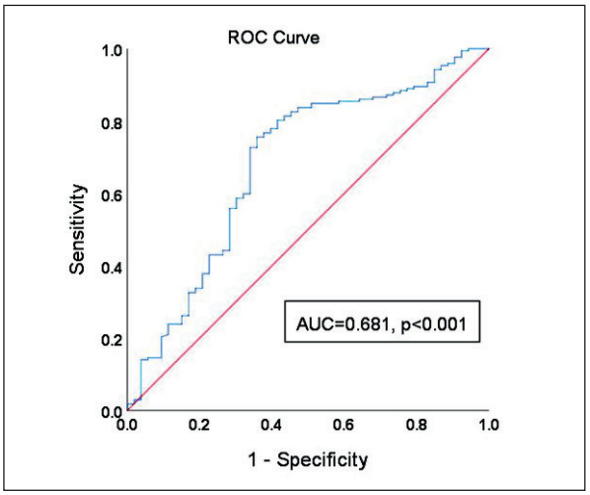

Figure 2. Receiver operating characteristic (ROC) curve of neutrophil to albumin ratio in predicting stage 3-4 disease.

We found that the neutrophil and white blood cell counts increased parallel to disease stage in patients with NSCLC. These high levels of WBC and neutrophil counts were associated with the invasive behavior of cancer cells.

Albumin is the largest protein of the extracellular matrix and synthesized in liver tissue. Serum albumin levels show the nutritional status of the body[12]. Low albumin levels are associated with malnutrition and cancer progression[13-15]. Cytokines, such as IL-6 and tumor necrosis factor synthesized in cancer patients increase catabolism and decrease albumin synthesis; therefore, hypoalbuminemia develops in advanced cancer patients[16]. We found that the albumin levels decreased as the disease stage increased in patients with NSCLC. This may be due to decreased nutrition of patients and cancer progression. Our findings are also compatible with the literature.

Several inflammations based prognostic indexes, such as Glasgow prognosis score (GPS), modified GPS, C-reactive protein/albumin ratio, albumin/globulin ratio, albumin/alkaline phosphatase ratio, Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio are used to reflect the prognosis of various tumors[17-21]. The neutrophil albumin ratio (NAR) is a recently emerging index. Tawfik et al[22] showed the relationship between NAR and pathological complete response in patients with rectal cancer. Tingle et al[23] studied NAR in palliative pancreatic cancer. Varım et al[24] demonstrated the relationship between NAR and mortality in patients with COVID-19. Wang et al[25] showed the relationship between NAR and mortality in patients with acute kidney injury. We tested a simple and new prognostic index of NAR for predicting the stage of NSCLC. We found high NAR levels in advanced stages of

Table III. Comparison of indicators of inflammation between stage 3 and stage 4.

	Stage III (n = 98)	Stage IV (n = 98)	*p*-value
White blood cell count, $10^3/mm^3$	9.7 ± 3.1	11.5 ± 7.5	0.027
Absolute neutrophil count, $10^3/mm^3$	6.5 ± 2.7	8.6 ± 6.9	0.007
Absolute lymphocyte count, $10^3/mm^3$	2.1 ± 0.8	2.0 ± 0.8	0.507
Platelet count, $10^3/mm^3$	307 ± 1 24	314 ± 103	0.636
Sedimentation, mm/h	51.7 ± 34	63.3 ± 35.7	0.062
C-reactive protein, mg/l	22 (9-81.5)	65.8 (17.7-131)	0.006
Albumin, gr/l	3.6 ± 0.5	3.3 ± 0.5	0.001
Ferritin, ng/ml	200 (103-329)	415 (176-1146)	0.002
Neutrophil/Albumin Ratio	1.8 ± 0.9	2.8 ± 2.4	0.001

Note: Descriptive results for continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution.

NSCLC. Advanced stages were associated with poor prognosis. NAR, at a cut-off level of 1.4, was predicting the advanced stages of NSCLC with a 76% sensitivity and 64% specificity. Our study is a single center and retrospective study. This is the major limitation of our study.

Conclusions

NAR is a valuable and independent marker for predicting advanced stages of NSCLC. Larger scale randomized studies should be conducted to clarify the relationship between NAR and NSCLC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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