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The Association between Inflammatory and Nutritional Markers and Survival in Elderly Patients Operated for Lung Cancer

Akciğer Kanseri Nedeniyle Ameliyat Edilen Yaşlı Hastalarda Sağkalım ile İnflamatuvar ve Beslenme Belirteçleri Arasındaki İlişki

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ABSTRACT

Aim: Today, there is an increase in cancer incidence and cancer-related deaths in the elderly population. This study aimed to evaluate the impact of neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI) levels on the survival rate in elderly patients diagnosed with non-small cell lung cancer (NSCLC).

Material and Methods: A total of 73 patients (aged ≥70 years) who operated for NSCLC between 2012 and 2018 were included in this study. Patient records were analyzed retrospectively. The NLR value was calculated with the blood neutrophil count/lymphocyte count formula. The cut-off value for NLR was considered as 2.5. The PNI value was calculated as 10 x serum albumin (g/dL) + 0.005 × total lymphocyte count (per millimeter). PNI values lower than 50 were considered as low.

Results: The mean age of the patients was 74.15±3.23 years, 59 (80.8%) patients were male and 14 (19.2%) were female. No statistically significant relation of postoperative complication was noted with PNI (p=0.354) and NLR (p=0.483). Postoperative mortality was not significantly associated with PNI (p=0.188) and NLR (p=0.465). For patients with NLR <2.5, 1-, 3-, and 5-year survival rates were at 86.0%, 86.1%, and 78.3%, respectively, while these rates were at 76.9%, 65.2%, and 24.8%, respectively, for patients with NLR >2.5 (p=0.028).

Conclusion: Results revealed a significant association of NLR with survival rates in elderly patients with NSCLC. NLR can be considered inexpensive, easily measurable, and reproducible marker that can be incorporated into routine clinical practice for guiding and optimizing treatment decisions in patients with NSCLC.

Keywords: Lung cancer; elderly population; NLR; PNI; postoperative mortality.

ÖZ

Amaç: Günümüzde yaşlı nüfusta kanser insidansında ve kansere bağlı ölümlerde artış görülmektedir. Bu çalışmanın amacı küçük hücreli dışı akciğer kanseri (KHDAK) tanılı olan yaşlı hastalarda nötrofil lenfosit oranı (NLO) ve prognostik beslenme indeksi (prognostic nutritional index, PNI) düzeylerinin sağkalım oranı üzerindeki etkisinin değerlendirilmesidir.

Gereç ve Yöntemler: Bu çalışmaya 2012 ve 2018 yılları arasında KHDAK nedeniyle opere edilmiş olan toplam 73 hasta (≥70 yaş) dahil edildi. Hasta kayıtları geriye dönük olarak analiz edildi. NLO değeri, kan nötrofil sayısı/lenfosit sayısı formülü ile hesaplandı. NLR için kesim değeri 2,5 olarak kabul edildi. PNI değeri, 10 x serum albümini (g/dL) + 0,005 x toplam lenfosit sayısı (milimetre başına) şeklinde hesaplandı. 50'nin altındaki PNI değerleri düşük olarak kabul edildi.

Bulgular: Hastaların ortalama yaşı 74,15±3,23 yıl, 59 (%80,8) hasta erkek ve 14'ü (%19,2) hasta kadındı. PNI (p=0,354) ve NLO (p=0,483) ile postoperatif komplikasyon arasında istatistiksel olarak anlamlı bir ilişki saptanmadı. Postoperatif mortalite de PNI (p=0,188) ve NLO (p=0,465) ile anlamlı olarak ilişkili değildi. NLO <2,5 olan hastalarda 1-, 3- ve 5-yıllık sağkalım oranları sırasıyla %86,0, %86,1 ve %78,3 iken bu oranlar NLR >2,5 olan hastalar için sırasıyla %76,9, %65,2 ve %24,8 idi (p=0,028).

Sonuç: Sonuçlar KHDAK olan yaşlı hastalarda NLO ile sağkalım oranları arasında anlamlı bir ilişki olduğunu ortaya koydu. NLO, KHDAK hastalarında tedavi kararlarını yönlendirmek ve optimize etmek için rutin klinik uygulamaya dahil edilebilecek ucuz, kolay ölçülebilir ve tekrarlanabilir bir belirteç olarak kabul edilebilir.

Anahtar kelimeler: Akciğer kanseri; yaşlı nüfus; NLO; PNI; postoperatif mortalite.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide, with high mortality, resulting in approximately 1.7 million deaths yearly (1). Lung cancers include two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), based on the natural course of the disease and treatment strategies. About 85% of lung cancers are NSCLC; the most common subtypes are squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (2).

There is an increase in cancer incidence and cancer-related deaths in the elderly population, along with rising average life expectancy and cancer occurrence. Approximately 50% of all cancers and 70% of cancer-related deaths occur in elderly persons aged ≥65 years. Hence, given the growing importance of cancer diagnosis, treatment, and follow-up in the elderly population, identifying effective biomarkers of prognosis and improved clinical outcomes is considered critical (3-5).

Inflammation and tumor microenvironment are associated with cancer development and progression. The cells that play a crucial role in inflammation can be involved in inflammation-induced cancer development and may affect tumor progression and life expectancy in cancer patients. Although there is increasing evidence for the roles of local immune response and the systemic inflammatory response in the formation and progression of cancer cells in recent studies, it is still unclear which inflammatory parameter is a better indicator of cancer prognosis (6,7).

The neutrophil-to-lymphocyte ratio (NLR) is a reliable and predictive inflammatory marker of the prognosis of cancer and inflammatory diseases. Current evidence indicates that high NLR has a prognostic value in various cancers, including lung cancer (8).

The prognostic nutritional index (PNI) is one of the immune nutritional parameters calculated based on serum albumin and the total lymphocyte count in peripheral blood. Although its use for stratification of operative risk and evaluation of perioperative nutritional and immunological conditions was recommended (9,10), increasing evidence has shown that its preoperative nutritional and immunological status not only affects the rapid postoperative complications but are also thoroughly related to the long-term oncological outcomes (11).

In this study, we investigated the relationship between NLR and PNI biomarkers and survival and postoperative mortality incidence in elderly lung cancer patients.

MATERIAL AND METHODS

A total of 73 elderly patients (aged ≥70 years of age) with operated NSCLC performed between 2012 and 2018 were included in this study. Patient medical records and hospitalization data were analyzed retrospectively in this study. The NLR level was assessed using the formula of blood neutrophil count/lymphocyte count. The cut-off value for NLR was considered as 2.5 (12). In addition, the PNI value was calculated as 10 x serum albumin (g/dL) + 0.005 × total lymphocyte count (per millimeter). PNI values lower than 50 were considered as low (10).

The study was approved by the Ministry of Health and Local Ethics Committee (Başkent University Local Ethic Committee's approval document dated 18.11.2020 and numbered KA20/410).

Statistical Analysis

Categorical and continuous measurements were expressed in numbers and percentages, and in mean and standard deviation values, respectively. The chi-square test or Fisher's test was used to compare categorical variables. Distributions were analyzed with the Kolmogorov-Smirnov test to compare continuous measurements between the groups. The Student's t-test was used for two groups and the one-way ANOVA for three or more groups. Survival curves for relapse and mortality were created using the Kaplan-Meier analysis and compared by log-rank test. All statistical analyzes were performed using the IBM SPSS software package v.25.0, and all p-values of <0.05 were considered statistically significant.

RESULTS

A total of 73 patients, 59 (80.8%) males and 14 (19.2%) females, participated in the study. The mean age of the patients was 74.15±3.23 (range, 70-83) years. Anatomical and wedge resections were performed in 53 (72.6%) and 20 (27.4%) patients, respectively. The number of patients in stage 1A was 14 (19.2%), and in stage 4 was 1 (1.4%). The demographic and clinical characteristics of the patients were summarized in Table 1.

No statistically significant relation in PNI (p=0.354) and NLR (p=0.483) was noted with postoperative complication. Postoperative mortality was also not significantly associated with PNI (p=0.188) and NLR (p=0.465). The comparison of NLR and PNI values according to the characteristics of the patients were shown in Table 2.

Table 1. General characteristics of the patients

Characteristics	n (%)
Gender	
Male	59 (80.8)
Female	14 (19.2)
Smoking	
Present	63 (86.3)
Absent	10 (13.7)
Localization	
Superior lobe	46 (63.0)
Inferior lobe	19 (26.0)
Middle lobe	3 (4.1)
Hiler	5 (6.9)
Resection	
Anatomical resection	53 (72.6)
Wedge resection	20 (27.4)
Surgery	
Lobectomy	43 (58.9)
Pneumonectomy	4 (5.5)
Lung-thoracic wall resection	4 (5.5)
Segmentectomy	2 (2.7)
VATS-wedge resection	20 (27.4)
Cell type	
Squamous cell	24 (32.9)
Adenocarcinoma	42 (57.5)
Others	7 (9.6)
Stage	
1A	14 (19.2)
1B	19 (26.0)
2A	19 (26.0)
2B	5 (6.8)
3A	15 (20.6)
4	1 (1.4)

Table 2. Comparison of NLR and PNI values according to the pre- and post-operative characteristics of the patients

	Smoking History		p
	Present (n=63)	**Absent (n=10)**	
NLR, mean±SD	3.26±1.32	2.03±1.02	**0.013**
PNI, mean±SD	49.45±6.83	52.60±7.79	0.231
	Lymph Node		**p**
	Present (n=9)	**Absent (n=64)**	
NLR, mean±SD	3.02±1.55	3.14±1.32	0.815
PNI, mean±SD	47.27±9.19	50.11±6.69	0.310
	Cell Type		**p**
	Squamous Cell (n=24)	**Adenocarcinoma (n=42)**	**Others (n=7)**
NLR, mean±SD	3.36±1.53	2.99±1.29	3.14±0.91	0.557
PNI, mean±SD	49.99±5.75	50.43±7.53	45.68±6.16	0.248
	Postoperative Complication		**p**
	Present (n=24)	**Absent (n=49)**	
NLR, mean±SD	2.96±1.20	3.20±1.41	0.483
PNI, mean±SD	48.71±6.77	50.37±7.06	0.354
	Postoperative Mortality		**p**
	Present (n=6)	**Absent (n=67)**	
NLR, mean±SD	3.51±1.72	3.09±1.31	0.465
PNI, mean±SD	46.23±5.89	50.16±6.99	0.188

NLR: neutrophil-to-lymphocyte ratio, PNI: prognostic nutritional index, SD: standard deviation

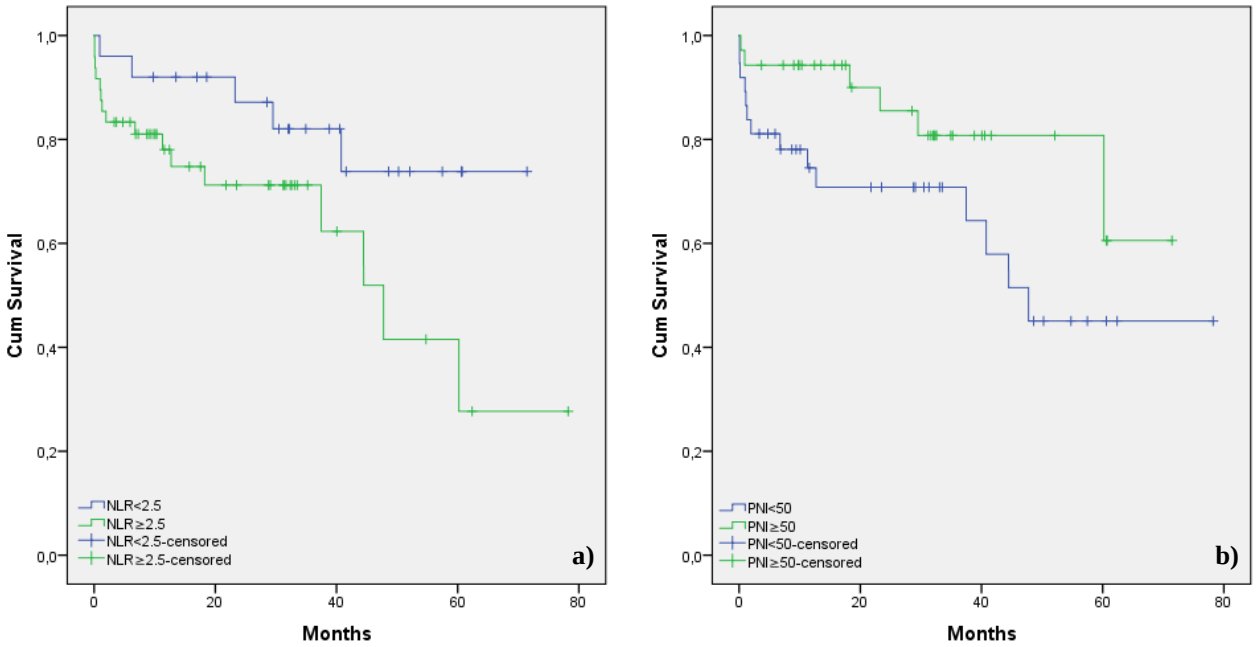

Figure 1. Kaplan-Meier curves for **a)** NLR, and **b)** PNI, NLR: neutrophil-to-lymphocyte ratio, PNI: prognostic nutritional index

For patients with NLR <2.5, 1-, 3-, and 5-year survival rates were at 86.0%, 86.1%, and 78.3%, respectively, while for patients with NLR >2.5, 1-, 3-, and 5-year survival rates were at 76.9%, 65.2%, and 24.8%, respectively (p=0.028, Figure 1a). While in patients with PNI <50, 1-, 3-, and 5-year survival rates were at 73.8%, 63.8%, and 44.6%, respectively, 1-, 3-, and 5-year survival rates were at 92.1%, 86.1%, and 61.2%, respectively, in patients with PNI >50 (p=0.065, Figure 1b).

DISCUSSION

There is growing evidence showing that the patient's nutritional and immunological status is strictly related to the long-standing outcomes of malignant tumors. Both NLR and PNI biomarkers can be calculated with simple blood analysis and can be used as prognostic indicators in determining survival and prognosis in elderly patients. Our findings revealed no significant association both for NLR and PNI values, with neither postoperative complications nor postoperative mortality. A statistically significant

association of NLR value was found with survival rate, while it was not found for PNI.

Albumin is the main protein component of plasma that maintains colloid osmotic pressure, reflecting nutritional status, and its levels tend to decline with age (13,14). Hypoalbuminemia is partly an indicator of the suppressed immune system. Therefore, a low albumin level can be associated with a weakened immune system and low survival. It has been shown that preoperative chronic inflammation and malnutrition could generate a microenvironment favorable to tumor recurrence. Considering elderly patients, chronic inflammation, malnutrition, and comorbidities often accompany the clinical picture (15). A low level of PNI is associated with a lower survival rate in several malignancies (15,16). Lymphocyte count also reflects the activation of the immune system and the inflammatory process, and low levels indicate a weakened immune system (17). The amount of lymph tissue decreases with age, consequently, the number and percentage of lymphocytes are known to decrease (18). Given its inhibitory effect on cytokine production and cytotoxic cell death, low lymphocyte counts can be associated with forming a weak immune reaction against tumor cell destruction (14-19).

In a recent meta-analysis, a low level of PNI indicated a lower survival rate in lung cancer, especially among NSCLC patients (13). In our study, the PNI value had no significant impact on the survival rate of 1-, 3-, or 5-year.

In a study by Kang et al. (20), the assessment of preoperative PNI values of 324 renal cell cancer patients, preoperative PNI values were found associated with both overall survival rate and cancer-specific survival.

In a meta-analysis study by Yang et al. (21), the authors concluded that PNI is a predictive indicator of survival rate and postoperative complications in gastric cancer patients. Albumin, the main element of serum plasma proteins, may reflect nutritional status (22). PNI reflects the host's nutritional and immunological status and can be suggested as a simple, inexpensive, easily calculated measure to predict postoperative complications and survival. In our study, no statistically significant association was observed between PNI values and postoperative complications.

Lymphocytes play an essential role in immunity against cancer, and higher lymphocyte levels are associated with better clinical outcomes. Neutrophils also play an essential role in tumor formation triggered by inflammation, and high neutrophil levels are associated with poor clinical outcomes. An increase in neutrophils inhibits the activity of lymphocytes and other immune cells (7,23,24). It is known that the leukocyte and neutrophil counts are also higher in smokers (25). Smoking is the main risk factor for lung cancer (26) and in our study, we found that NLR was significantly higher in smokers.

In a study among 171 patients diagnosed with stage 4 NSCLC, a high NLR ratio was reported negatively correlated with survival rate. The NLR ratio was suggested to be a simple, inexpensive, and reproducible survival marker (27). Similarly, our findings also revealed the significant association of NLR value with survival rate.

In a study conducted on 388 chemo-naive patients with stage IIIB or IV NSCLC, the authors reported that the pretreatment neutrophil count was significantly associated with overall and progression-free survival rates. A multivariate analysis observed a linear association between pretreatment elevated neutrophil count and shorter overall and progression-free survival. However, the relationship between NLR and overall survival was weak and non-linear (24).

Due to the retrospective single-center design of the study and the relatively small sample size, the potential lack of generalizability is an important limitation of the current study.

CONCLUSION

Our findings revealed a significant association of NLR with survival rate in elderly NSCLC patients. Several parameters are required to perform a stage-independent assessment of the surgical treatment in advanced-age cancer patients. NLR can be considered inexpensive, easily measurable, and reproducible markers that can be incorporated into routine clinical practice for guiding and optimizing treatment decisions in NSCLC patients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Başkent University Institutional Review Board (18.11.2020, KA20/410).

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