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Research Article

Prognostic Impact of Prognostic Nutritional Index and Neutrophil/Lymphocyte Ratio in Patients with Small-Cell Lung Cancer

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Abstract

Objectives: Small-cell lung cancer (SCLC) is approximately 20% of total lung cancer cases. A lot of prognostic factors have been identified in SCLC; however, new prognostic factors, which are separately assessed because of the frequency of the disease, rapid progression, and high mortality, are also required. Several recent studies have demonstrated that pretreatment prognostic nutritional index (PNI) and neutrophil/lymphocyte ratio (NLR) is associated with the prognosis in various malignancies.

Methods: Patients with SCLC were enrolled in the study. The patient's pretreatment characteristics, hemoglobin, lymphocyte-neutrophil count, C-reactive protein, platelet, and albumin levels were recorded. The PNI was calculated based on the serum albumin concentration and peripheral blood lymphocyte count ([Albuminx10]+[Lymphocytex0.005]). NLR was calculated as peripheral neutrophil counts/lymphocyte counts.

Results: Out of 81 patients, nine were female, while 72 patients were male. There was a significant survival difference between groups when patients divided into two groups with a cut-off value of 40 and 3.5 in terms of PNI and NLR, respectively. The median survivals were 3 and 13 months in low and high PNI groups, respectively.

Conclusion: Based on the results of the present study, it can be recommended to use PNI and NLR as independent prognostic markers for overall survival for patients with SCLC.

Keywords: Neutrophil/lymphocyte ratio, prognostic nutritional index, small-cell lung cancer

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Small-cell lung cancer (SCLC) accounts for about 20% of lung cancer cases, the most common cause of cancer deaths worldwide.[1] It is a clinically aggressive form of lung cancer with a dismal prognosis.[1,2] Even though works and studies for diagnosis and treatment of lung cancer have carried on, the overall survival (OS) of patients suffering from this cancer type is still low, and their median survival rates vary between 16 to 24 months.[1,3] Sex, age, tumor stage, weight loss, performance status, histopathology, lactate dehydrogenase (LDH), and carcinoembryonic antigen (CEA) levels are previously determined prognostic factors.[4] Recently identified histological and immunological biomarkers like epidermal growth factor receptor (EGFR) and intercellular adhesion molecule-1 (IDM-1) are costly and frequently take a long time to consider. For this reason, no promising prognostic factors have been found for lung can-

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cer patients that are easily detectable and closely related to clinical outcomes.[5–7] A biomarker found for prognosis will be utilized to identify patients at risk for tumor progression and metastasis to estimate their results and develop effective interventions.

Numerous recent studies have investigated complicated and high-priced genomic tests. Still, the prognostic values of biochemical markers that are available in the clinics are considerably ignored, and they have not been investigated further exploration.

Many researchers have revealed that nutrition and immune status is strictly related to tumor progression and prognosis.[8,9] It is stated that is calculated by using serum albumin levels and the total circulating lymphocyte count together, the prognostic nutritional index (PNI) could be employed to determine the nutritional and immunological status of cancer patients.[10] Several recent studies have demonstrated that pretreatment PNI is associated with the prognosis ofpatients suffering from various human malignancies including esophageal squamous cancer, colorectal cancer, gastric cancer, and lung cancer.[11–16]

The results of recent studies have revealed that the tumor immune environment increases tumor metastasis, tumor angiogenesis, and cancer cell proliferation and interferes with the response to systemic treatment so that it importantly takes part in tumor progression.[17,18]

Additionally, inflammation has an essential role in the survival and for some cancer types such as breast, lung, gastric and esophageal cancer.[19–24] Some systemic inflammatory response (SIR) markers such as C-reactive protein (CRP), levels of albumin, serum cancer markers, and fibrinogen, have already been investigated to find their impacts on tumor progression, survival, and development of metastases.[25,26] In several studies, the researchers have examined what kind of role cytokines such as IL-6, TNF, or IL-1have as significant crosstalk factors that may cause metastases.[18] Neutrophils and lymphocytes being inflammatory cells secrete chemokines, cytokines, and growth factors. They have an essential role in increasing tumor progression.[27] Neutrophil–lymphocyte-ratio (NLR) is also a reliable indicator of systemic inflammation.[28]

On the other hand, healthcare professionals do not utilize these factors during their clinical routine, and their prognostic relevance has been still ambiguous. The prognostic impact of platelet-to-lymphocyte rate (PLR) and neutrophil-to-lymphocyte ratio (NLR) has been determined for some cancer types, such as colorectal, pancreas, and lung cancer.[19,28–30]

It is easy to decide on NLR and PLR by using blood samples. Researchers have not adequately examined NLR and PLR as potential prognostic factors in SCLC. Furthermore, several studies have revealed the correlation of NLR with a prognosis of lung cancer. But, their results have indicated that there are incoherent and indefinite views about the NLR's prognostic role in lung cancer.

A lot of prognostic factors have been identified in SCLC; however, new prognostic factors, which are separately assessed because of the frequency of the disease, rapid progression, and high mortality, are also required.

This study was conducted to examine the effect of pretreatment clinical features and hematological inflammatory markers (platelet count, total lymphocyte count [TLC], PLR, and NLR) as a manifestation of systemic inflammation and immune status on overall outcome in SCLC.

Methods

Participants

In the retrospective cohort study, the archive records of patients diagnosed with lung cancer at the Akdeniz University Oncology Department were retrospectively analyzed between 2008 and 2020. Patients with small-cell lung cancer were enrolled in the study. The patient characteristics, hemoglobin, lymphocyte-neutrophil count, C-reactive protein, platelet, and albumin levels at the time of diagnosis were recorded. Also, the overall survival of the patients was calculated. The exclusion criteria were lack of adequate cancer diagnosis, clinical parameters, and follow-up.

Prognostic Indicators

The body mass index is calculated with the division of weight to the square of height in terms of meters. The prognostic nutritional index (PNI), which is calculated based on the serum albumin concentration and peripheral blood lymphocyte count ([Albumin x 10] + [Lymphocytex0.005]). Neutrophil/lymphocyte ratio is based on the division of peripheral neutrophil and lymphocyte counts.

Ethics

The study was approved by the institutional board of Akdeniz University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations.

Statistics

The statistical analysis of the study performed with SPSS software (Statistical Package for The Social Sciences, version 22.0, SPSS Inc, Chicago, IL). Descriptive data are presented as either means or median for continuous variables, frequencies and percentages are reported for categorical variables. The Kolmogorov–Smirnov test was used to determine whether data conformed to a normal distribution.

Table 1. Clinical features of the study population

Clinical features	Median	Mean
Age (years)	69	70.3
Hemoglobin (g/dl)	13	13.15
Neutrophils (µl)	6110	6152
Lymphocytes (µl)	590	1822
Monocytes (µl)	550	607
Albumin (g/dl)	4	3.85
C reactive protein (mg/dl)	2.17	4.3
Platelets (µl)	309000	325963
Weight (kg)	74	72.2
Height (m)	1.68	1.66
BMI (kg/m^2)	25.3	25.7
NLR	3.5	5.9
PNI	47.9	47.6

BMI: Body mass index; NLR: Neutrophil/lymphocyte ratio; PNI: Prognostic nutritional index.

Pearson χ^2 test is used to assessing the associations in categorical variables. OS and PFS curves are estimated by the Kaplan-Meier product-limit method. The ROC analysis was used to determine the optimal cut-off value.

Results

Out of 81 patients, nine were female, while 72 patients were male. The median age was 69. Fifty-three patients had a widespread disease, while 28 were considered a limited stage. The clinical features summarized in Table 1.

The OS between genders was not different (p=0.24). There was a statistically significant survival difference due to the stage between limited and extended stage. The median OS in the limited and extended disease was 18 and 5 months, respectively (p=0.001). When the hemoglobin levels categorized with a cut-off value of 10 g/dl, an OS difference between two groups. The median OS of low and high hemoglobin groups was 1 and 11 months, respectively (p<0.001). There was a significant survival difference between groups when patients divided into two groups with a cut-off value of 40 in terms of PNI (Fig. 1) The median survivals were 3 and 13 months in low and high PNI groups, respectively (p=0.03). Also, CRP levels have a prognostic effect on survival in univariate analysis (Fig. 2) When the patients grouped via cut-off value 10 mg/dl, the median OS was 11 and 5 months in low and high groups, respectively (p=0.03). The NLR value had a significant prognostic effect when the cut-off value determined as 3.5 (p=0.008). The cut-off value was found via ROC analysis. The prognostic impact of hemoglobin and NLR remained in multivariate analysis (p=0.02; p=0.05).

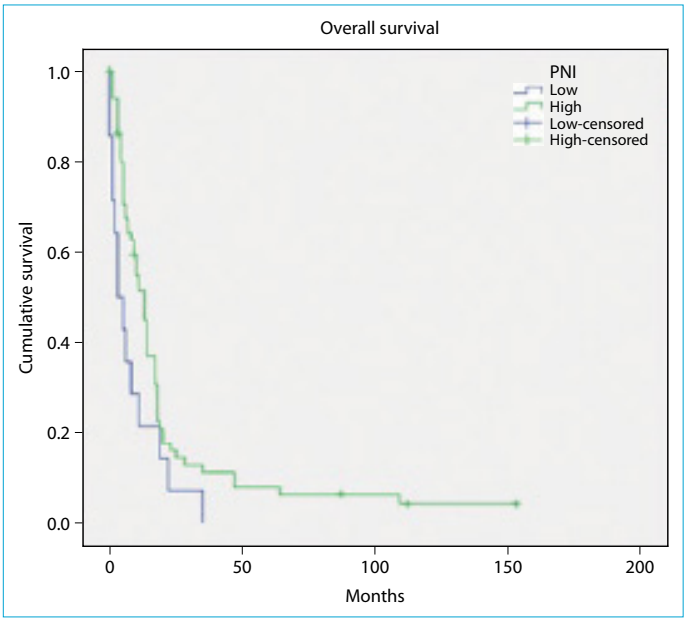

Figure 1. OS according to PNI levels.
OS: Overall survival; PNI: Prognostic nutritional index.

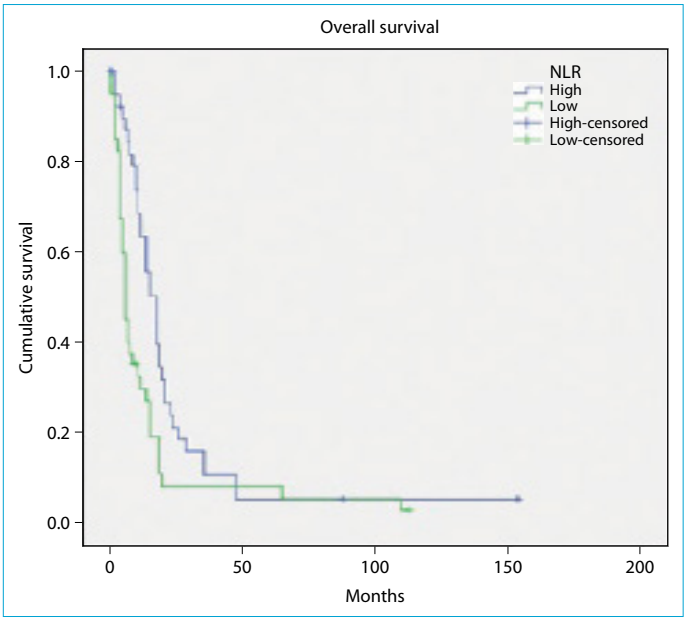

Figure 2. OS according to NLR levels.
OS: Overall survival; NLR: Neutrophil–lymphocyte-ratio.

Discussion

In this study, we found that PNI and NLR have prognostic value in SCLC. Besides these parameters, the prognostic impact of hemoglobin and NLR remained in multivariate analysis.

The PNI calculated based on serum albumin level and total lymphocyte count. These standard laboratory tests are easily accessible. A low PNI correlates with a decrease in absolute lymphocyte count and serum albumin level. Serum

albumin is an essential marker for the host's nutritional status. In various cancer types, albumin is related to both for the inflammatory reaction of the tumor and prognosis.[31–33] Cytokines are essential for both albumin production in hepatocytes, and cancer growth, and progression.[17] PNI has a critical role by initiating the cytotoxic immune response and inhibiting cancer cell proliferation, migration, and invasion.[17,34] Lymphocytopenia, which can be induced by a systemic inflammatory reaction, is associated with disease severity and poor prognosis.[35,36] Total lymphocyte count and serum albumin level may serve as indicators of nutritional status, immunity, and chronic inflammation, and all of them are of prognostic significance.

In this study examining the effect of hematological parameters and clinical features at the time of diagnosis on prognosis, it was revealed that the baseline NLR is influenced overall survival for patients with SCLC. Patients with high neutrophil-lymphocyte ratio (NLR) had lower median OS. However, PLR and lymphocytopenia were not related to survival. The results of the present study indicated that NLR was an independent prognostic marker for patients with SCLC. The results of the present study are compatible with previous reports and also a recent systematic review and meta-analysis.[37]

The tumor immune environment increases tumor angiogenesis, cancer cell proliferation, and tumor metastasis and interferes with the response to systemic treatment so that it importantly takes part in tumor progression.[17,18] Neutrophils and B and T lymphocytes have essential roles in tumor inflammation, and it is considered that the imbalance between lymphocytes and neutrophils is secondary to tumor hypoxia or necrosis and related to anti-apoptotic effects.[38–40] Representing the combined circulating lymphocyte and neutrophil counts, the neutrophil to lymphocyte ratio (NLR) may show the imbalance between neutrophils and lymphocytes in patients with tumors and functions as a representative index of systemic inflammation.

The systemic inflammatory response in colon, gastric, lung cancer, and other solid malignancies, as well as diverse solid tumors, has been associated with poor prognosis. NLR is a biomarker having prognostic significance for several cancer types.[41]

NLR, PLR, and lymphocyte are parameters that can be easily measured and repeated. Cancer-related inflammation can increase the NLR. Both neutrophilia and relative lymphocytopenia develop in various tumors.[42] Studies have recently evaluated the predictive value of NLR in some types of cancer.[24–27]

The number of recent studies investigating and identifying new prognostic factors in cancers has increased day by day. But, the majority of them have been conducted using biomarkers; therefore, sophisticated molecular and/or genetic tests are needed.[43,44] The complexity and cost of these novel tests limit their practical application. On the other hand, in the present study, prognostic factors were determined through initial laboratory test results that were available as a result of conventional medicine, without any extra cost. Also, the results of the blood tests routinely used in clinical monitoring are more reliable than most of the assays performed in a biological laboratory, and any specialized expertise or equipment is not required.

In the present study, it was found with the multivariate analysis that pretreatment high NLR (≥3.5) worsened median survival, and NLR was an independent risk factor influencing overall survival. But differently from the literature, the present study did not indicate the prognostic value of PLR and lymphocytopenia.

The stratified analyses demonstrated that low PNI was still a risk factor for poor OS in SCLC, which revealed that the pooled result of OS determined in the present study was stable.

The results of the present study have several clinical implications. Lower PNI and higher NLR have a significant correlation with shorter OS in SCLC patients. For this reason, it is required to improve the inflammatory and nutritional status of patients with SCLC at the time of diagnosis. The SCLC patients having low PNI and high NLR need additional treatment options, such as radiotherapy or induction therapy and adjuvant chemotherapy, and more intense postoperative follow-up.

Limitations

The study was retrospectively designed and had a small sample group, including heterogeneous patients from a single center. The fact that the patients were diagnosed in a relatively long period between 2008-2019 created heterogeneity in the treatment. Although procedures had been included in the multivariate model, a simplified dichotomized treatment variable may not responsible for changes in regimens over the ten years. It may not provide predictive models for the effect of different radiotherapy doses and techniques or chemotherapy combinations on patient survival. Despite all these limitations, being a cost-effective and easy-to-apply method, pretreatment PNI and NLR can be used as a prognostic marker in SCLC.

Conclusion

Consequently, based on the results of the present study with a hospital-based large cohort, it can be recommended to use PNI and NLR as an independent prognostic marker

for overall survival for patients with SCLC and to validate it in future clinical trials further. PNI and NLR may be a proper, readily available, cost-effective, and reliable biomarker with prognostic potential for SCLC. The combined utility of demographic and essential clinical information, PNI and NLR can enable help physicians and patients to predict survival and thereby enhance medical decision making for newly diagnosed SCLC patients. Accordingly, it is recommended to conduct more extensive prospective additional studies with large sample groups examining primary PNI and NLR role through other serum inflammation markers like IL-6, TNF alfa, or tissue inflammation signs like tumor-infiltrating lymphocytes.

Disclosures

Ethics Committee Approval: The Akdeniz University Clinical Research Ethics Committee granted approval for this study (Date: 08.04.2020, Number: 258).

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Conflict of Interest: None declared.

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