Globally, lung cancer (LC) is the leading cause of cancer-related death. Nearly 85% of the malignant lung tumors occur due to non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).\textsuperscript{1,2} Although rapid advances have taken place in both lung cancer detection and treatment, and the 5-year survival rates are still inconclusive.\textsuperscript{3} Nearly one-fourth of the patients with NSCLC are diagnosed with locally advanced stage (stage III) and have a poor prognosis.\textsuperscript{4} For this condition, two treatment choices may be offered, induction chemotherapy followed by surgery or concurrent chemoradiation therapy.\textsuperscript{5,6} Nevertheless, even with advanced surgical techniques and postoperative consolidation chemotherapies, the local recurrence rates are 20-40%.\textsuperscript{7}

Many prognostic factors for lung cancer, such as tumor size, lymph node involvement, gender, age, weight loss, and smoking, may affect the course of the disease.\textsuperscript{8} Recently several studies have reported that immunological parameters can affect the outcome.\textsuperscript{9,10} The systemic inflammatory response has an essential role in the development and progression of many solid tumors.\textsuperscript{11} Increased neutrophil count was found to be associated with poor prognosis, and lymphocyte count is an independent prognostic factor in solid cancers.\textsuperscript{12} Some methods to measure systemic inflammation were established, such as platelet to...
lymphocyte ratio (PLR), PNI, and neutrophil to lymphocyte ratio (NLR). These parameters were found to be correlated with poor prognosis in a variety of cancers including NSCLC.\textsuperscript{13-17}

Besides immunological parameters, the impact of nutritional status on prognosis in advance stage cancers is known, and high serum albumin level correlates with better survival in lung cancer.\textsuperscript{18}

The prognostic nutritional index (PNI), defined for the first time by Onodera et al., is calculated by using serum albumin level and circulating lymphocyte count, which can reflect both immunological and nutritional status of the cancer patients.\textsuperscript{19}

Various studies recently showed that PNI correlates with prognosis in different types of human cancers such as colorectal, lung, gastric and, esophageal cancers.\textsuperscript{2,20-24}

Several hypotheses tried to comprehend this relationship between prognosis and lymphocyte counts. Lymphocytes are essential parts of the immune system and are both controllers and effectors in response to tumor progression.\textsuperscript{25} Low lymphocyte count correlates with decreased survival in cancer patients.\textsuperscript{26-28} In addition, the PNI reflects both the nutritional and immunological status of the patients, which may be associated with reduced survival.\textsuperscript{29} Alternatively, the poor immune and nutritional course may have an association with postoperative morbidity and complications.\textsuperscript{30,31}

The prognostic significance of PNI in lung cancer is being explored extensively. However, to our knowledge, no study has investigated the relationship of PNI to chemoradiotherapy. Therefore, in this study, we tried to elucidate the relationship between PNI and chemoradiation in stage III lung cancer and whether it can be used as an independent prognostic factor before chemoradiotherapy.

\section*{MATERIAL METHODS}

\section*{STUDY PARTICIPANTS}

In the retrospective cohort study, the archive records of patients diagnosed with lung cancer at the Afyon Kocatepe University Oncology Department were analyzed between 2012 and 2018. The patients in stage III of disease and treated with concurrent chemoradiotherapy and radiotherapy were included in the study regardless of histology. For staging, the patients’ American Joint Committee on Cancer (AJCC) 7\textsuperscript{th} edition TNM was used.

The exclusion criteria were lack of adequate cancer diagnosis, platinum-based first-line chemotherapy, and lack of follow-up. Patients with hematologic malignancies, chronic inflammatory disease, clinical suspected acute infection were also excluded.

The patient characteristics, lymphocyte-neutrophil count, hemoglobin, levels of albumin, C-reactive protein, and CEA, pathologic subtype, stage of the disease, treatment modalities, chemotherapeutic agents, and chemoradiotherapy outcome after the treatment were recorded. Also, the patients’ progression-free survival (PFS), and overall survival (OS) were calculated. PFS was defined as the time from diagnosis to progression or exitus, and OS was defined as the time from diagnosis to the date of exitus due to any cause or last control.

We calculated PNI using the formula, serum albumin levels (g/dL) x 10 + total lymphocyte count (per mm\textsuperscript{3}) x 0.005 as suggest by Onodera et al.\textsuperscript{19} We used 50 as the cut-off value of PNI, which was also its median value.

Blood samples were taken during outpatient control before chemoradiotherapy and patient without prior blood tests was not included in the study.

Radiotherapy was delivered 1.8-2 Gy/day for five days a week with a total dose of 60-66 Gy. Concurrent chemotherapy was started on day 1 at the beginning of radiotherapy and continued every week during radiotherapy.

\section*{RADIOLOGIC EVALUATION}

The radiologic response evaluations were made via computed tomography (CT). The Response Evaluate Criteria for Solid Tumors (RECIST) was used to measure disease response. Progressive disease (PD) was determined as the rise of new lesions or increase in primary tumor volume by more than a 20%; partial response (PR) was described as the decrease by at least 30% in the sum of the longest diameters of the target lesions; complete response (CR) was defined as
the disappearance of all assessable lesions; the remaining patients who did not meet the criteria of PD or PR were considered as having stable disease (SD).32

ETHICS
The study was approved by the institutional board of Afyonkarahisar Health Sciences University, Faculty of Medicine, and carried out by the Declaration of Helsinki principles and all applicable regulations.

STATISTICAL ANALYSIS
The statistical analysis of the study data was performed with SPSS software (Statistical Package for The Social Sciences, version 22.0, SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to determine whether data conformed to a normal distribution. Descriptive data were presented as either means or median for continuous variables, frequencies, and percentages were reported for categorical variables. Pearson’s X² test was used to assess the associations between categorical variables. OS and PFS curves were estimated by the Kaplan-Meier product-limit estimator.

RESULTS
Sixty-three patients were enrolled in the study. The mean age of the participants was 65.2 years. All of the patients were male, and 98.4% had a history of smoking. The mean duration of smoking was 49.4 pack-years. The most frequent histologic subtype was squamous cell carcinoma. The most concurrent chemotherapy protocol included carboplatin and paclitaxel. Of the patients, 61.9% have partial remission after chemoradiation. The features of the study population are summarized in Table 1. The patients were categorized according to the PNI. The cut-off value of the PNI was determined as 50 according to the median value. In terms of chemoradiotherapy responses, there were differences between PNI groups in both the general population and non-small cell cancer histology (p=0.18; p=0.19). The comparison between groups due to PNI is presented in Table 2. While there was a numerical difference in median OS between groups, no statistical difference was observed in terms of OS, according to the PNI groups (p=0.13) (Figure 1). Median OS of the low and high PNI groups were 16 and 27 months, respectively. After excluding

<table>
<thead>
<tr>
<th>TABLE 1: The features of the study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Features</td>
</tr>
<tr>
<td>Age (years) Mean Median</td>
</tr>
<tr>
<td>Gender Male Female</td>
</tr>
<tr>
<td>Smoking Yes No</td>
</tr>
<tr>
<td>Histologic Subtype SCC ADC SCLC NOS</td>
</tr>
<tr>
<td>T stage 1 2 3 4</td>
</tr>
<tr>
<td>N stage 0 1 2 3</td>
</tr>
<tr>
<td>N (%) 1 (1.6%) 9 (14.3%) 25 (39.7%) 28 (44.4%)</td>
</tr>
<tr>
<td>Chemotherapy Protocol Cisplatin+Etoposide Carboplatin+Paclitaxel Cisplatin Unknown</td>
</tr>
<tr>
<td>N (%) 6 (12.7%) 43 (86.3%) 11 (17.5%) 1 (1.6%)</td>
</tr>
<tr>
<td>Response to CRT N/A PR SD PD</td>
</tr>
<tr>
<td>N (%) 3 (4.8%) 39 (61.9%) 15 (23.8%) 6 (9.5%)</td>
</tr>
</tbody>
</table>

SCLC patients, there was no difference in terms of survival (p=0.24). Also, no difference was observed between groups when NLR was categorized for both cut-off levels two and three for non-small cell cancers (p=0.31; p=0.36). The chemoradiation responses were different in NLR subgroups if the cut-off value was determined as 2; otherwise, no difference was observed (p=0.012; p=0.45). The number of patients who exhibited partial response was significantly higher in the low NLR group, while the stable disease favored the high NLR group. The percentage of the patients in NLR low and high groups was 74% and 30% in PR and 19% and 46% in SD, respectively (p=0.003; p=0.04). The significant statistical difference has remained in the non-small cell group (p=0.02) (Table 3). Multivariate analysis revealed that none of the clinical and inflammatory markers had a prognostic effect on survival. The comparison of the groups in terms of PNI is presented in Table 2.

### Table 2: The comparison of characteristics of the patients according to prognostic nutritional index (PNI).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>66</th>
<th>63</th>
<th>0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>33/0</td>
<td>30/0</td>
<td>N/A</td>
</tr>
<tr>
<td>Smoking history</td>
<td>32</td>
<td>30</td>
<td>0.33</td>
</tr>
<tr>
<td>Histology (ADC/SCC/SCLC/NOS)</td>
<td>1/23/5/4</td>
<td>4/21/5/0</td>
<td>0.12</td>
</tr>
<tr>
<td>T stage (1/2/3/4)</td>
<td>0/5/14/14</td>
<td>1/4/11/14</td>
<td>0.72</td>
</tr>
<tr>
<td>N stage (0/1/2/3)</td>
<td>1/8/21/3</td>
<td>0/5/17/8</td>
<td>0.23</td>
</tr>
<tr>
<td>Response to CRT (NA/PR/SD/PD)</td>
<td>2/21/5/5</td>
<td>1/19/10/1</td>
<td>0.19</td>
</tr>
<tr>
<td>Hemoglobin Level (g/L)</td>
<td>11.5</td>
<td>13.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet Level (µL)</td>
<td>268.3</td>
<td>282.2</td>
<td>0.70</td>
</tr>
<tr>
<td>C-Reactive Protein (mg/dL)</td>
<td>3.9</td>
<td>1.5</td>
<td>0.008</td>
</tr>
<tr>
<td>Neutrophils (10³/µL)</td>
<td>7.9</td>
<td>6.7</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**PNI:** Prognostic nutritional index, **ADC:** Adenocarcinoma, **SCC:** Squamous Cell Carcinoma, **SCLC:** Small Cell Carcinoma, **NOS:** Not other specified, **N/A:** Not-available, **PR:** Partial Response, **SD:** Stable Disease, **PD:** Progressive Disease.

### Table 3: The difference in chemoradiation response between groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
<th>High</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNI* (%)</td>
<td>21/31 (67)</td>
<td>18/28 (62)</td>
<td>5/31 (16)</td>
<td>10/29 (34)</td>
<td>5/31 (16)</td>
<td>1/29 (3)</td>
<td>0.10</td>
</tr>
<tr>
<td>NLR2 (%)</td>
<td>4/13 (30)</td>
<td>35/47 (74)1</td>
<td>6/13 (46)</td>
<td>9/47 (19)1</td>
<td>3/13 (23)</td>
<td>3/47 (6)</td>
<td>0.012</td>
</tr>
<tr>
<td>NLR3 (%)</td>
<td>16/28 (57)</td>
<td>23/32 (71)1</td>
<td>9/28 (32)</td>
<td>6/32 (19)</td>
<td>3/28 (10)</td>
<td>3/32 (9)</td>
<td>0.46</td>
</tr>
<tr>
<td>PNI (%)</td>
<td>16/26 (61)</td>
<td>13/24 (54)</td>
<td>5/26 (19)</td>
<td>10/24 (41)</td>
<td>5/26 (19)</td>
<td>1/24 (4)</td>
<td>0.10</td>
</tr>
<tr>
<td>NLR2 (%)</td>
<td>3/12 (25)</td>
<td>26/38 (68)1</td>
<td>6/12 (50)</td>
<td>9/38 (23)</td>
<td>3/12 (25)</td>
<td>3/38 (7)</td>
<td>0.026</td>
</tr>
<tr>
<td>NLR3 (%)</td>
<td>12/24 (50)</td>
<td>17/28 (65)</td>
<td>9/24 (37)</td>
<td>6/26 (23)</td>
<td>3/24 (12)</td>
<td>3/26 (11)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**PR:** Partial Response, **SD:** Stable Disease, **PD:** Progressive Disease, **PNI:** Prognostic Nutritional Index, **NLR2:** Neutrophil Lymphocyte Ratio Cut-Off Value 2, **NLR3:** Neutrophil Lymphocyte Ratio Cut-Off Value 3, * General population, 1: Non-Small Cell Patient Group, ¶: Statistical significance.

**Figure 1:** The effect of the prognostic nutritional index (PNI) on overall survival (OS) in locally advanced lung cancer.
**DISCUSSION**

In this study, we observed no relationship between inflammatory markers and prognosis in patients in stage III lung cancer who underwent chemoradiation treatment. Although the difference was statistically insignificant, the OS was numerically different between groups favoring high PNI (16 vs. 27 months). There is a close relationship between the inflammatory response, albumin, and lymphocyte levels in cancer patients. Further, malnutrition and cachexia are frequently seen in patients with advanced cancer; often, hypoalbuminemia is observed as a reflection of this condition. Hypoalbuminemia not only shows nutritional status but also reflects tumor- or host-induced inflammatory response. PNI, which has been calculated by using albumin and absolute lymphocyte count, is an important immune nutritional biomarker.

For various solid tumors, PNI can be used to determine prognosis, but, to our knowledge, its relationship with chemoradiotherapy has not been studied before. This is the first study that evaluates the relationship between chemoradiotherapy and PNI inpatient in stage III of lung cancer.

The effect of the PNI on prognosis was shown in the pre-operative setting of NSCLC patients. Low levels of the PNI relate strongly to decreased survival. In this meta-analysis, the DFS also correlated with PNI. In patients who had low PNI levels had lower DFS compared with those with high PNI levels. In this study, low PNI levels seemed to correlate with a more advanced disease, which indicated that higher PNI levels had a protective effect against disease progression. Mori et al. evaluated the PNI in patients with completely resected lung cancer and they observed that high PNI is a good independent prognostic factor for survival. Furthermore rate of postoperative complications were higher in patients with low PNI levels, although not statistically significant.

A Turkish study evaluated the prognostic significance of NLR and PNI in NSCLC stage I to stage IV, and they found that low NLR and high PNI levels associated with better prognosis in both early-stage and metastatic patient groups. In this study, we used 49.5 as the cut off value for PNI. The mean OS for the low and high group patients was 7 and 33 months, respectively.

Although the treatment or the stage of the NSCLC differs, the prognostic impact of inflammatory markers is still observed. Deng et al. reported the prognostic effect of inflammatory markers in patients treated with first-generation tyrosine kinase inhibitors in advanced lung adenocarcinoma. Also, in patients undergoing immunotherapy, inflammatory markers were reported as being prognostic in advanced NSCLC. In a different study, low PNI values correlated with inferior OS in NSCLC. These patients had lower DFS when compared with those in the high PNI group. In another pooled analysis of this study, SCLC patients were confirmed to have lower OS associated with lower PNI. Tong et al. investigated the role of inflammatory markers in lung cancer and compared the prognostic power of neutrophil-lymphocyte ratio, PNI, and serum inflammatory index (SII) in locally advanced disease. While SII was confirmed to be a more potent prognostic factor than PNI in this study, PNI was still prognostic in a locally advanced group for patients who received concurrent chemoradiation.

CRP is an important inflammatory marker, and high levels of CRP can promote tumorigenesis and lead to poor prognosis in various cancer types. Fu et al. reported a negative correlation between CRP and PNI in patients with stage III and IV laryngeal cancer who underwent radiotherapy. In this study, patients with high CRP levels were observed to have worse survival rates. Following these study observations, we found a negative relationship between PNI and CRP in our study, and the low PNI group had statistically significant high CRP levels.

Our study enrolled locally advanced patients who had undergone chemoradiation differently than other studies. Although PNI was reported being prognostic in other studies, a small sample size possibly prevented a significant prognostic effect in our research. Further studies investigating the prognostic impact of inflammatory markers, particularly on chemoradiation plus immunotherapy may be elucidative in this area.
LIMITATIONS
The study was designed retrospectively, which limited the quality of data. The disease intensity and tumor volume were not available, which may be related to PNI and prognosis. The study population was heterogeneous and not specific for one histologic subgroup. Also, the response of some patients to chemoradiation was not available.

CONCLUSION
In this study, we evaluated the effect of PNI on treatment response and survival in stage III lung cancer patients receiving chemoradiotherapy. Although the results of our study were not statistically significant, the low PNI group had a worse prognosis and relatively short overall survival. These findings suggest that PNI may be an independent prognostic factor, although not statistically significant when performed with a large number of patients.

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