Factors affecting survival and recurrence in patients with operated non-small cell lung cancer

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Platelet-to-lymphocyte ratio

Abstract

\textbf{Aim:} The most serious problem after curative treatment of non-metastatic lung cancer is disease recurrence. This study was designed to detect markers affecting disease recurrence and survival in operated lung cancer patients.

\textbf{Materials and Methods:} In this study, the data of 109 patients diagnosed with lung cancer were analyzed retrospectively. Cut-off values for neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), alkaline phosphatase (ALP), and gamma glutamyl transpeptidase (GGT) were determined by performing ROC Curve analysis. According to these cut-off values, the patients were divided into two groups. Based on the cut-off value of the markers, their effects on both overall survival (OS) and disease-free survival (DFS) were examined.

\textbf{Results:} In this study, the median OS of the patients was 53.9 months, and the median DFS was 20.6 months. The patients were re-evaluated by targeting the cut-off value of 2.35 for NLR obtained by ROC analysis. Below this value, mOS and mDFS were calculated as 78.2 and 43.2 months, respectively. Above this value, it was determined as 35.6 and 20.6 months, respectively. A similar evaluation was made for the PLR. As a result of the ROC analysis, the cut-off value was determined as 124.7. Below this value, mOS and mDFS were calculated as 72.4 and 36.9 months, respectively. Above this value, it was determined as 41.7 and 21.8 months, respectively. Both results were statistically significant (p<0.05).

\textbf{Conclusion:} This study showed that NLR and PLR predict statistical significance for OS and DFS.

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Introduction

Lung cancer is one of the most frequently detected malignancies worldwide and is the leading cause of cancer-related death [1]. Despite recent advances in treatment options, including molecularly targeted agents and immune checkpoint inhibitors, the average 5-year relative survival rate for lung cancer patients is only about 17% [2]. These poor survival rates may be due to two main reasons. These reasons are that the patients were diagnosed at a more advanced stage and that the patients relapsed after definitive treatment. The follow-up of patients after definitive treatment is carried out with the current recommendations of international guidelines. However, it may not be possible to detect recurrences in the early period due to the inadequacy of conventional imaging methods. For this purpose, the concept of biochemical recurrence, which is detected before radiological recurrence, gains importance. There is a definition of minimal residual disease (MRD), which cannot be reliably detected by conventional radiological imaging studies due to poor resolution, but is an important source for early recurrence and metastasis [3].

As known from previous studies, inflammatory prognostic markers (IPM) have an important place in both the prognosis and prediction of the disease. The most well-known of these inflammatory prognostic markers are neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and Pan-Immune-Inflammation score. Immune cells in the tumor microenvironment are associated with improved outcome. The most important of these cells are cytotoxic CD8 T cells. Among the immune cells associated with tumor progression and poor prognosis, the best known are neutrophils, M2 polarized macrophages, and FOXP3 positive regulatory T cells [4-6]. In addition to all these cell elements, platelets are also part of an inflammatory process and thus thrombocytosis is common in solid tumors [7].

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These inflammatory prognostic markers, obtained by the ratios of the measurements of these cell elements in the peripheral blood, have been shown to be associated with survival in most cancer types, including lung cancer [8]. The mechanism of the relationship between the systemic inflammatory response and the progression of cancer is clearly known. One reason for this correlation is that tumor growth in patients with high NLR may be promoted by neutrophil-derived cytokines such as vascular endothelial growth factor, interleukin-18, and matrix metalloproteinases. In addition, increased neutrophils around the tumor may be due to natural killer cells and activated T cells suppressing anti-tumor immune responses. Concomitantly, lymphocyte-mediated anti-tumor cellular immune response may be weakened due to decreased lymphocytes around the tumor. Therefore, the coexistence of neutrophilia and lymphocytopenia causes a high NLR. Thus, it is likely to promote angiogenesis and inhibit anti-tumor reactivity, ultimately promoting tumor growth and progression [9-11].

Our aim in this study is to investigate the effectiveness of inflammatory prognostic markers such as NLR and PLR on parameters such as disease-free survival and overall survival in patients with operated lung cancer.

Materials and Methods

Study population

In this study, the data of 109 lung cancer patients who were operated on in our hospital between 2013 and 2020 were analyzed retrospectively. Patients over the age of 18 were included in our study. Patients who received neoadjuvant therapy before surgical treatment were excluded from the study as it may alter the pathological staging. In addition, patients with missing laboratory parameters required for our study before surgery and patients with a previous cancer diagnosis were excluded from the study. Patients had no preoperative hematological disease or infection. Patients were classified according to age, gender, type of imaging, pathological subtype, and type of operation, pathological staging, differentiation, and adjuvant chemotherapy status. In addition, some inflammatory prognostic markers obtained using the laboratory parameters of the patients were also evaluated in the study. The first of these parameters, $NLR = \frac{\text{absolute neutrophil count}}{\text{absolute lymphocyte count}}$ was calculated. Another inflammatory prognostic marker, $PLR = \frac{\text{absolute platelet count}}{\text{absolute lymphocyte count}}$ was calculated. DFS was calculated in months based on the time to relapse in patients who completed their postoperative systemic therapy in relapsed patients. OS was evaluated by calculating the time from diagnosis to death in months during the follow-up period. All procedures performed in studies involving human participants were under the national research committee’s ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Before the study, ethical approval was obtained from the Inonu University Clinical Research Ethics Committee (Decision number: 2022/2881, Date: 11.01.2022).

Statistical analysis

IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as median and standard deviation (median and minimum-maximum where appropriate). Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Kaplan-Meier method and Log Rank tests were used for survival analysis. The sensitivity and specificity values for Alkaline phosphatase (ALP), Gamma Glutamyl Transpeptidase (GGT), NLR, and PLR values were calculated based on the mortality variable of the patients included in the study, and the cut-off value was determined by examining the area under the ROC curve. The statistical significance level was taken as 0.05 in all tests.

Results

Considering the inclusion and exclusion criteria, the data of 109 patients were retrospectively analyzed and included in the study. The clinicopathological features of the patients are shown in Table 1. The relationship between radiological examination, pathological subtype and disease stage of the patients and survival (months) is shown in
Table 1. The Clinico-pathological features of the patients.

<table>
<thead>
<tr>
<th>Sex</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>95</td>
<td>87.2</td>
</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>12.8</td>
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</table>

Radiological Examination

<table>
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<tr>
<th>Examination</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>48</td>
<td>44.0</td>
</tr>
<tr>
<td>PET/CT</td>
<td>61</td>
<td>56.0</td>
</tr>
</tbody>
</table>

Tumor subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>56</td>
<td>51.3</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>51</td>
<td>46.8</td>
</tr>
<tr>
<td>Large Cell Carcinoma</td>
<td>2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Tumor Location

<table>
<thead>
<tr>
<th>Location</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Lung Upper Lobe</td>
<td>27</td>
<td>24.8</td>
</tr>
<tr>
<td>Right Lung Mid Lobe</td>
<td>8</td>
<td>7.3</td>
</tr>
<tr>
<td>Right Lung Lower Lobe</td>
<td>28</td>
<td>25.7</td>
</tr>
<tr>
<td>Left Lung Upper Lobe</td>
<td>28</td>
<td>25.7</td>
</tr>
<tr>
<td>Left Lung Lower Lobe</td>
<td>18</td>
<td>16.5</td>
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Lymph Node Status

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<th>Status</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>51</td>
<td>46.8</td>
</tr>
<tr>
<td>Negative</td>
<td>58</td>
<td>53.2</td>
</tr>
</tbody>
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Recurrence

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>41</td>
<td>37.6</td>
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<tr>
<td>No</td>
<td>68</td>
<td>62.4</td>
</tr>
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</table>

Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Stage II</td>
<td>39</td>
<td>35.7</td>
</tr>
<tr>
<td>Stage III</td>
<td>34</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Type of operation

<table>
<thead>
<tr>
<th>Operation</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>62</td>
<td>56.9</td>
</tr>
<tr>
<td>Wedge Resection</td>
<td>12</td>
<td>11.0</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>24</td>
<td>22.0</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>10.1</td>
</tr>
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Lymph vascular Invasion

<table>
<thead>
<tr>
<th>Positive</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63</td>
<td>57.8</td>
</tr>
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</table>

Perineural Invasion Positive

<table>
<thead>
<tr>
<th>Positive</th>
<th>N (number of patients)</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>35</td>
<td>32.1</td>
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</table>

Differentiation

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Differentiation</td>
<td>28</td>
<td>25.7</td>
</tr>
<tr>
<td>Middle Differentiation</td>
<td>37</td>
<td>33.9</td>
</tr>
<tr>
<td>Poorly Differentiation</td>
<td>42</td>
<td>38.5</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Yes</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53</td>
<td>48.6</td>
</tr>
<tr>
<td>No</td>
<td>35</td>
<td>32.2</td>
</tr>
<tr>
<td>Could not receive</td>
<td>9</td>
<td>8.2</td>
</tr>
<tr>
<td>Postoperative Exitus</td>
<td>6</td>
<td>5.5</td>
</tr>
<tr>
<td>Data Not Available</td>
<td>6</td>
<td>5.5</td>
</tr>
</tbody>
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Current status of the patient

<table>
<thead>
<tr>
<th>Status</th>
<th>N (number of patients)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>55</td>
<td>50.5</td>
</tr>
<tr>
<td>Exitus</td>
<td>54</td>
<td>49.5</td>
</tr>
</tbody>
</table>

Table 2. The Relationship between Radiological Examination, Pathological Subtype, and Disease Stage with Survival (Month).

<table>
<thead>
<tr>
<th></th>
<th>Mean ±std</th>
<th>%95 CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Limit</td>
<td>Upper Limit</td>
<td></td>
</tr>
<tr>
<td>Radiological Selection (OS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>56.1 ±5.2</td>
<td>46.0</td>
<td>66.2</td>
</tr>
<tr>
<td>PET/CT</td>
<td>57.3 ±4.7</td>
<td>48.2</td>
<td>66.5</td>
</tr>
<tr>
<td>Radiological Selection (DFS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>33.7 ±4.8</td>
<td>24.2</td>
<td>43.1</td>
</tr>
<tr>
<td>PET/CT</td>
<td>18.5 ±3.8</td>
<td>11.1</td>
<td>25.9</td>
</tr>
<tr>
<td>Tumor Type (OS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>57.1 ±5.0</td>
<td>47.2</td>
<td>67.0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>57.4 ±4.9</td>
<td>47.8</td>
<td>67.0</td>
</tr>
<tr>
<td>Other+</td>
<td>39.1 ±13.1</td>
<td>13.4</td>
<td>64.8</td>
</tr>
<tr>
<td>Tumor Type (DFS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>24.9 ±4.5</td>
<td>16.2</td>
<td>33.8</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>28.9 ±5.0</td>
<td>19.0</td>
<td>38.8</td>
</tr>
<tr>
<td>Other+</td>
<td>9.9 ±1.0</td>
<td>9.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Stage (OS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>69.3 ±5.3</td>
<td>58.9</td>
<td>79.7</td>
</tr>
<tr>
<td>Stage II</td>
<td>52.1 ±5.8</td>
<td>40.7</td>
<td>63.5</td>
</tr>
<tr>
<td>Stage III</td>
<td>47.5 ±6.3</td>
<td>35.3</td>
<td>59.8</td>
</tr>
<tr>
<td>Stage (DFS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>33.2 ±7.2</td>
<td>19.1</td>
<td>47.3</td>
</tr>
<tr>
<td>Stage II</td>
<td>24.9 ±5.9</td>
<td>13.3</td>
<td>36.6</td>
</tr>
<tr>
<td>Stage III</td>
<td>24.1 ±4.5</td>
<td>15.2</td>
<td>32.9</td>
</tr>
</tbody>
</table>

Table 2. The relationship between NLR and PLR, which is one of the main research subjects of our study, and survival was also evaluated. ROC analysis and ROC curve were created to establish a cut-off value for NLR and PLR values. The patients were divided into two groups according to survival and ROC analysis was performed according to these groups. As a result of the ROC analysis, the area under the ROC curve was calculated as 80.8%. According to this cut-off value we determined, it is assumed that if the NLR value is 2.35 and below, it has a positive effect on overall survival with 74.6% sensitivity and 79.6% specificity. According to the determined cut-off value, it is assumed that if the PLR value is 124.7 and below, it affects the survival with 70.9% sensitivity and 74.1% specificity. In addition, the Kaplan Meier plot showing ROC curve analysis of NLR and PLR was shown in Figures 1. As a result, both NLR and PLR are statistically significantly predictive for survival parameters using threshold values obtained using ROC curve analysis. The relationship of NLR and PLR with OS is shown in Figure 2 with Kaplan Meier curves. The relationship of NLR and PLR with DFS is shown in Figure 3 with Kaplan Meier curves. It is known that elevated ALP and GGT levels are badly associated
analyses regarding this have been reported in the literature to survival in most cancer types. Comprehensive meta-
terms of DFS and OS based on IPMs in operated lung can-
whether there is a statistically significant difference in
lymph node dissection [12]. Our aim in this study is to find
cancer is a complete surgical resection with mediastinal
In inflammatory prognostic markers such as NLR are not
survival in metastatic diseases. In this study, we also
aimed to evaluate whether it is associated with survival in
eye-stage disease. The relationship between ALP and
GGT, another research topic of our study, with survival
times was also evaluated. To establish a cut-off value for
ALP and GGT values, ROC analysis and ROC curve were
created and divided into two groups according to survival.
A statistically significant relationship between ALP and
DFS and GGT with both OS and DFS could not be deter-
mined. The cut-off values for NLR, PLR, ALP and GGT
and all survival information for these values are shown in
Table 3.

### Table 3. Association of NLR, PLR, ALP, and GGT with Survival (Month).

<table>
<thead>
<tr>
<th></th>
<th>Mean ±std</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NLR (OS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.35</td>
<td>78.2±3.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>&gt;2.35</td>
<td>35.6±3.9</td>
<td></td>
</tr>
<tr>
<td><strong>NLR (DFS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.35</td>
<td>43.2±6.7</td>
<td>0.006*</td>
</tr>
<tr>
<td>&gt;2.35</td>
<td>20.6±3.2</td>
<td></td>
</tr>
<tr>
<td><strong>PLR (OS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;124.7</td>
<td>72.4±4.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>&gt;124.7</td>
<td>41.7±4.3</td>
<td></td>
</tr>
<tr>
<td><strong>PLR (DFS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;124.7</td>
<td>36.9±6.7</td>
<td>0.035*</td>
</tr>
<tr>
<td>&gt;124.7</td>
<td>21.8±3.4</td>
<td></td>
</tr>
<tr>
<td><strong>ALP (OS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;112</td>
<td>61.9±3.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>&gt;112</td>
<td>38.3±6.4</td>
<td></td>
</tr>
<tr>
<td><strong>ALP (DFS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;112</td>
<td>29.6±4.2</td>
<td>0.101</td>
</tr>
<tr>
<td>&gt;112</td>
<td>20.3±5.1</td>
<td></td>
</tr>
<tr>
<td><strong>GGT (OS)</strong></td>
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<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>48.8±4.9</td>
<td>0.080</td>
</tr>
<tr>
<td>&gt;25</td>
<td>60.8±4.5</td>
<td></td>
</tr>
<tr>
<td><strong>GGT (DFS)</strong></td>
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<tr>
<td>&lt;25</td>
<td>26.4±4.7</td>
<td>0.912</td>
</tr>
<tr>
<td>&gt;25</td>
<td>26.8±4.8</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The curative treatment of patients with early-stage lung
cancer is a complete surgical resection with mediastinal lymph node dissection [12]. Our aim in this study is to find
out whether there is a statistically significant difference in
terms of DFS and OS based on IPMs in operated lung cancer patients. For this purpose, the parameters used in our study can guide patient selection. In particular, inflammatory prognostic markers are known to be directly related to survival in most cancer types. Comprehensive meta-
analyses regarding this have been reported in the literature
[13,14]. Similarly, a recent study showed that patients with Stage-I lung cancer with low PLR had a better survival [15]. In previous studies on gastric cancer, the NLR value was calculated using the parameters obtained from the peripheral blood count of the patients in the pre-operative period. These studies have shown that OS is worse in patients with high pre-operative NLR. The pathogenesis responsible for this condition is that systemic inflammatory responses with an elevated NLR increase the generation of inflammatory cytokine cascades, including tumor necrosis factor-α and interleukin-1, interleukin-6, and interleukin-8-related cascades. These immune modulators can affect the function and regulation of natural killer cells, cytotoxic T lymphocytes and antigen presenting cells. As a result, micrometastases can progress rapidly during periods of short- or long-term relative immunosuppression resulting from postoperative complications [16,17].
in the literature support that these IPMs are positively associated with survival. In a study on pancreatic cancer, no significant relationship was found between IPMs and survival [23]. However, when we look at these studies in general, there are retrospective studies with large patient numbers showing the relationship of these IPMs with survival. To use the available opportunities most effectively, a risk score should be made and a different treatment and post-treatment follow-up plan should be prepared for each patient. A similar scoring system has been used for Renal Cell Cancer (RCC) for a long time. Patients are treated according to the data obtained from this scoring system. In metastatic RCC, the survival of patients can be predicted by using the IMDC score [24]. According to this scoring system, patients are classified as favorable, intermediate, and poor prognostic, and their treatment is determined according to this plan. We support the idea that we can use a similar situation in other cancer patients. It is possible to optimally plan the adjuvant treatment given as a result of the calculation of the clinical risks of the patients. In addition, these patients can be grouped by clinical risk calculation and their follow-up can be done in accordance with these risk groups.

We performed a similar evaluation based on the ALP and GGT values of the patients. In the ROC curve analysis, the cut-off values for ALP and GGT were determined as 112 and 25, respectively. While no statistically significant result could be reached for both OS and DFS for GGT, it was determined that there was a statistically significant survival contribution for OS in patients below the cut-off value for ALP. A numerical improvement was found for DFS without any statistical significance. Studies in the literature have shown that ALP is associated with lower survival, especially in prostate cancer patients with bone metastases [25,26]. In this study, all patients were patients with early-stage lung cancer who had undergone surgery and had no metastases. Despite this situation, when the ALP elevation in these patients were evaluated based on the cut-off value, it was seen that it contributed to survival, which was statistically significant for OS.

There are also some limitations of this study. These limitations are the low number of patients, retrospective trial, the inclusion of patient data from a single center, and the lack of standardization of surgical procedures applied to patients.

Conclusion

Consequently, until the cost of ctDNA measurement is reasonable to evaluate in each patient, a specific scoring system should be used for both adjuvant therapy and post-treatment relapse follow-up. In this scoring system, inflammatory prognostic markers such as NLR and PLR can be used, as well as easily accessible laboratory parameters such as ALP. We think that this study that we have completed will contribute to the literature in terms of giving ideas for future studies.

Ethics approval

Ethical approval was obtained from the Inonu University Clinical Research Ethics Committee (Decision number: 2022/2881, Date: 11.01.2022).

References


