



The value of preoperative inflammatory markers in patients through total laryngectomy for advanced stage larynx carcinoma

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Abstract

The aim of this study is to evaluate the difference between neutrophil, lymphocyte, platelet and RDW (red cell distribution width) counts and NLR (neutrophil/lymphocyte ratio) and PLR (platelet/lymphocyte ratio) between patients who underwent total laryngectomy for advanced stage laryngeal squamous cell carcinoma and healthy control group. The study group consisted of 37 patients (36 male, 1 female) who underwent total laryngectomy and bilateral neck dissection for advanced stage laryngeal squamous cell carcinoma between January 2017 and December 2019. As a control group, complete blood count records of 35 healthy individuals who were routinely examined in 2019 within the scope of occupational health and safety were compiled. Blood was collected preoperatively from the patient in the study group. The data obtained from the whole blood counts of the two groups were analyzed statistically by comparing neutrophil, lymphocyte, platelet, RDW, NLR and PLR values. The age difference between the study and control groups was not significant ($p>0.05$). Neutrophil, platelet and RDW counts were higher in the study group compared to the control group and this difference was statistically significant ($p=0.001$, $p=0.035$, $p=0.001$, respectively). Although the lymphocyte count was high in the study group, the difference was not significant ($p=0.061$). The difference between NLR and PLR between the two groups was high in the study group and this difference was statistically significant ($p=0.001$, $p=0.007$, respectively). Neutrophil, platelet, RDW, NLR, PLR values were significantly higher in patients with advanced stage laryngeal cancer than in the control group. NLR, PLR and RDW values, which can be obtained cheap, simple and rapidly at the diagnosis stage of laryngeal cancers, may be biomarkers in determining prognosis. For this, multicenter, prospective studies are needed.

Keywords: laryngeal carcinoma, neutrophil lymphocyte ratio, platelet lymphocyte ratio, red cell distribution width

1. Introduction

Laryngeal cancer accounts for 30-40% of malignant tumors of the head and neck, and 1-2.5% of all malignant neoplasms in the human body. Histopathologically, 95-98% of laryngeal cancers are squamous cell carcinoma (SCC). Laryngeal cancer is more common between the 5th and 7th decades of life and in male gender. Many factors such as viral infections, smoking and alcohol exposure, exposure to carcinogens, gastroesophageal reflux and heredity are effective in the etiology (1).

Although the most important factor determining the prognosis of laryngeal carcinoma is the pathological TNM stage, vascular and perineural invasion, depth of invasion, patient's general condition, age, sex and treatment-related factors affect the process (2). In studies conducted, it has been reported that inflammation that occurs as a host response in tumor tissue affects tumor development, metastasis and response to treatment (3). Neutrophils, T and B lymphocytes and thrombocytes (platelets) play an important role in tumor

inflammation and immunology (4).

Increased neutrophil count, lymphopenia and thrombocytosis have been associated with malignancies. While lymphocytes prevent tumor growth, cytokines secreted by tumor cells cause an increase in the number of neutrophils. Neutrophils play an important role in enlargement and metastasis. Platelets contribute to the development of the tumor by increasing angiogenesis by means of vascular endothelial growth factor (VEGF) (5). NLR and PLR are considered to be an important prognostic factor in many carcinomas and it is accepted that NLR is a better predictor than PLR (6). There are studies showing that RDW adversely affects the clinical outcomes of various cancers as an indicator of systemic inflammatory response (7).

The aim of this study was to evaluate the difference between neutrophil, lymphocyte, platelet, RDW counts, NLR and PLR between patients undergoing total laryngectomy for advanced stage laryngeal carcinoma.

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2. Materials and Methods

This retrospective study was approved by the Health Sciences University Samsun Training and Research Hospital Ethics Committee with the 2019/3/5 numbered decision. Between January 2017 and December 2109, 37 patients who underwent total laryngectomy and bilateral neck dissection for advanced stage laryngeal squamous cell carcinoma were included in the study. As a control group, complete blood count records of 35 healthy individuals who were routinely examined in 2019 within the scope of occupational health and safety were compiled.

Of the 37 patients in the study group, 36 were male and 1 was female, while the control group consisted of 35 men. Patients who had autoimmune disease, impaired thyroid function tests, diabetes mellitus, chronic renal failure, second malignancy, hematologic disease, active infection, chemotherapy-radiotherapy, steroid treatment in the last month and immunosuppressive were not included. All patients in the study group had transglottic tumors and were in the T4a stage clinically and pathologically according to the American Cancer Committee Association (AJCC) 8th edition. Thyroid cartilage invasion by the tumor was reported pathologically in all patients.

Preoperative examination of the patients in the study group was performed with 2cc venous blood from the forearm. The control group included complete blood counts from venous blood. Blood counts were performed with Coulter LH 780 Analyzer (Beckman, USA). Neutrophil, lymphocyte, platelet, RDW counts were recorded separately for the study and control groups and then NLR and PLR were calculated.

SPSS 21.0 analysis program was used for statistical analysis. The normal distribution of the data of the study and control groups was analyzed by using the Shapiro-Wilk test. The values of normally distributed and abnormally distributed groups were shown as mean ± sd. The difference between the groups was evaluated by Independent Student-t test and Mann-Whitney U test. Logistic regression analysis was used to investigate the effects of the parameters on the groups. Descriptive statistics were expressed with Odds ratio and 95% confidence intervals. p<0.05 was considered statistically significant. The diagnostic decision-making characteristics of serum NLR and PLR values in advanced stage laryngeal cancers were examined by receiver operating characteristics (ROC) curve. Sensitivity, specificity, area under curve (AUC) of these limits were calculated in the presence of significant limit values and p<0.05 was considered statistically significant.

3. Results

The age of the patients in the study group of 37 patients with total laryngectomy ranged from 44 to 75, with an average of 59.89 years. In the control group of healthy individuals, mean age was 59.49 between 45 and 68 years. The mean age of all subjects was 59.69 years. Of the patients in the study group, 36 were male and 1 was female. All subjects in the control group

were male. Age difference between the two groups was not statistically significant (p>0.05) (Table1).

Table 1. Age distribution of the study and control groups

| Groups | n | Male/ Female | Mean age | Sd | Min. | Max | p |
|---------|----|-----------------|-------------|-------|------|-----|------|
| Patient | 37 | 36/1 | 59.89 | 7.214 | 44 | 75 | |
| Control | 35 | 35/0 | 59.49 | 5.431 | 45 | 68 | |
| Total | 72 | 71/1 | 59.69 | 6.368 | 44 | 75 | 0.05 |

All patients in the study group had transglottic tumors and thyroid cartilage invasion in the pathology report. Seven patients had perineural invasion, 6 had perivascular invasion, 16 had subglottic extension, 13 had extralaryngeal involvement, and 7 had neck lymph node metastasis (bilateral metastasis in 2 patients).

Neutrophil, platelet and RDW counts were higher in the study group compared to the control group and this difference was statistically significant (p=0.001, p=0.035, p=0.001, respectively). Although lymphocyte counts were high in the study group, the difference was not statistically significant (p=0.061). The difference between NLR and PLR between the two groups was high in the study group and this difference was statistically significant (p=0.001, p=0.007, respectively) (Table 2).

Table 2. Distribution and analysis of hematological parameters and inflammatory markers

| | Patient group (n=37) | Control group (n=35) | p | OR | 95% CI | p |
|------------|----------------------------|----------------------------|-------|------|-----------------|-------|
| Neutrophil | 6.43±2.45 | 4.54±1.55 | 0.001 | 2.55 | 0.751- 8.665 | 0.133 |
| Lymphocyte | 1.88±0.71 | 2.15±0.62 | 0.061 | 0.55 | 0.058- 5.295 | 0.607 |
| Platelet | 291.95±94.26 | 249.23±64.45 | 0.035 | 0.99 | 0.972- 1.233 | 0.651 |
| RDW | 14.66±2.05 | 13.522±0.89 | 0.001 | 2.25 | 1.093- 4.639 | 0.028 |
| NLR | 4.021±2.82 | 2.31±1.10 | 0.001 | 0.51 | 0.076- 3.459 | 0.493 |
| PLR | 175.65±86.75 | 123.77±42.23 | 0.007 | 1.01 | 0.974- 1.059 | 0.462 |

Neutrophil, lymphocyte, platelet and RDW values are calculated as x10³
NLR: neutrophil/lymphocyte ratio PLR: platelet/lymphocyte ratio OR: Odds ratio

The sensitivity, specificity and AUC values for NLR were 75.7%, 62.9% and 0.772, respectively. The sensitivity, specificity and AUC for PLR were 70.3%, 51.4%, 0.685 respectively. In addition, the diagnostic cut off value for NLR and PLR calculated with data from both groups is summarized in Table 3.

Table 3. Cut-off value of parameters

| | Cut-off Value | AUC | 95 % CI Sensitivity | Specificity | p |
|-----|------------------|----------------------------|------------------------|-------------|-------|
| NLR | >2.26 | 0.772 (0.664- 0.880) | %62.9 | %75.7 | 0.001 |
| PLR | >121.08 | 0.685 (0.560- 0.809) | %51.4 | %70.3 | 0.007 |

4. Discussion

Laryngeal carcinomas accounts for 30% to 40% of malignant tumors of the head and neck; 1% to 2.5% of all malignant neoplasms in the human body. Histopathologically, 95-98% of laryngeal carcinomas are epithelial-originated squamous cell carcinoma (1). Advances in the diagnosis and treatment of laryngeal carcinomas provide protection of the larynx and prolonged survival. However, the 5-year survival rate remains low for patients with advanced laryngeal carcinoma (8). As a result of the intensive treatments applied to advanced staged patients, the patients' swallowing, respiratory and speech functions deteriorate, social problems are experienced and eventually their quality of life decreases (9). Total laryngectomy and bilateral neck dissection were performed in all 37 patients constituting the study group. Pathological evaluation revealed that all patients had T4a stage tumor and all of them had thyroid cartilage invasion.

There are many studies in which chronic inflammation contributes to the initiation and progression of cancer (4,10). Increasing neutrophil count contributes to tumor growth by reducing the cytolytic activity of lymphocytes and natural killer (NK) cells, producing proangiogenic factors such as VEGF, chemokines and proteases (11). Lymphocytes play an important role against the tumor progression by inhibiting proliferation-migration of tumor cells and inducing cytotoxic cell death. In animal studies, the deficiency in the development and / or function of CD4 + Th1 helper cells, CD8 + cytotoxic T cells or NK cells has been shown to increase susceptibility to cancer formation in the host (12). Reduced lymphocyte count negatively affects prognosis in some cancers (13). Tumor cells can increase the number of peripheral platelets through thrombopoietin, IL-6 or leukemia-inhibiting factor. The increase in the number of platelets contributes to the progression of the tumor by increasing angiogenesis through VEGF. Brown et al. reported that thrombocytosis is a negative prognostic factor in different malignancies (14). In our study, neutrophil and platelet counts were higher in the patient group compared to the control group, and this difference was statistically significant ($p = 0.001$, $p = 0.035$, respectively). Although the lymphocyte counts were lower in the patient group compared to the control group, the difference between the two groups was not statistically significant ($p = 0.061$).

Rise of RDW has been reported as a finding of inflammation and oxidative stress (15). In a meta-analysis consisting of eight cohort studies, increased RDW level has been reported as an indicator of poor prognosis in upper aerodigestive tract cancers (16). Bozkurt et al. (17) reported the results of 132 patients with laryngeal cancer that the risk of local and regional recurrences increased in patients with high RDW. Hsueh et al. reported that disease-free survival, cancer-specific survival and overall survival were low in patients have squamous cell laryngeal carcinoma with high RDW levels (18). In our study, RDW level was found to be significantly higher in the patient group compared to the control group ($p =$

0.001).

NLR and PLR values have been shown to be associated with poor prognosis in terms of mortality and recurrence (7). Increased NLR and PLR has been shown to be associated with poor prognosis in liver, parotis, oropharyngeal SCC and esophageal cancers. These markers were found to be independent prognostic factors in the head and neck SCC (19). Kara et al. (10) reported in their study on patients with laryngeal cancer that those who were at the T4 stage found PLR higher than those at the T1-2 stage, and those with higher NLR had higher local recurrence and survival was low. Tu et al. (20) showed that patients with advanced laryngeal cancer have high NLR and PLR values, NLR or PLR not only reflects tumor burden, but can also stimulate tumor progression by affecting tumor metabolism and microenvironment. They found that the combination of these markers, rather than using them separately, was more valuable in predicting prognosis. In our study, the specificity for NLR was 62.9% and the sensitivity was 75.7%. PLR specificity was calculated as 51.4% and sensitivity as 70.3%. NLR and PLR were found high in favor of the patient group, and this difference was found to be statistically significant ($p = 0.001$, $p = 0.007$, respectively). The limitations of our study wereto be retrospective, single-centered, and less number of cases.

In our study, neutrophil, platelet, NLR, PLR, RDW values were found to be statistically significantly higher in the patient group with advanced laryngeal cancer compared to the control group. NLR, PLR and RDW values, which can be examined easily, cheap and fast at the diagnosis step of laryngeal cancers, can be biological markers to determine the prognosis. To support these findings, multi-center, prospective studies need to be done.

Ethical Statement

This retrospective study was approved by the Health Sciences University Samsun Training and Research Hospital Ethics Committee with the 2019/3/5 numbered decision.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: M.Ç., Design: D.M.M, Data Collection or Processing: S.V., Analysis or Interpretation: S.N.C., Literature Search: D.Ö., Writing: A.Ö.

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