

# Neutrophil–Lymphocyte Ratio as a Prognostic Factor in Laryngeal Carcinoma

Beyhan Yılmaz · Engin Şengül · Aylin Gül · Ulaş Alabalık · Fazıl Emre Özkurt · Mehmet Akdağ · İsmail Topçu

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**Abstract** Aim of this study; investigate whether neutrophils/lymphocyte ratio (NLR) could be used as a prognostic factor in larynx cancer. The correlation between preoperative peripheral blood NLR and age, gender, smoking, alcohol use, clinical stage and differentiation degree was examined. One hundred forty-four patients in Dicle University Department of Otorhinolaryngology between the years of 2005 and 2014 were included in the study. Clinical and preoperative laboratory data of patients were screened retrospectively from archive files of otorhinolaryngology and the pathology results were screened retrospectively from archive files of pathology. The study was approved by the local ethics committee of the department and carried out in accordance with the declaration of Helsinki as amended in 2013. Statistical analyses were performed using the SPSS 15.0 software package for Windows (SPSS inc., Chicago, IL, USA). There was a significant difference between NLR and clinical stage ( $p = 0.003$ ) smoking ( $p = 0.001$ ) and alcohol use ( $p = 0.001$ ). When NLR was analyzed in detail according to the degree of tumor differentiation; significant differences were observed between G1 and G2 ( $p = 0.007$ ) and between G1 and G3 ( $p = 0.001$ ). Light of these findings, NLR is a cheap and easily accessible marker which can be used as a prognostic factor in laryngeal cancer. It is thought

to shed light on the studies which will be conducted with more patients.

**Keywords** Neutrophils lymphocyte ratio · Laryngeal cancer · Prognostic factor

## Introduction

Laryngeal cancer is a malignant disease with high incidence. It consists approximately 2–4 % of all cancers that newly diagnosed in the world each year [1]. In the etiology; tobacco, alcohol, air pollution, sex hormones and occupational factors are known to be associated [2, 3].

In predicting disease progression; prognostic factors such as the patient's age, gender, smoking—alcohol use, clinical staging, thyroid cartilage invasion, positive surgical margins are routinely used. However, histopathological studies also provide important information about prognosis. The degree of cell differentiation, inflammatory reactions and cell invasion in small vessels are main prognostic factors used histopathologically in laryngeal neoplasms [4].

These prognostic factors are generally useful, but inadequate in determining the prognosis of some patients. Therefore, in recent years, cancer researches have focused on the identification of new tumor markers. These markers; should be easily accessible, cheaper, repeatable and most importantly able to identify potential diseases carrying high risk in terms of disease recurrence and death [5].

In the early 19th century, the relationship between inflammation and cancer has been realized with the presence of neutrophils in the cancer tissue and the role of inflammation in cancer pathogenesis and progression has been accepted in the studies performed in the last few

B. Yılmaz (✉) · E. Şengül · A. Gül · F. E. Özkurt · M. Akdağ · İ. Topçu  
Department of ENT, Dicle University School of Medicine,  
Diyarbakir 21280, Turkey  
e-mail: drbeyhanyilmaz@gmail.com

U. Alabalık  
Dicle University Medical School Pathology Department,  
Diyarbakir, Turkey

decades [6]. The relationship between poor prognosis of various cancers including non-small cell lung cancer [7], small cell lung cancer [8] and renal cell carcinoma [9] and an increase in neutrophils, lymphocytes, and monocytes in tissue has been demonstrated.

After the display of inflammatory markers in the tissue; this time, increase in neutrophils, lymphocytes in the peripheral blood called attention and the studies in this direction have progressed. Again, neutrophils, lymphocytes and neutrophils/lymphocyte ratio (NLR) were compared with prognostic factors of cancer were investigated in various cancers and significant relationship was observed between them. These cancers in these studies are mostly epithelial ovarian cancer [10], colorectal cancer [11], advanced gastric cancer [12], hepatocellular carcinoma [13], and pancreatic ductal adenocarcinoma [14]. While the relationship between NLR and the prognosis of many types of cancer is known, information on this relationship with head and neck cancer is limited.

More recently, a few studies have been published showing the relationship between the prognosis in patients with nasopharyngeal carcinoma and cancer of the oral cavity and NLR [5, 15, 16]. However, any study showing the relationship between the prognosis of laryngeal cancer and NLR has not been found.

In this study; the correlation between preoperative peripheral blood NLR and age, gender, smoking, alcohol use, clinical stage and differentiation degree, which are used as prognostic factors for larynx cancer, was examined, it was aimed to investigate whether NLR could be used as a prognostic factor in larynx cancer. In addition, it was aimed to demonstrate the role of inflammation on cancer pathogenesis and progression by comparing ratios of NLR in patients diagnosed with laryngeal benign pathology and malignant pathology.

## Materials and methods

One hundred forty-four patients underwent biopsy under direct laryngoscopy due to laryngeal pathology in Dicle University Department of Otorhinolaryngology between the years of 2005 and 2014 were included in the study. The study was approved by the local ethics committee of the department and carried out in accordance with the declaration of Helsinki as amended in 2013.

Clinical and preoperative laboratory data of patients were screened retrospectively from archive files of otorhinolaryngology and the pathology results were screened retrospectively from archive files of pathology.

Patients' demographic data were recorded. Smoking and alcohol use were recorded. Neutrophils (NEU), lymphocytes (LYMP), platelet (PLT), white blood cells (WBC)

and hemoglobin (HGB) values of routine preoperative laboratory tests were recorded retrospectively.

First, the patients were separated into two groups according to the pathology results as benign and malignant. According to the 2002 AJCC clinical staging system, 34 patients (40.5 %) were classified as stage III, 50 patients (59.5 %) as stage IV disease. The patients, whose malignant pathology diagnosis were squamous cell cancer (SCC), were divided into three groups according to the degree of pathological differentiation as; well-differentiated laryngeal carcinoma, moderately differentiated laryngeal carcinoma and poorly differentiated laryngeal carcinoma.

Neutrophils lymphocyte ratio was obtained by dividing the number of neutrophil with lymphocytes count. The relationship between NLR and age, gender, smoking, alcohol use, clinical stage and degree of differentiation were compared.

In addition, the comparison between parameters such as NEU, LYMP, PLT, HGB and WBC; and age, gender, smoking, alcohol use, clinical stage and degree of differentiation was performed. In patients with benign and malignant laryngeal pathology, NLR, NEU, LYMP, PLT, HGB and WBC values were compared.

Statistical analyses were performed using the SPSS 15.0 software package for Windows (SPSS inc., Chicago, IL, USA). The averages and the frequency distributions were examined. The normality of the intergroup distribution was checked. For normally distributed data, the Student's *t* test and a one-way Anova were applied. For abnormally distributed data, the Kruskal–Wallis and Mann–Whitney *U* tests were applied.  $p < 0.05$  was considered statistically significant.

## Results

One hundred and forty-four patients were included in the study. Sixty and eighty-four of them were diagnosed with benign and malignant pathology, respectively. Distribution of benign diseases are given in Table 1.

There was a significant difference between NLR and clinical stage ( $p = 0.003$ ), smoking ( $p = 0.001$ ) and alcohol use ( $p = 0.001$ ). When NLR was analyzed in detail according to the degree of tumor differentiation; significant differences were observed between G1–G2 ( $p = 0.007$ ) and between G1–G3 ( $p = 0.001$ ). However, NLR is higher group G3 than group G2 but this difference was not statistically significant (Table 2). NEU, HGB, WBC and PLT values were compared with age, gender, smoking, alcohol use, degree of differentiation and clinical stage. A significant relationship was not found in the comparison made with age, gender, smoking, alcohol use. While significant differences were observed in the parameters of NEU,

**Table 1** Distribution of benign diseases

Variable	Patients [ <i>n</i> (%)]
Benign pathology (All)	60 (100)
Age median, range (years)	48.9 (11–86)
Sex	
Male	43 (71.7)
Female	17 (28.3)
Diagnosis	
Nodule	34 (56.6)
Polyp	17 (28.3)
Papilloma	4 (6.7)
Ulcer	2 (3.3)
Hamartoma	1 (1.7)
Seborrheic keratosis	1 (1.7)
Pyogenic granuloma	1 (1.7)

The diagnosis of all of the patients who were reported as malignant pathology was squamous cell carcinoma. Correlations between clinicopathological variables and pretreatment NLR status in patients with larynx cancer are given in Table 2

LYMP and HGB in comparison with the degree of differentiation and clinical stage, the differences in WBC and PLT parameters were not statistically significant.

In patients with the diagnosis of benign and malignant pathology; the averages of laboratory values such as NLR, NEU, LYMP, WBC, HGB and PLT were obtained and statistical comparison was made and given in Table 3. When benign and malignant pathologies were compared, while there were significant differences between NLR NEU, LYM, HGB and WBC parameters, no significant difference was observed in the PLT value.

## Discussion

Many markers are used as a prognostic factor in laryngeal cancers. Kowalski et al. [17], studied some demographic, clinical, pathologic, and therapeutic variables in relation to the disease-free interval (DFI) and to the overall survival of laryngeal cancer patients. The primary tumor stage, age, sex, histological grade, site of primary tumor, surgical margins, prior tracheostomy, extracapsular spread, N-stage and vascular embolization were independent predictors of the risk of death.

In one study performed in last few decades, the role of inflammation in cancer pathogenesis and progression has been accepted [6]. With these development, some parameters such as peripheral NEU, LYMP and NLR, which are inflammatory precursors, were compared with prognostic factors routinely used in various cancer diseases.

**Table 2** Correlations between clinicopathological variables and pretreatment NLR status in patients with larynx cancer

Variable	Patients [ <i>n</i> (%)]	<i>p</i> value*
Malign pathology (All)	84 (100)	
Age		
Median, range (years)	63.7 (38–89)	
60 ≥ (mean)	47 (%56) (72)	0.226
60 < (mean)	37 (%44) (52.9)	
Sex		
Male	79 (94)	0.603
Female	5 (6)	
Smoking		
Yes	62 (73.8)	<b>0.001</b>
No	22 (26.2)	
Alcohol		
Yes	41 (48.8)	<b>0.001</b>
No	43 (51.2)	
Histological grade		
G1	31 (36.9)	<b>0.007 (G1–G2)</b>
G2	36 (42.9)	0.295 (G2–G3)
G3	17 (20.2)	<b>0.001 (G1–G3)</b>
Clinical TNM stage		
Stage III	31 (36.9)	
Stage IV	53 (53.1)	<b>0.003</b>

G1: well-differentiated, G2: moderately differentiated, G3: poorly differentiated

\* *p* value, shows the difference between the value of NLR according to the variable groups

There are many studies reporting that NLR can be used as a prognostic factor in different types of cancer such as epithelial ovarian cancer [10], colorectal cancer [11], advanced gastric cancer [12], hepatocellular carcinoma [13], and pancreatic ductal adenocarcinoma [14].

However, when viewed to the literature, only three studies investigating the relationship between head and neck cancers and NLR were found. Two of them are related to nasopharyngeal carcinomas and one of them is related to oral cavity cancer. He et al. [15], reported that, there was a significant correlation between poor survival and increased NLR prior to treatment in the patients underwent radiotherapy or chemoradiotherapy due to nasopharyngeal carcinoma.

In another study related to nasopharyngeal carcinoma is the study that An et al. [16] conducted retrospectively with 363 patients. In this study, they found that, increased NLR was poor prognosis in nasopharyngeal carcinoma. In fact,

**Table 3** Comparison of laboratory values in benign and malignant diseases

Variable	Patients [n]	NLR	NEU	LYMP	WBC	HGB	PLT
Benign pathology	60	1,97	4,52	2,53	7,9	14,44	261,98
Malign pathology	84	0,09	6,42	1 0.74	9,1	13,35	262,75
<i>p</i> value		<b>0.001</b>	<b>0.001</b>	<b>0.001</b>	0.021	<b>0.001</b>	0.415

WBC White blood cells, HGB Hemoglobine, NEU Neutrophil, PLT Platelet, LYMP Lymphocyte, NLR Neutrophil–lymphocyte ratio

Bold value shows the difference between the value of NLR, NEU, LYMP, WBC, HGB, PLT according to the variable groups, respectively

they argued that, increased NLR was not only prognostic factor, also decisive in receiving the response to chemoradiotherapy.

Perisanidis et al. [5], examined 97 patients with locally advanced oral squamous cell carcinoma receiving preoperative chemoradiotherapy retrospectively. They found that a high pretreatment NLR is a significant independent predictor of shorter disease-specific survival in patients with oral cancer receiving preoperative chemoradiotherapy.

In our study, similar to He et al., An et al. and Perisanidis et al. studies, it was considered that, NLR could be used as a prognostic factor in laryngeal cancer. Because when the results were analyzed; significant relationships were monitored between NLR and many prognostic factors.

When the relationship of NLR with the degree of differentiation of tumor was examined, significant results were observed. Significant differences were observed between well-differentiated SCC and moderately differentiated and between well-differentiated and poorly differentiated SCC. NLR was significantly higher in patients with poor differentiation. This finding is very important. Because NLR is easily accessible from routine laboratory tests, inexpensive and a universal biomarker. Besides, significant difference was not seen between moderately differentiated and poorly differentiated SCC in terms of NLR. This situation can be caused by the differences of the number of patients groups in well differentiated (n:31) and moderately differentiated (n:36) group poorly differentiated (n:17). A study with more number of patients may be more effective.

When NLR was compared with clinical stage, it was found to be significantly higher in stage IV laryngeal cancer than stage III. In our study, the comparison of early and advanced stage was not made due to there was no patients with laryngeal cancer in early stage. But, significantly high results of NLR in stage IV than stage III has enabled us to consider that, NLR can be used as prognostic factors.

NLR was significantly higher in people who were smokers and alcohol users. The significant correlation of NLR with all these prognostic factors supposed that NLR

can be used in the laryngeal cancer as a prognostic factor due to the significant correlation of NLR with all these prognostic factors.

The relationship of NLR with gender was meaningless. The reason for this can be that, there were only five female patients in the study, and this may be adversely affected the results. When the rates of NLR were compared between the patients over the age of 60 and under the age of 60, no significant difference was seen between them. More meaningful results may be obtained with study group with more homogeneous group distribution and higher and equal number of patients.

As a result of the comparison of; laryngeal benign-malignant pathologies, NLR has been significantly higher in patients with malignancy than in patients with benign pathology. Prior studies have shown correlations between the degree of systemic inflammatory response and outcomes in various malignancies. This finding proves once again that, inflammation has a role in cancer pathogenesis and progression. Furthermore, this finding may be helpful in predicting preoperatively that the lesion is benign or malignant in patients planned undergo surgery for laryngeal pathology. High NLR values may lead us to consider the tumor more malignant.

Light of these findings, NLR is a cheap and easily accessible marker which can be used as a prognostic factor in laryngeal cancer. It is thought to shed light on the studies which will be conducted with more patients.

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