



## A single center experience of neutrophil to lymphocyte ratios (NRL) in determining the prognosis of nasopharyngeal cancer

### Nazofarenks kanseri hastalarında nötrofil lenfosit oranının prognoz üzerine etkisi, tek merkez deneyimi

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#### Abstract

**Purpose:** Neutrophil to lymphocyte ratio (NRL) is an immunological parameter which indicates inflammatory response, as well as anti-tumor immunity and solid tumor recurrence. The most significant results of the NRL ratio related prognostic state of the patients were found in colorectal, and renal cancers. Our study will investigate whether this ratio could be a useful marker of progression free survival and prognosis in nasopharyngeal cancer patients (NPC).

**Materials and Methods:** The study including 133 patients with valid samples diagnosed with nasopharyngeal carcinoma were evaluated retrospectively. We included only the patients diagnosed pathologically with non-metastatic, locally advanced nasopharyngeal carcinoma who were treated with induction chemotherapy. Blood parameters and neutrophil to lymphocyte ratios (NLR) were taken into account for interpretation.

**Results:** The results indicated that the mean neutrophil to lymphocyte ratio was 2.78, showing high variance within the cohort. (0.5-30.5 confidence interval). Among this group, the distribution of the patients falling into each percentile of the NRL (which are <2.1, 2.1-2.77, 2.77-3.85 and >3.86 was found to be as follows: 24.8%, 25.6%, 24.8% and 24.8%). PFS and OS rates were not statistically significant in each percentile of the NRL (p:0.86 and p:0.54).

**Conclusion:** According to literature NRL was found not only an independent prognostic factor, also a predictor of response to chemoradiotherapy. Opposite to this, in our study NRL seems not to be a parameter to predict progression free survival and prognosis in nasopharyngeal carcinoma.

**Keywords:** Nasopharyngeal Carcinoma; Neutrophil To Lymphocyte Ratios; Prognosis.

#### Öz

**Amaç:** Nötrofil lenfosit oranı (NLO) immünolojik bir parametredir ve tümör immunité ve rekürrens gibi inflamatuvar cevapları gösterir. Prognoz ile NLO arasındaki en belirgin ilişki kolorektal ve renal kanserde saptanmıştır. Çalışmamızda NLO'nun nazofarenks kanseri hastalarında hastalıksız sağkalım ve genel sağkalım üzerindeki etkisine bakılmıştır.

**Gerç ve yöntemler:** Bu çalışmaya Nisan 1998-Şubat 2013 tarihleri arasında Hacettepe Üniversitesi Kanser Enstitüsü, Medikal Onkoloji Bölümüne başvuran 133 nazofarenks kanseri hastası dahil edildi. Tanı anında lokal ileri nazofarenks kanseri tanısı alan hastalar çalışmaya alındı ve metastatik hastalar çalışmaya dahil edilmedi. Hastalar tedavi olarak öncelikle indüksiyon kemoterapisi takibinde konkomitant kemoradyoterapi tedavisi almıştı. Hematolojik parametreler incelendi ve nötrofil lenfosit oranı hesaplandı.

**Bulgular:** Ortalama NLO 2.78 idi ve çok sayıda varyasyonlar göstermekteydi. NLO <2.1 olan hasta grubu 24.8%, NLO 2.1-2.77 olan 25.6%, NLO 2.77-3.85 olan 24.8% ve >3.86 24.8% oranındaydı. Hastaların hastalıksız sağkalım ve genel sağkalım verileri hesaplandı. NLO değerleri ile hastalıksız sağkalım ve genel sağkalım arasında fark saptanmadı (p:0.86 ve p:0.54).

**Sonuç:** Literatürde NLO sadece bağımsız bir prognostik faktör değil aynı zamanda kemoradyoterapi cevabını belirleyen bir prediktif faktördür. Yüksek NLO değerlerinin kötü prognozu, yüksek tümör yükünü ve yüksek malignite gradesini gösterdiğine dair yayınlar mevcuttur. Bunun tersi olarak, çalışmamıza göre nazofarenks kanseri takibinde NLO bir prognostik faktör değildir ve hastalıksız sağkalım ve genel sağkalımın belirlenmesinde etkin değildir.

**Anahtar Kelimeler:** Nazofarengeal Kanser; Nötrofil Lenfosit Oranı; Prognoz.

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## INTRODUCTION

Neutrophil to lymphocyte ratio is an immunological parameter which indicates inflammatory response (1), as well as anti-tumor immunity and is being used as an indicator of recurrence of solid tumor metastases with increasing popularity in previous decade especially in gastrointestinal tumors such as advanced stage colorectal carcinoma, hepatocellular carcinoma, renal cell carcinoma and solid tumor bone metastases (2-6). A recent study also showed that an elevated NLR was a significant indicator of increased perioperative mortality amongst earlier stage colorectal cancer patients whose tumors were surgically resected. These conclusions can be made based upon various cytokine-related hypotheses that neutrophils and lymphocytes are competent white blood cells that reflect the state of the malignancy which is effected by cytokines.

Different blood parameters related with systemic inflammation such as white blood cell (WBC), C-reactive protein (CRP), lactate dehydrogenase (LDH), albumin, globulin and neutrophil, lymphocyte have been found to be associated with prognosis in patients with nasopharyngeal carcinoma (7). Recent studies also showed that pre-treatment levels of peripheral neutrophils and lymphocytes were independent prognostic factors in NPC patients (7-9). In the present study we investigated whether a new parameter called neutrophil-to-lymphocyte ratio (NLR) can have prognostic significance in our NPC population.

## MATERIALS and METHODS

### Patients

Clinical data from patients diagnosed with non-metastatic, locally advanced nasopharyngeal cancer during May 1998 to February 2013 in the Oncology Hospital of Hacettepe University Faculty of Medicine were collected. The ethical committee approval and patients informed consent form were taken for this retrospective study

We included only the patients diagnosed pathologically with non-metastatic, locally advanced nasopharyngeal carcinoma who were treated with induction chemotherapy. Laboratory measurements of white blood cells were performed, including the counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

The screening for presence of metastasis was done by using whole body computed tomography (CT), magnetic resonance (MRI) or positron emission tomography/CT scans or pathological results. Exclusion criteria include presence of infections such as pneumonia and urinary tract infections, blood disorders, inflammatory abnormalities, which can cause to decrease or increase in neutrophil and lymphocyte counts and lack of follow-up data. All data of these measurements were retrospectively collected from medical records. For stage classification, American Joint Committee of Cancer Staging System was used.

### Statistical Analysis

NLR were calculated as neutrophil count divided by lymphocyte count and patients were divided into four quartiles. Survival status was retrieved from our cancer registry. Survival analysis, stratified by NLR quartiles, was used to evaluate the predictive value of NLR.

All analyses were performed using statistical software, Statistical Package for the Social Sciences, release 11 (SPSS, Chicago, IL).

Overall survival (OS) and progression-free survival (PFS) was performed using the Kaplan–Meier method. Survival plots were constructed using the Kaplan–Meier method. Statistical significance was set at  $P < 0.05$ . OS time was described as time from diagnosis until death; the follow-up of patients still alive has been censored at their latest date of follow-up. PFS time was defined as the time from diagnosis until progression or death; the follow-up of patients still alive without progression has been censored at the latest date of their follow-up. All statistical tests were 2-tailed with  $p < .05$  considered to be significant.

## RESULTS

The study included 133 patients and the median age at diagnosis was 47. Demographic features were given in Table 1. The tumors obtained from biopsies from these patients were graded histologically according to WHO tumor-grading system for head and neck cancers. The majority of the patients (106 out of a cohort of 133) pertained to WHO grades II and III indicating a high-grade tumor status. The recurrence and metastasis status were given in Table 2. The majority of the patients received induction chemotherapy and then concomitant chemo-radiotherapy (81.6% of the patients).

Table 1. Demographic Data

Demographic Variables		
Subgroups	N(133)	%
<b>Gender</b>		
Male	101	76,6
Female	32	23,4
<b>Age at diagnosis, median (range)</b>	47(20-73)	
<b>Stage</b>		
Grade II	15	11,4
Grade III	46	34,8
Grade IV	65	49,4
<b>Histological Subtype</b>		
WHO Grade I	2	1,3
WHO Grade II	62	46,8
WHO Grade III	44	33,5

**Table 2.** Recurrence and Metastasis Status

Patient Variables		
Patient Variable	N	%
<b>Local recurrence</b>		
Absent	114	86,4
Present	19	13,6
<b>Distant metastasis</b>		
Absent	109	82,5
Present	24	17,5
<b>Local- Distant metastasis</b>		
Absent	95	71,4
Present	38	28,6

The blood parameters that were assessed apart from the target of this study, neutrophil to lymphocyte ratio; were monocyte and thrombocyte counts, median platelet volume, platelet distribution width and finally monocyte to lymphocyte ratio as a parameter for comparison of the significance of NLR over tumor prognosis and clinical status.

The results indicated that the mean neutrophil to lymphocyte ratio was 2.78, showing high variance within the cohort. (0.5-30.5 confidence interval). PFS and OS rates were not statistically significant in each percentile of the NLR in nasopharyngeal cancer patients (p:0.86 and p:0.54).

## DISCUSSIONS

Neutrophil to lymphocyte ratio has been popular in recent years not only in oncology (9-14). The most significant results of the NLR ratio related prognostic state of the patients were found in colorectal, and renal cancers, in which inflammation in the tumor stroma as well as the tumor-induced vascular proliferation linked to inflammatory factors are prominent(3,5). In nasopharyngeal carcinoma, the state of being an EBV carrier and smoking are important as they create a similar surrounding for the intact cells as they are being exposed to foreign agents or carcinogens which also aggravate inflammation.

Some recent studies have highlighted the meaning of leukocyte levels in predicting survival in patients with NPC whose lesions were limited to the local site without distant metastases. The mechanism for the relationship of pretreatment of different leukocytes and prognosis of patients with NPC has not been fully clarified. It may be partially explained by the link between chronic inflammation and cancer cells. He et al.( 8) showed that NLR was significantly associated with OS and PFS in patients with NPC and found that pretreatment lymphocyte variables, particularly lymphocyte percentage, were also independent prognostic factors in patients with NPC. In An X et al.(9) trial disease-specific survival (DSS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRFS) rates were compared according to NLR level. NLR was not only an independent prognostic factor, also a predictor of response to chemoradiotherapy. Ying Jin et al.(10 ) demonstrated that pretreatment NLR is an independent

predictor of survival outcome for patients with metastatic NPC (p < .001). In our study NLR is not a predictor factor for PFS and OS in nasopharyngeal cancer patients population. The results indicated that the mean neutrophil to lymphocyte ratio was 2.78, showing high variance within the cohort. (0.5-30.5 confidence interval). PFS and OS rates were not statistically significant in each percentile of the NLR in nasopharyngeal cancer patients( p:0.86 and p:0.54). Due to small number of patients, different tumor biology in our cohort, lack of knowledge of the relationship in the majority of patients with EBV may have led to the emergence of these results. Opposite to our study , in the literature higher neutrophil to lymphocyte ratios predicted poor prognosis, high tumor burden and high grade malignancies (15).

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