NORTHWESTERN MEDICAL JOURNAL

Northwestern Med J. 2025;5(1):16-24
**DOI:** 10.54307/NWMJ.2025.77

RESEARCH ARTICLE

# The prognostic value of neutrophil-to-lymphocyte ratio in nasopharyngeal cancer

**Mustafa Kandaz**[1], **Atalay Balsak**[1], **Hatice Bengü Çobanoğlu**[2]

[1]Department of Radiation Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Türkiye
[2]Department of Otorhinolaryngology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Türkiye

**Cite as:** Kandaz M, Balsak A, Çobanoğlu HB. The prognostic value of neutrophil-to-lymphocyte ratio in nasopharyngeal cancer. Northwestern Med J. 2025;5(1):16-24.

## ABSTRACT

**Introduction:** The prognostic value of the neutrophil-to-lymphocyte ratio (NLR) for nasopharyngeal carcinoma (NPC) continues to be debated. This study was conducted to enhance the accuracy of its prognostic value through a single-centre analysis.

**Methods:** Ninety-seven patients with NPC who received adjuvant radiotherapy between 1998 and 2022 were analyzed retrospectively.

**Results:** The study included a total of 97 patients who were treated for NPC and had available data. In 54 (56%) patients the NLR was ≤3 and in 43 (44%) the NLR was >3. The mean age of the patients was 49.64±14.51 (range: 12-82) years. Four patients were ≤18 years old and 93 patients were >19 years old. Sixty-three (65%) patients were male, 34 (35%) patients were female. For stage I patients, NLR was ≤3 in 2 (2%) and >3 in 2 (2%) patients. For stage II patients, NLR was ≤3 in 10 (11%) and >3 in 8 (8%) patients. For stage III patients, NLR was ≤3 in 29 (30%) and >3 in 25 (26%) patients. For stage IVA patients, NLR was ≤3 in 12 (12%) and >3 in 8 (8%) patients. For stage IVB patients, NLR was >3 in 1 (1%). The follow-up period was 79.4±72.1 (2-279) months. In all patients, mean overall survival (OS) was 159.37±13.66 (132.97-185.76) months, median 205±31.11 (144-265.99) months, The 1-, 2- , 3- and 5-year survival rates were 87.3%, 81.5%, 74.3%, and 65.3%, respectively. In general, 54 (56%) of the patients had NLR ≤3, while 43 (44%) had NLR >3. Mean survival times were 169.72±14.2 (95%CI 141.86-197.56) and 133.88±18.95 (95%CI 96.72-171.03) months for NLR ≤3 and NLR >3 patients, respectively. Median survival time was 223 months for NLR ≤3 patients, whereas it was 118±66.11 (95%CI 0-247.58) for >3 patients. The 1-, 2-, 3- and 5- year survival rates were 92.6%, 86.4%, 82% and 72.3% for NLR ≤3 and 80.3%, 75.6%, 65% and 56.8% for NLR >3 patients, respectively, indicating statistical significance (p=0.047).

**Conclusion:** In NPC, a pre-treatment NLR above three indicates an unfavorable prognosis in survival and may be a valuable prognostic biomarker. A large-scale prospective study is necessary to validate the prognostic significance of NLR in NPC patients and to determine precise cut-off values.

**Keywords:** nasopharyngeal carcinoma, neutrophil-to-lymphocyte ratio, survival

**Corresponding author:** Hatice Bengü Çobanoğlu **E-mail:** benguyc@gmail.com
**Received:** 13.01.2024 **Accepted:** 19.03.2024 **Published:** 31.01.2025

## INTRODUCTION

Nasopharyngeal cancer (NFC) is a malignant tumor developing in the nasopharyngeal region. This area is located at the back of the nasal cavity and NFC is a rare type of cancer worldwide (1). However, it is more common in Asia and Southeast Asia. Especially in China, the incidence is as high as 80 per 100,000 person-years (2,3).

Diagnosis of NFC involves various methods, such as imaging tests and tissue biopsy, as well as symptoms and physical examination. Symptoms include prolonged nasal congestion, nosebleeds, difficulty swallowing, earache, and voice changes. During a physical exam, an endoscopy may be performed to examine the back of the throat. Imaging tests such as magnetic resonance imaging (MRI) and computed tomography (CT) are used. Tissue biopsy provides a definitive diagnosis of cancer cells and helps to determine the stage of the tumor (4,5).

Treatment of NFC depends on the stage of the tumor, the patient's overall health, and other factors. Treatment options include radiotherapy (RT) and chemoradiotherapy (CRT). T1 tumor detected at an early stage can only be treated with radiotherapy, while other stages can be treated with chemoradiotherapy. The most common form of treatment for NPC is radiotherapy, with 5-year overall survival (OS) rates ranging from 66% to 70% (6). However, the long-term survival of many patients remains poor due to high rates of distant metastasis and local recurrence after radiation (7,8).

The prognosis of NFC varies based on staging, response to treatment, and other factors. Patients diagnosed at the early stages usually have a better prognosis. However, patients diagnosed in advanced stages may have a poorer prognosis. Post-treatment follow-up includes regular evaluation of the patients' health and ensures early detection of possible recurrence or complications. However, these factors alone are not always sufficient for accurate prognostic predictions. Therefore, it is essential to identify biomarkers that are accurate and easy to use to for improving prognostic evaluations in NPC patients.

Evidence suggests that proinflammatory tumor microenvironments are closely linked to the occurrence and spread of cancer. While neutrophils are inflammatory cells that have an impact on the immune system's cytotoxic activity, lymphocytes are immune cells that have an anticancer effect. The neutrophil-to-lymphocyte ratio (NLR) serves as a key biomarker indicative of systemic inflammation. As a biomarker, NLR has been shown to improve prognostic evaluations in vairous malignancies, such as breast cancer, gastric neuroendocrine neoplasms, esophageal squamous cell carcinoma, and non-small cell lung cancer (9). An increased NLR, along with elevated neutrophil levels and/or reduced lymphocyte levels, serves as a biomarker reflecting the imbalance between pro- and antitumor immune activity in the host. Additionally, NLR can be easily derived from complete blood count results, making it a potential prognostic biomarker for NPC. Several studies have already explored the relationship between pretreatment NLR and NPC characteristics, as well as its prognostic significance in NPC patients. NLR has several suggested cutoff values (ranging from 2.28-3.00, with a median of 2.32), but the research indicates that, regardless of the cutoff value, NLR is a reliable predictive marker (9). However, the findings of these investigations have been proven contradictory.

In this study, we aim to evaluate the effect of neutrophil-lymphocyte ratio (NLR) on survival in NFC to enable a more accurate assessment of pre-treatment NLR as a predictive biomarker for patients with NPC, in light of its potential prognostic utility.

## MATERIALS AND METHODS

### Patient selection

We retrospectively reviewed all patients who received NPC treatment at our facility between 1998 and 2022. Patients with metastatic disease and prior or ongoing cancers were excluded from the study. The study population comprised 150 NPC patients with histological diagnoses and curative care between January 1998 and December 2022. This retrospective study was approved by the Ethics Committee (Project No. 2017-77, Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee).

Prior to therapy, all patients underwent a customary thorough physical examination. Biochemical assays and a complete blood counts were assessed. Routine clinical staging and imaging, such as computed tomography of the thorax and MRI scans of the head and neck, were carried out. Some patients were eligible for whole-body fludoxyglucose F 18 (18 F-FDG) positron emission tomography (PET)-CT imaging. The patients were staged according to the American Joint Committee on Cancer (AJCC).

### Patients and treatment

Patients with T1N0M0 were treated with radiotherapy (RT) alone, while those with T2 or N1, M0 received chemoradiotherapy (CRT). The three cycles of cisplatin 100 mg/m2 (days 1, 21, and 42) or 40 mg/m2 weekly were employed as the chemotherapeutic dosage. Between 1998 and 2010, the 2D-RT technique was used, while the Intensity-Modulated Radiation Therapy (IMRT) technique was adopted from 2010 to 2022.

### Radiotherapy area

Primary tumor and positive lymph nodes were included in the RT region. A margin of 5–10 mm was given around the area, with a 1 mm margin allowed for the brainstem, spinal cord, optic nerve, and chiasm, and 70 Gy RT is administered in 2Gy fractions. The entire nasopharynx, the clivus, the base of the skull, the pterygoid fossa, the parapharyngeal space, the sphenoid sinus, posterior ethmoid sinuses, posterior maxillary sinuses, and the posterior third of the nasal cavity level 1b- for N+ disease in both bilateral cervical lymph nodes, 4, skip level 1b for N0 disease, and 2Gy to 60 Gy RT was given to the retropharyngeal lymph nodes.

### Follow-up

Follow-up visits were scheduled every three months for the first three years and every six months for the subsequent three years. To confirm locoregional insufficiency or distant metastases, fine-needle aspiration or biopsy was performed. Each visit included a thorough physical examination, repeat complete blood count, biochemical testing, brain and neck MRI, a thorax and abdomen computed tomography, and any other clinically indicated procedures. Follow-up continued from the initial diagnosis until the last visit or the date of death.

### Statistical analysis

Statistical analysis of the collected data was performed using IBM SPSS Statistics 23. Time to local recurrence, regional recurrence, metastatic development, or death after RT or CRT were considered clinical outcomes. OS and disease-free survival rates (DFS) were calculated using the Kaplan-Meier technique. To examine differences between subgroups and identify variables having independent prognostic relevance on survival, a bilateral log-rank test was utilized. A p-value of 0.05 was used as the threshold for statistical significance in all tests

## RESULTS

### Patient characteristics

A total of 97 patients, who were treated for NPC between 1998 and 2022 and had available data, were included in the study. NLR was ≤3 in 54 (56%) and 43 (44%) NLR >3. The mean age of the patients was 49.64±14.51 (range: 12-82) years. Four patients were ≤18 years old and 93 patients were >19 years old. Sixty-three (65%) patients were male, 34 (35%) patients were female. NLR was ≤3 in 38 (39%) of male patients and >3 in 25 (26%). NLR was ≤3 in 16 (16%) of female patients and >3 in 18 (19%).

Ebstein Barr Virus (EBV) was negative in 3 (3%) patients (1 (1%) with NLR ≤3 and 2 (2%) with NLR >3). EBV was positive in 25 (26%) patients (17 (18%) with NLR ≤3 and 8 (8%) with NLR >3). EBV status was unknown in 69 (71%) patients (36 (37%) with NLR ≤3 and 33 (34%) with NLR >3).

Histology was unknown in 8 (8%) patients, 6 (6%) patients type I (keratinized squamous cell carcinoma), 10 (10%) patients type IIA (Non- keratinized squamous cell carcinoma, no lymphoid infiltration), and 73 (76%) patients were type IIB (Non- keratinized squamous cell carcinoma, lymphoid infiltration is present). In 2 (2%) patients whose histology was unknown, NLR was ≤3 and 6 (6%) NLR was >3. NLR was ≤3 in 1 (1%) type I patients and NLR was >3 in 5 (5%) patients. NLR was

≤3 in 5 (5%) type IIA patients and NLR was >3 in 5 (5%) patients. NLR was ≤3 in 46 (48%) type IIB patients and NLR was >3 in 27 (28%).

29 (30%) patients were T1, 27 (28%) patients were T2, 22 (23%) patients were T3 and 19 (19%) patients were T4. 17 (17%) patients had N0, 18 (19%) patients had N1, 58 (60%) patients had N2 and 4 (4%) patients had N3. 1 (1%) patient was M1. According to the stages; 4 (4%) patients were stage I, 18 (19%) patients were stage II, 54 (56%) patients were stage III, 20 (20%) patients were stage IVA, and 1 (1%) patient was stage IVB. NLR was ≤3 in 2 (2%) of stage I patients and NLR was >3 in 2 (2%) patients. NLR was ≤3 in 10 (11%) of stage II patients and NLR was >3 in 8 (8%) patients. NLR was ≤3 in 29 (30%) of stage III patients and NLR was >3 in 25 (26%) patients. NLR was ≤3 in 12 (12%) of stage IVA patients and NLR was >3 in 8 (8%) patients. NLR was >3 in stage IVB 1 (1%) patient. Patient characteristics are shown in Table 1.

**Table 1.** Patient characteristics according to NLR

| | | N (%) | NRL N (%) | |
|---|---|---|---|---|
| | | | ≤3 | >3 |
| **Age** | ≤18 | 4 (4%) | 3 (3%) | 1(1%) |
| | >19 | 93 (96%) | 51 (53%) | 42 (44%) |
| **Sex** | Male | 63 (65%) | 38 (39%) | 25 (26%) |
| | Female | 34 (35%) | 16 (16%) | 18 (19%) |
| **T** | 1 | 29 (30%) | 22 (23%) | 7 (7%) |
| | 2 | 27 (28%) | 14 (15%) | 13 (13%) |
| | 3 | 22 (23%) | 7 (7%) | 15 (16%) |
| | 4 | 19 (19%) | 12 (12%) | 7 (7%) |
| **N** | 0 | 17 (17%) | 8 (8%) | 9 (9%) |
| | 1 | 18 (19%) | 10 (11%) | 8 (8%) |
| | 2 | 58 (60%) | 34 (35%) | 24 (25%) |
| | 3 | 4 (4%) | 2 (2%) | 2 (2%) |
| **M** | 0 | 96 (99%) | 55 (57%) | 41 (42%) |
| | 1 | 1 (1%) | 0 (0%) | 1 (1%) |
| **Stage** | I | 4 (4%) | 2 (2%) | 2 (2%) |
| | II | 18 (19%) | 10 (11%) | 8 (8%) |
| | III | 54 (56%) | 29 (30%) | 25 (26%) |
| | IVA | 20 (20%) | 12 (12%) | 8 (8%) |
| | IVB | 1 (1%) | 0 (0%) | 1 (1%) |
| **Histology** | I | 6 (6%) | 1 (1%) | 5 (5%) |
| | IIA | 10 (10%) | 5 (5%) | 5 (5%) |
| | IIB | 73 (76%) | 46 (48%) | 27 (28%) |
| | Unknown | 8 (8%) | 2 (2%) | 6 (6%) |
| **EBV** | Negative | 3 (3%) | 1 (1%) | 2 (2%) |
| | Positive | 25 (26%) | 17 (18%) | 8 (8%) |
| | Unknown | 69 (71%) | 36 (37%) | 33 (34%) |

t: tumor stage, n: nodal stage, m: methastasis, NLR: neutrophil to lymphocyte ratio, EBV: Ebstein-Barr Virus.

## Survival

The follow-up period was 79.4±72.1 (2-279) months. The mean OS of all patients was 159.37±13.66 (132.97-185.76) months, with a median of 205±31.11 (144-265.99) months. The 1-, 2-, 3- and 5-year survival rates were 87.3%, 81.5%, 74.3%, and 65.3%, respectively (Figure 1).

## Neutrophil-to-lymphocyte ratio (NLR)

NLR was calculated by the neutrophil and lymphocyte measurements of the patients before radiotherapy/chemoradiotherapy. NLR cut-off value was accepted as 3 and patients were divided into two groups (≤3 and >3).

In total, 54 (56%) of patients had NLR ≤3, while 43 (44%) had NLR >3. The mean survival times were 169.72±14.2 (95%CI 141.86-197.56) and 133.88±18.95 (95%CI 96.72-171.03) months for NLR ≤3 and NLR >3 patients, respectively. The median survival time was 223 months for NLR ≤3 patients, whereas it was 118±66.11 (95%CI 0-247.58) for >3 patients. The 1-, 2-, 3- and 5-year survival rates were 92.6%, 86.4%, 82% and 72.3% for NLR ≤3 and 80.3%, 75.6%, 65% and 56.8% for NLR >3 patients, respectively, indicating statistical significance (p=0.047) (Figure 2).

Three (3%) of patients aged ≤18 years had NLR ≤3 and the 1-, 2-, 3- and 5-year survival rates were 100%, 100%, 100% and 100%. There was 1 (1%) patient with NLR >3 and did not survive beyond a year. There was no statistical difference between the two groups

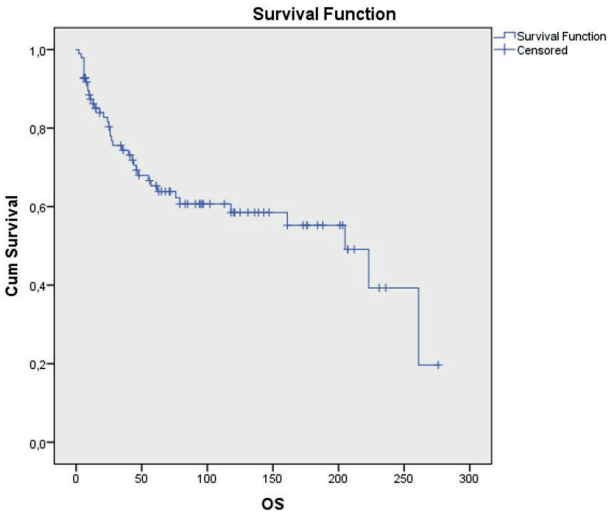


**Figure 1.** Overall survival.

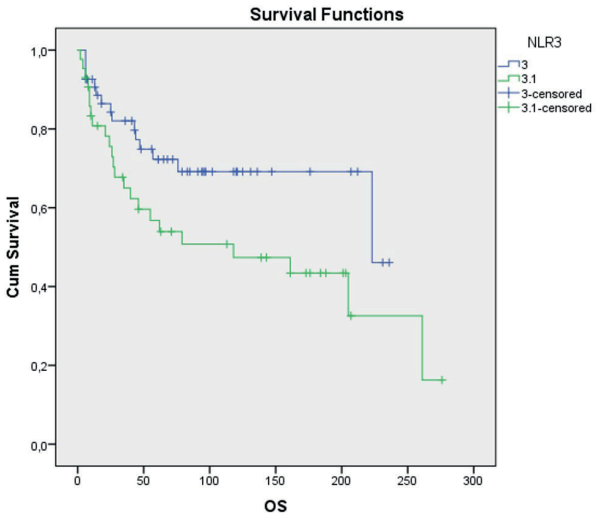


**Figure 2.** Overall survival by NLR.

according to age (p=0.157). Among patients aged >19 years, 51 (53%) patients had NLR ≤3 and 42 (44%) had NLR >3. The mean survival time was 166.94±14.66 (95%CI 138.2-195.68) and 137±19.17 (95%CI 99.43) -174.58) months, the median survival time was 223 and 118.77.63±36.37 (0-270.16) months. The 1-, 2-, 3- and 5-year survival rates were 92.2%, 85.7%, 81.1% and 70.9% for NLR ≤3 and 82.8%, 77.5%, 66.7% and 58.2% for NLR >3, respectively. This difference was not statistically significant (p=0.088).

Among male patients, 38 (39%) had NLR ≤3 and 25 (26%) had NLR >3. The mean survival time was 165.13±16.64 (95%CI 132.51-197.75) and 119.9±24.88 (95%CI 71.11-1186.68) months, median survival time was 223±105.56 (95%CI 16.09-429.9) and 62±36.37 (0-133.29) months. The 1-, 2-, 3- and 5-year survival rates were 89.5%, 83.6%, 80.4% and 73% for NLR ≤3 and 70.3%, 65.9%, 57.1% and 47.6% for NLR >3, respectively. This difference was not statistically significant (p=0.061). Among female patients, 16 (16%) had NLR ≤3 and 18 (19%) had NLR >3. The mean survival time was 175.07±25.62 (95%CI 124.84-225.29) and 159.08±28.81 (95%CI 102.6-215.57) months, the median survival time of NLR >3 patients was 205±81.82 (95%CI 44.63-365.37) months. The 1-, 2-, 3- and 5-year survival rates were 100%, 85.7%, 77.9% and 70.1% for NLR ≤3 and 94.4%, 81.9%, 75.5% and 63% for NLR >3, respectively. This difference was not statistically significant (p=0.355).

When the patients were evaluated according to EBV; 1 (1%) of EBV negative patients had an NLR ≤3, and 2 (2%) patients with NLR>3 had a1-, 2-, 3- and 5-year survival rate of 50%, and this difference shows no statistical significance (p=0.480). 17 (18%) of EBV positive patients had NLR ≤3 and 8 (8%) patients had NLR>3. The mean survival time was 69.36±9.03 (95%CI 51.66-87.07) and 60.66±9.43 (95%CI 42.17-79.15) months; the 1-, 2-, 3- and 5-year survival rates were 88.2%, 79.4%, 69.5% and 69.5% for NLR ≤3 and 83.3%, 83.3%, 83.3% and 83.3% for NLR >3, respectively. This difference was not statistically significant (p=0.636). In patients with unknown EBV, 36 (37%) has been NLR ≤3 and 33 (34%) NLR >3, mean survival time was 176.99±15.91 (95%CI 145.81-208.18) and 129.49±19.88 (95%CI 90.51) -168.48) months, median survival time was 223 and 79±62.16 (95%CI 0-200.84) months; the 1-, 2-, 3- and 5-year survival rates were 94.4%, 85.9%, 82.9% and 73.3% for NLR ≤3 and 81.8%, 75.8%, 63.6% and 51.5% for NLR >3, respectively. This difference was not statistically significant (p=0.026).

When the patients were evaluated according to histology; 1 (1%) of type I patients had NLR ≤3 and 5 (5%) NLR > 3, the mean survival time was 6 and 62.2±27.28 (95%CI 8.71-115.68) months; median survival time was 6 and 35±7.66 (95%CI 19.97-50.03) months;1, 2, 3 and 5 year survival rates were 80%, 40% and 40% for NLR >3 respectively. There were no NLR ≤3 patients

surviving 1 year. This difference was statistically significant (p=0.025). Type IIA patients had 5 (5%) NLR ≤3 and 5 (5%) NLR > 3, the mean survival time was 179.5±44.6 (95%CI 92.08-266.91) and 32.13±9.68 (95%CI 13.15-51.11) months respectively. The 1-, 2-, 3- and 5- year survival rates were 100%, 100%, 75% and 75% for NLR ≤3 and 80%, 80%, 53%- and 54-years survival rates for NLR >3, respectively. This difference was not statistically significant (p=0.171). Type IIB patients had 46 (48%) NLR ≤3 and 27 (28%) NLR > 3, the mean survival time was 171.55±15.65 (95%CI 70.86-202.23) and 169.75±23.7 (95%CI 123.29-216.21) months respectively. The median survival time was 205±57.36 (95%CI 92.57-317.42) months for NLR >3. The 1-, 2-, 3- and 5-year survival rates were 93.5%, 86.5%, 83.7% and 72% for NLR ≤3 and 88%, 79.6%, 71.2% and 66.8% for NLR >3, respectively, and this difference was not statistically significant (p=0.540). Of the patients whose histology was unknown, 2 (2%) NLR ≤3 and 6 (6%) NLR > 3, the mean survival time was 223 and 71.33±31.01 (95%CI 10.55-132.11) months respectively. The median survival time was 223 and 11±30 (95%CI 0-69.81) months. The 1-, 2-, 3- and 5-year survival rates were 100%, 100%, 100% and 100% for NLR ≤3 and 50%, 50%, 50% and 33.3% for NLR >3, respectively. This difference was not statistically significant (p=0.170). Survival according to patient characteristics is shown in Table 2.

According to stage, there were 2 (2%) NLR ≤3 and 2 (2%) NLR >3 Stage I patients, mean survival time was 14±2.82 (95%CI 8.45-19.54) and 10 months; median survival time was 10 and 10 months; the 1-, 2-, 3- and 5-year survival rates were 50%, 50%, 50% and 50% for NLR ≤3 and 50%, 50%, 50% and 50% for NLR >3, respectively, and this difference was not statistically significant (p=0.317). There were 10 (10%) NLR ≤3 and 8 (8%) NLR >3 Stage II patients, mean survival time was 186.62±19.05 (95%CI 149.26-223.98) and 212.57±37.94 (95%CI 138.2-286.93) months; the 1-, 2-, 3- and 5-year survival rates were 100%, 100%, 100% and 87.5%for NLR ≤3 and 100%, 100%, 100% and 85.7% for NLR >3, respectively, and this difference was not statistically significant (p=0.538). There were 29 (30%) NLR ≤3 and 25 (26%) NLR >3 Stage III patients, mean survival time was 158.86±20.54 (95%CI 118.58-199.15) and 141.55±25.58 (95%CI 91.4-191.7) months; the 1-, 2-, 3- and 5-year survival rates were 92.9%, 84.6%, 80.4% and 67.2%for NLR ≤3 and 87.1%, 82.3%, 67.4% and 62.2% for NLR >3, respectively, and this difference was not statistically significant (p=0.403). There were 12 (13%) NLR ≤3 and 8 (8%) NLR >3 Stage IVA patients, mean survival time was 141.92±35.77 (95%CI 71.81-212.03) and 80.37±26.88 (95%CI 27.67-133.07) months; median survival time was 223 (95%CI 12.94-30.85) and 28±24.04 (95%CI 0-75.12) months; the 1-, 2-, 3- and 5-year survival rates were 81.8%, 71.6%, 61.4% and 61.4% for NLR ≤3 and 75%, 62.5%, 50% and 37.5% for NLR >3, respectively, and this difference was not statistically significant (p=0.340). There were stage IVB 1 (1%) patient with NLR >3 and the mean survival time was 3 months. Survival by stage and NLR characteristics are shown in Table 3.

## DISCUSSION

The TNM staging system for NPC is the primary model used for predicting survival outcomes (9). However, it does not consider the tumor's inherent biological variability. In this study, we aimed to investigate the relationship between NLR rate and OS to predict overall survival in nasopharyngeal carcinoma. We included age, stage, EBV status, and histology in the nomogram for OS.

Recent studies have indicated that EBV DNA levels in plasma, serum, or peripheral blood cells serve as a valuable prognostic marker for NPC patients (10). However, routine EBV DNA testing has only recently been implemented in our clinic. In addition, EBV DNA testing procedures may vary between clinics. Therefore, the prognostic significance of NLR in OS could not be demonstrated in a small number of patients who underwent EBV testing in our study.

Recent research highlights the pivotal role of inflammation in tumor pathogenesis, with proinflammatory tumor microenvironments closely linked to cancer progression (9). Neutrophils and lymphocytes are key indicators of systemic inflammation and immune status. A higher NLR signifies an increase in neutrophils and/or a reduction in lymphocytes. Lymphocytes generally have antitumor functions, while neutrophils are associated with inflammation and may impair the cytolytic

**Table 2.** Overall Survival by patient and NLR characteristics

| | | NLR | n (%) | Mean (95% CI) | Median (95% CI) | 1 y (%) | 2 y (%) | 3 y (%) | 5 y (%) | p |
|---|---|---|---|---|---|---|---|---|---|---|
| General | | ≤3 | 54 (56%) | 169.72±14.2<br>141.86-197.56 | 223 | 92.6 | 86.4 | 82 | 72.3 | 0.047 |
| | | >3 | 43 (44%) | 133.88±18.95<br>96.72-171.03 | 118±66.11<br>0-247.58 | 80.3 | 75.6 | 65 | 56.8 | |
| Age | ≤18 | ≤3 | 3 (3%) | - | - | 100 | 100 | 100 | 100 | 0.157 |
| | | >3 | 1 (1%) | 10 | 10 | 0 | 0 | 0 | 0 | |
| | >19 | ≤3 | 51 (53%) | 166.94±14.66<br>138.2-195.68 | 223 | 92.2 | 85.7 | 81.1 | 70.9 | 0.088 |
| | | >3 | 42 (44%) | 137±19.17<br>99.43-174.58 | 118±77.63<br>0-270.16 | 82.8 | 77.5 | 66.7 | 58.2 | |
| Sex | Male | ≤3 | 38 (39%) | 165.13±16.64<br>132.51-197.75 | 223±105.56<br>16.09-429.9 | 89.5 | 83.6 | 80.4 | 73 | 0.061 |
| | | >3 | 25 (26%) | 119.9±24.88<br>71.11-168.68 | 62±36.37<br>0-133.29 | 70.3 | 65.9 | 57.1 | 47.6 | |
| | Female | ≤3 | 16 (16%) | 175.07±25.62<br>124.84-225.29 | | 100 | 85.7 | 77.9 | 70.1 | 0.355 |
| | | >3 | 18 (19%) | 159.08±28.81<br>102.6-215.57 | 205±81.82<br>44.63-365.37 | 94.4 | 81.9 | 75.5 | 63 | |
| EBV | Negative | ≤3 | 1 (1%) | - | - | - | - | - | - | 0.480 |
| | | >3 | 2 (2%) | - | - | 50 | 50 | 50 | 50 | |
| | Positive | ≤3 | 17 (18%) | 69.36±9.03<br>51.66-87.07 | - | 88.2 | 79.4 | 69.5 | 69.5 | 0.636 |
| | | >3 | 8 (8%) | 60.66±9.43<br>42.17-79.15 | - | 83.3 | 83.3 | 83.3 | 83.3 | |
| | Unknown | ≤3 | 36 (37%) | 176.99±15.91<br>145.81-208.18 | 223 | 94.4 | 85.9 | 82.9 | 73.3 | 0.026 |
| | | >3 | 33 (34%) | 129.49±19.88<br>90.51-168.48 | 79±62.16<br>0-200.84 | 81.8 | 75.8 | 63.6 | 51.5 | |
| Histology | I | ≤3 | 1 (1%) | 6 | 6 | 0 | - | - | - | 0.025 |
| | | >3 | 5 (5%) | 62.2±27.28<br>8.71-115.68 | 35±7.66<br>19.97-50.03 | 80 | 80 | 40 | 40 | |
| | IIA | ≤3 | 5 (5%) | 179.5±44.6<br>92.08-266.91 | | 100 | 100 | 75 | 75 | 0.171 |
| | | >3 | 5 (5%) | 32.13±9.68<br>13.15-51.11 | 46 | 80 | 80 | 53 | 0 | |
| | IIB | ≤3 | 46 (48%) | 171.55±15.65<br>70.86-202.23 | | 93.5 | 86.5 | 83.7 | 72 | 0.540 |
| | | >3 | 27 (28%) | 169.75±23.7<br>123.29-216.21 | 205±57.36<br>92.57-317.42 | 88 | 79.6 | 71.2 | 66.8 | |
| | Unknown | ≤3 | 2 (2%) | 223 | 223 | 100 | 100 | 100 | 100 | 0.170 |
| | | >3 | 6 (6%) | 71.33±31.01<br>10.55-132.11 | 11±30<br>0-69.81 | 50 | 50 | 50 | 33.3 | |

EBV: Ebstein-Barr Virus, NLR: neutrophil to lymphocyte ratio.

**Table 3.** Overall Survival by stage and NLR characteristics

| | | NLR | N (%) | Mean (95% CI) | Median (95% CI) | 1 y (%) | 2 y (%) | 3 y (%) | 5 y (%) | p |
|---|---|---|---|---|---|---|---|---|---|---|
| Stage | I | ≤3 | 2 (2%) | 14±2.82<br>8.45-19.54 | 10 | 50 | 50 | 50 | 50 | 0.317 |
| | | >3 | 2 (2%) | 10<br>10-10 | 10 | 50 | 50 | 50 | 50 | |
| | II | ≤3 | 10 (10%) | 186.62±19.05<br>149.26-223.98 | - | 100 | 100 | 100 | 87.5 | 0.538 |
| | | >3 | 8 (8%) | 212.57±37.94<br>138.2-286.93 | - | 100 | 100 | 100 | 85.7 | |
| | III | ≤3 | 29 (30%) | 158.86±20.54<br>118.58-199.15 | - | 92.9 | 84.6 | 80.4 | 67.2 | 0.403 |
| | | >3 | 25 (26%) | 141.55±25.58<br>91.4-191.7 | 118±64.1<br>0-243.64 | 87.1 | 82.3 | 67.4 | 62.2 | |
| | IVA | ≤3 | 12 (13%) | 141.92±35.77<br>71.81-212.03 | 223 | 81.8 | 71.6 | 61.4 | 61.4 | 0.340 |
| | | >3 | 8 (8%) | 80.37±26.88<br>27.67-133.07 | 28±24.04<br>0-75.12 | 75 | 62.5 | 50 | 37.5 | |
| | IVB | ≤3 | 0 (0%) | - | - | - | - | - | - | |
| | | >3 | 1 (1%) | 4 | 4 | 0 | - | - | - | |

NLR: neutrophil to lymphocyte ratio.

activity of lymphocytes and natural killer cells. Tumor growth is believed to be suppressed when a substantial infiltration of neutrophils occurs within the tumor microenvironment (9). Therefore, NLR acts as a biomarker that reflects the imbalance between pro- and anti-tumor activities within the inflammatory response.

Compared to other prognostic biomarkers, NLR stands out due to its simplicity and affordability (9). As a routine test that incurs no additional costs for patients, it is particularly appealing as a prognostic marker for NPC in clinical practice. Furthermore, NLR has been shown to have prognostic value in various cancers, including pancreatic tumors (11), brain tumors (12), gastric neuroendocrine neoplasms (13), esophageal squamous cell carcinoma (14), non-small cell lung cancer (15), and breast cancer (16).

However, the practical application of NLR, especially in NPC patients, needs to be better defined. Sun et al. demonstrated that an NLR ≥2.7 was significantly correlated with progression-free survival (17). Conversely, Chua et al. found that an NLR ≥3.0 did not serve as a prognostic factor in their randomized controlled trial (18). Jin et al. reported that an NLR of 3.6 was associated with survival in patients with metastatic NPC (19). Pan et al. identified an NLR cut-off of 2.92 for overall survival in stage II NPC patients, noting it as an independent prognostic factor (10). In our study, we used an NLR cut-off of 3 for overall survival in NPC patients. Aligned with prior findings in other cancer types, our study indicates that pre-treatment NLR holds significant potential as a prognostic biomarker for NPC, with higher pre-treatment NLR levels possibly acting as a prognostic marker in various cancers (9).

This study has several limitations. First, it is a retrospective study. Second, it covers a long period of time, and our patient group is heterogeneous.

## CONCLUSION

In NPC, NLR above three before treatment suggests that it may suggest an unfavorable prognosis in survival and may be a valuable prognostic biomarker. A large-scale prospective study is necessary to validate

the prognostic significance of NLR in NPC patients and to determine precise cut-off values.

### Ethical approval

This study has been approved by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval date 15/05/2017, number 2017/77). Written informed consent was obtained from the participants.

### Author contribution

Surgical and Medical Practices: HBÇ; Concept: MK; Data collection or Processing: MK, AB, HBÇ; Analysis or Interpretation: MK; Literature search: MK, AB; Writing: MK, AB, HBÇ. All authors reviewed the results and approved the final version of the article.

### Source of funding

The authors declare the study received no funding.

### Conflict of interest

The authors declare that there is no conflict of interest.

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