



## IS NEUTROPHIL TO LYMPHOCYTE RATIO (NLR) AN ADVERSE PROGNOSTIC FACTOR IN HEAD AND NECK CANCER? A RETROSPECTIVE ANALYSIS

### Oncology

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### KEYWORDS

#### INTRODUCTION

Head and neck cancer (HNC) represent a significant public health concern in India, with its incidence rising sharply in recent years. According to the National Cancer Registry Programme (NCRP) of India, HNC accounts for approximately 30% of all cancers in males and around 15% in females, making it one of the most prevalent cancer types in the country<sup>1</sup>. As per the GLOBOCAN 2022, Oral cavity cancer is the second most common cancer in India, the most common in men and the 4<sup>th</sup> most common in women<sup>2</sup>. The majority of cases are attributed to tobacco use, alcohol consumption, and the prevalence of oral squamous cell carcinoma (OSCC), which is particularly high in regions where chewing tobacco and betel quid are common practices<sup>3</sup>.

In our center, about 75% of patients come with a diagnosis of residual disease or disease progression after definitive treatment. Late-stage presentation has been blamed for such a high treatment failure rate, with many patients being in advanced stages, not amenable to surgery, when no chances of a curative treatment remain. This may have occurred due to unawareness of early symptoms, cultural factors, and lack of access of patients to health facilities.

The role of inflammation in cancer progression is gaining increasing attention with systemic inflammatory responses being implicated in tumor development and metastasis. The neutrophil to lymphocyte ratio (NLR) has emerged as a possible systemic inflammatory biomarker and has been hypothesized to correlate with prognostic capability in various cancers, including HNC. Elevated NLR levels are related to poor outcomes, indicating that higher neutrophil counts relative to lymphocyte counts might indicate a pro-tumor inflammatory environment.

Earlier studies have pointed toward NLR as a possible prognosticator in HNC. One study, from Ma et al., found that high values of NLR were related to low survival rates in HNC patients<sup>4</sup>. Kumarasamy et al., too, demonstrated the prognostic value of NLR together with other inflammatory markers, hence pointing back to more extensive validation by way of clinico-epidemiological scope<sup>5</sup>.

Despite a burgeoning literature on NLR as a prognostic marker worldwide, there are hardly any studies from India suggesting its role in HNC. That justifies the need for further local studies to address the demographic and epidemiological variability in cancer outcomes in the Indian context. Our study aspires to evaluate the prognostic significance of NLR in patients with head and neck cancer who were treated at our institution, providing useful insights regarding its possible role as a prognosticator of treatment responses.

#### METHODS

This study is a retrospective, observational study conducted at a tertiary care center, Government Stanley Medical College, Tamil Nadu Dr MGR Medical University from January 2019 to December 2022. The medical records of all the head and neck cancer patients treated at our center during this time were studied and the data was collected. Pre-treatment data of total counts, absolute neutrophil and absolute lymphocyte count were collected within one week of initiating treatment. Absolute counts of neutrophils and lymphocytes were divided to calculate the NLR. Statistical analyses were performed

using SPSS version 25. The survival analysis was conducted using Kaplan-Meier curves and the log-rank test.

#### RESULTS

A total of 104 patients were included in the study, with a median age of 53 years; 82 patients (78.8%) were male. Majority of the patients, 66 (63.5%) had oral cavity cancer with around 54 (51.9%) having moderately differentiated squamous cell carcinoma histology. 46 (44.2%) patients had well differentiated squamous cell carcinoma. Most of the patients presented in advanced stages, 38 patients (36.5%) had T3 disease and 36 (34.6%) had T2 disease. 72 cases (69.2%) were node positive (Figure 1).

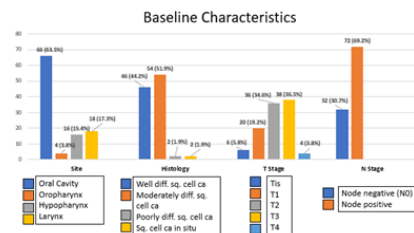


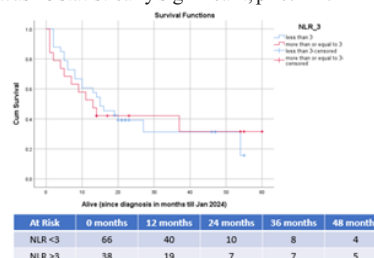
Figure 1: Baseline Characteristics

Only 6 patients (5.7%) included in this study had metastasis; all were pulmonary metastasis. The median NLR was 2.3 and an arbitrary cut off of NLR less than 3 and more than or equal to 3 was chosen to assess the survival in these patients. None of the confounding factors – smoking, tobacco chewing, T stage or N stage, were found to be significant in this study (Table 1).

Table 1: Confounding Factors

|                | Pearson Chi square test |
|----------------|-------------------------|
| Smoker         | p = 0.481               |
| Tobacco Chewer | p = 0.148               |
| T stage        | p = 0.186               |
| N stage        | p = 0.082               |

The median follow-up duration was 14 months. Through Kaplan Meier curve method, survival in patients with NLR less than 3 had a survival of 15 months and those with NLR more than or equal to 3 had a survival of 13 months; p=0.842 (Figure 2). The Spearman's rho correlation was not statistically significant, p=0.122.



**Figure 2:** Overall survival**DISCUSSION**

NLR as a surrogate marker of inflammation is a biomarker of interest in head and neck cancer (HNC). Inflammation is an important hallmark of cancer, with neutrophils playing a dual role in tumor promotion and suppression. NLR may be viewed as a potential prognostic factor due to its association with inflammatory responses that may relate to tumor behavior. Elevated levels of neutrophils can indicate a response that may facilitate tumor progression, while lymphocytes are usually associated with anti-tumor immunity. Thus, an increased NLR may reflect a pro-tumor inflammatory tumor microenvironment, suggesting a poorer prognosis for patients.

**NLR as a Prognostic Marker**

Many studies evaluate the prognostic significance of NLR, particularly in different types of cancers. A meta-analysis conducted by Templeton et al. pointed out that an elevated NLR is a constant factor toward poor overall survival in various solid tumors, including HNC<sup>6</sup>.

This is in agreement with our study, where a patient with NLR higher than 3 had a median survival of 13 months as compared to 15 months when the NLR was lower than 3. However, this difference could not be substantiated further, and  $p = 0.842$  ended up being not significant.

The lack of significance of our results could be related to several reasons, i.e., small sample size and the majority of early-stage oral cavity cancers among our population. Cho et al. mentioned the need for consensus on NLR cutoff points in HNC since methodology and patient population can alter results markedly<sup>7</sup>. There is need for multicenter trials on larger sample sizes; this assertion is required to prove NLR's prognostic significance.

**Role Of Inflammation In Tumor Microenvironment**

Neutrophils may contribute to tumor growth, mainly by enhancing angiogenesis, preventing metastasis and inhibiting the adaptive immune response. For instance, Piccard et al. discussed how tumor-associated neutrophils adopt pro-tumor phenotypes that enhance cancer cell proliferation and survival<sup>8</sup>. This duality suggests that while neutrophils might play a detrimental role with respect to tumor progression, the effects are entirely context-dependent, and that they may be determined in large part by the tumor microenvironment.

Other than that, lymphocytes are trend-setters of effective anti-tumor immunity. A higher ratio of lymphocytes to neutrophils could suggest a high degree of anti-tumor immunity, with the capacity to control tumor cell growth. Enhancing NLR would indicate the imbalance favoring tumor growth against immune interventions.

**Confounding Factors**

Certain confounding factors, for example, smoking status and nodal involvement, were evaluated in the current analysis; however, they yielded no significant associations with either NLR or survival outcomes in this study. Such factors include malnutrition and chemotherapy regimens, which were not assessed for their potential interactions in the context of these results. Previous studies indicated that nutritional status affected significantly immune function and tolerance to treatment in patients with cancer. Moreover, several studies have provided significant evidence that HPV status influences survival outcomes in head and neck cancer; HPV-positive patients enjoy a comparatively favorable prognosis, independent of their HPV-negative counterparts. The omission of HPV-testing renders discussing its relationship with NLR, computed for all patients in the study, futile.

**Implications For Future Research**

Since NLR, even if very promising, is an inconclusive prognostic marker in HNC, more studies have to be performed. In future work, aims should be set to achieve standardized thresholds for NLR across different populations and treatment modalities. Moreover, a prospective direction is to combine a comprehensive evaluation of other inflammatory markers with NLR assessments, in order to characterize the inflammation milieu more accurately in HNC.

**Limitations**

This study's limitations include its small sample size and single-center, retrospective design. Notably, a majority of cases involved early-stage carcinoma of the tongue, which may have skewed results toward non-

significance. Additionally, several confounding factors such as malnutrition and chemotherapy regimens were not accounted for, and HPV testing was not performed to explore potential associations with survival outcomes.

**CONCLUSION**

The role of the Neutrophil Lymphocyte Ratio (NLR) as a prognostic factor in head and neck cancer remains ambiguous based on our findings as it was not found to be not significant in this study. While this study contributes to the ever-increasing literature on NLR being a potential prognostic indicator in head and neck cancer, further studies are needed to clarify its clinical utility and develop determined prognostic criteria.

**REFERENCES:**

1. National Cancer Registry Programme (NCRP). Indian Council of Medical Research (ICMR).
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.who.int/today>, accessed [29 December 2024]
3. Gupta B, Johnson NW, Kumar S. Epidemiology of head and neck cancers in India. Asian Pacific Journal of Cancer Prevention. 2012;13(3): 1031-1036.
4. Ma SJ et al. Evaluation of Optimal Threshold of Neutrophil-Lymphocyte Ratio and Its Association With Survival Outcomes Among Patients With Head and Neck Cancer. JAMA Netw Open. 2022;5(4):e227567.
5. Kumarasamy C et al. Prognostic Utility of Platelet-Lymphocyte Ratio, Neutrophil-Lymphocyte Ratio and Monocyte-Lymphocyte Ratio in Head and Neck Cancers: A Detailed PRISMA Compliant Systematic Review and Meta-Analysis. Cancers (Basel). 2021;13(16):4166.
6. Templeton AJ et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju124.
7. Cho JK et al. Optimal cutoff of pretreatment neutrophil-to-lymphocyte ratio in head and neck cancer patients: a meta-analysis and validation study. BMC Cancer. 2018;18(1):969.
8. Piccard H et al. On the dual roles and polarized phenotypes of neutrophils in tumor development and progression. Crit Rev Oncol Hematol. 2012;82(3):296-309.