Elevated Neutrophil-To-Lymphocyte Ratio as a Predictive Tool for Laryngeal Squamous Cell Carcinoma

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Abstract

Objective: To determine the mean value of Neutrophil-to-Lymphocyte Ratio (NLR) in laryngeal squamous cell carcinoma, premalignant laryngeal lesions, and benign laryngeal lesions.

Material and Methods: A cross-sectional study spanning over 6 months 12th July 2016 to 11th January 2017 at Department of ENT (Ear, Nose and Throat), Benazir Bhutto Hospital (BBH), Rawalpindi. A total of 30 patients with age 15-60 years having hoarseness of voice were included via convenience sampling for the study. Patients with vocal cord paralysis, acute infection, cardiovascular disease and unfit for GA (General anesthesia) were excluded. Complete Blood count with peripheral smear was done for NLR (Neutrophil-To-Lymphocyte Ratio). Informed consent for direct laryngoscope (DL) with biopsy under GA was obtained. Patient was prepared for GA. DL (Direct Laryngoscopy) was done under GA and sample was sent in formalin to the Department of Pathology Benazir Bhutto Hospital for histopathology.

Results: The mean age was 43.37±10.40 years. Out of these 30 patients, 20(66.67%) were male and 10 (33.33%) were females with male to female ratio of 2:1. Mean neutrophil-to-lymphocytic ratio was 2.79 ± 0.82. Mean value of NLR in laryngeal squamous cell carcinoma, premalignant laryngeal lesions and benign laryngeal lesions was 3.80 ± 0.26, 2.42±0.09 and 2.04 ± 0.13 respectively.

Conclusion: This study concluded that NLR can help to predict the likelihood of laryngeal squamous cell carcinoma in a patient presenting with hoarseness of voice and any laryngeal lesion on indirect laryngoscopy prior to direct laryngoscopy and biopsy.

Keywords: Hoarseness of Voice, Laryngeal Squamous Cell Carcinoma, Neutrophil-to-Lymphocytic Ratio.

How to cite: Ajmal A, Madiha, Iqbal S, Haq MF, Akbar F, Jawwad S. Elevated Neutrophil-To-Lymphocyte Ratio as a Predictive Tool for Laryngeal Squamous Cell Carcinoma. Esculapio - JSIMS 2024;20(03): 300-304

DOI: https://doi.org/10.51273/esc24.25132032

Introduction

Head and neck cancer (HNCA) refers to a heterogeneous group of primary cancers involving upper aerodigestive tract. They rank sixth among the most common cancers worldwide.[1] It is estimated that 6,400,000 new cases of HNCA and 350,000 deaths occur each year worldwide.[2] The etiology of head and neck cancers is unclear like all other cancers. However, several risk factors are associated like alcohol consumption and tobacco use.[3]

Hoarseness of voice is the commonest symptom related to laryngeal pathology that can be a laryngeal carcinoma or any benign laryngeal lesions. Efforts are still made to find a reliable marker for prediction of laryngeal squamous cell carcinoma (LSCC) from benign laryngeal lesion (BLL) and premalignant laryngeal lesions (PLL). The neutrophil-to-lymphocyte ratio (NLR) is a marker that shows the systemic inflammatory responses which also occur in any malignant condition.[4] Elevated neutrophil-to-lymphocyte ratio is an important diagnostic and

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Submission Date: 12-06-2024
1st Revision Date: 18-07-2024
Acceptance Date: 09-09-2024

prognostic biomarker in several carcinomas like it is independent diagnostic predictor in hepatocellular carcinoma.[5] In addition, preoperative high NLR is a significant diagnostic predictor of distinction of breast cancer from benign proliferative breast disease and differentiates between benign and malignant thyroid disorder.[6] Few studies linked elevated NLR to Head and Neck carcinomas, thus NLR of more than 5 in non-metastatic stages was set as predictive indicator of mortality[4]. Accor-ding to Rassouli et al[9] systemic inflammatory marker such as NLR are the independent predictors of recurrence in head and neck squamous cell carcinoma. Early diagnosis can lead to a good prognosis in laryngeal carcinoma in upto one third of the malignant cancers.[7] Survival mainly depends on tumor stage, patient age, tumor location, cervical lymph node invasion, and a variety of other histopathological prognostic parameters. Glottic tumors are typically detected at an earlier stage than supraglottic tumors, which can impact treatment options and prognosis.[8] The aim of our study was to determine NLR can be used as an indicator for differentiating LSCC from PLL and BLL in our population. This shall prove useful in low socioeconomic setup as NLR is an inexpensive is widely available marker. It can be used prior to direct laryngoscopy and biopsy to predict the likelihood of laryngeal squamous cell carcinoma in a patient presenting with hoarseness of voice and any laryngeal lesion on indirect laryngoscopy.

Material and Methods

A Cross-sectional study was conducted at Department of ENT, Benzair Bhutto Hospital (BBH) Rawalpindi from 12th July 2016 to 11th January 2017 after formal ethical approval. A total of 45 patients were admitted to the ENT ward during this period. Out of these 30 patients having age 15 to 60 years presented with hoarseness of voice were included in the study. Patients with mass/lesion in the larynx, supraglottic, and glottis regions, Transglottic growth, hyperemia and thickening of vocal cords, poloidal/papillomatous growth, cystic or nodular swelling and reddish mass in larynx were included for the study. Patients with vocal cord paralysis, acute infection, extra-laryngeal malignancy, history of cardiovascular disease or any condition that made the patent unfit for GA were excluded.

Demographic data including age, sex and type of lesion were recorded on structured proforma. Data was entered and analyzed by using SPSS.v.20.0. Mean & Standard Deviation was calculated for quantitative variables (age and NLR). Frequency & percentages were calculated for qualitative variable like gender, residence (rural/urban) and diabetes mellitus status (controlled/uncontrolled). Effect modifier like age, gender and type of lesion were controlled through stratification. Post stratification Student 't' test was applied and p-value ≤0.05 was taken as significant.

Results

The mean age of the patients in the study was 43.37 ± 10.40 years as represented in **(Table-1),** whereas Distri-bution of patients according to type of lesion is shown in **(Table-2),**. Out of 30 patients, 20 (66.67%) were male and 10 (33.33%) were females with male to female ratio of 2:1 **(Fig-I).** Mean value of NLR in laryngeal squamous cell carcinoma, premalignant laryngeal lesions and benign laryngeal lesions is depicted in **(Table-3),** and is found to be statistically significant among groups of different types of lesions. Stratification of mean NLR with respect to age groups and gender are indicated in **(Table-4,5)**.

Figure 1: *Distribution of patients according to Gender (n=30).*

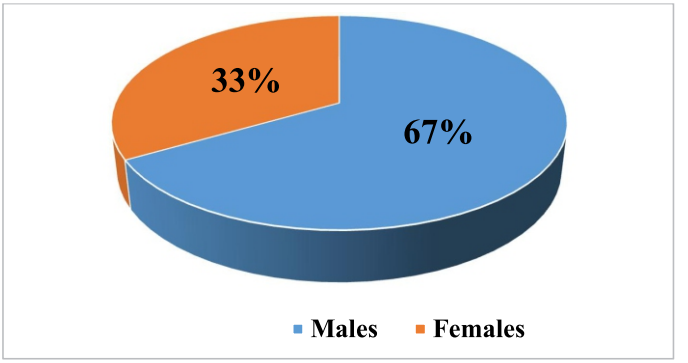

Table 1: *Distribution of patients according to Age (n=30)*

Age (in years)	No. of Patients	Percentage (%)
15-40	13	43.33
41-60	17	56.67
Total	30	100.0

**Mean ± SD = 43.37 ± 10.40 years

Table 2: *Distribution of patients according to type of lesion (n=30)*

Type of lesion	No. of Patients	%age
Benign	11	36.67
Pre-malignant	08	26.67
Malignant	11	36.67

Table 3: *Mean value of NLR in laryngeal squamous cell carcinoma, premalignant laryngeal lesions and benign laryngeal lesions*

Type of lesion	Neutrophil-to-lymphocytic ratio (NLR)		P-value
	Mean	SD	
Benign	2.04	0.13	0.0001
Pre-malignant	2.42	0.09	
Malignant	3.80	0.26	

Table-4: *Stratification of Mean NLR with respect to age groups*

Age groups (years)	Neutrophil-to-lymphocytic ratio (NLR)		P-value
	Mean	SD	
15-40	2.93	0.80	0.407
41-60	2.68	0.83	

Table-5: *Stratification of Mean NLR with respect to age groups*

Gender	Neutrophil-to-lymphocytic ratio (NLR)		P-value
	Mean	SD	
Male	2.82	0.82	0.783
Female	2.73	0.86	

Discusion

Larynx cancer is one of the most common cancers of head and neck. In 2012, the estimated new cases with laryngeal carcinoma were 157,000 and cancer related deaths was 83,000 worldwide.[9] The NLR and derived neutrophil–lymphocyte ratio (dNLR) has recently gained popularity as systemic inflammatory response biomarkers.[10] Neutrophil–lymphocyte ratio principally determines the systemic inflammation, particularly in chronic inflammatory diseases.[11] Several clinical studies have demonstrated that a high NLR value is associated with poor prognosis and survival in several cancers such as nasopharyngeal, gastrointestinal, lung and renal cancers.[12,13] In addition, dNLR, a modified form of NLR, is also used to demonstrate the systemic inflammation and prognosis in a variety of cancers such as gastrointestinal and breast cancers.[14] The pathophysiological relationship between high NLR or dNLR values and poor prognosis still remains unclear. It is hypothesized that it may be related to a decrease in the number of lymphocytes and increase in neutrophil counts in patients with cancer.[15] In fact, lymphocytes are responsible for anticancer immunity response, and CD8(+) T cells specifically control the tumor activity by apoptosis and cytotoxic effect. Therefore, lymphocyte counts are inversely correlated with severity of cancer.[16,17] Cancer-related inflammation may also lead to an increase in number of neutrophils.[18] Furthermore, cytokines, which are produced by cancerous cells, may trigger the migration of neutrophils from blood to tumor microenvironment; thus, neutrophils may stimulate the tumor growth and angiogenesis by vascular endothelial growth factor, IL-8 and matrix metalloproteinase.[19,20]

Age range in my study was from 15 to 60 years with mean age of 43.37 ± 10.40 years. Majority of the patients i.e. 17 (56.67%) were between 41 to 60 years of age. Out of these 30 patients, 20 (66.67%) were male and 10(33.33%) were females with male to female ratio of 2:1. In my study, mean value of NLR in laryngeal squamous cell carcinoma, premalignant laryngeal lesions and benign laryngeal lesions was 3.80 ± 0.26, 2.42 ± 0.09 and 2.04 ± 0.13 respectively.[21]

Recent study by Haddad CR et al5 concluded that in advanced Head and Neck cancer patients without metastasis, an NLR=5 was a prognostic indicator for mortality. According to Rassouli et al[22] systemic inflammatory marker such as NLR are the independent predictors of recurrence in head and neck squamous cell carcinoma as the group with NLR <4.2 that was only 7%. Moreover, the study investigating NLR in LSCS, premalignant laryngeal lesions and benign laryngeal lesions showed that mean NLR of the BLL, PLL and the LSCC groups were 2.12 ± 0.86, 2.32±0.68 and 3.46±1.51, respectfully.[23] So the NLR can be used to predict the LSCC from PLL and benign lesions.

The NLR is now routinely measured as part of the cancer work-up, as it is easily calculated from the white blood cell count and is universally available. However, the clinical relevance of the NLR is complicated because it represents a combination of factors related to both inflammation and host immunity. Recent studies have confirmed a link between the local inflammatory microenvironment that is favorable for tumor growth and metastasis of a tumor, and systemic responses induced by the tumor. Moreover, lymphocytopenia indicates a generalized state of immunodepression.[24]

These may be the possible mechanisms for decreased survival in patients with LSCC so the recognition of the NLR as a key component of tumor growth is important when using cancer therapies to decrease laryngeal carcinoma cell proliferation and metastasis in patients.

Conclusion

This study concluded that the mean value of neutrophil-to-lymphocytic ratio in laryngeal squamous cell carcinoma was higher than premalignant laryngeal lesions and benign laryngeal lesions subsequently. It is suggested to use this inexpensive test can be used prior to direct laryngoscopy and biopsy to predict the likelihood of laryngeal squamous cell carcinoma in a patient presenting with hoarseness of voice and any laryngeal lesion on indirect laryngoscopy.

Conflict of Interest: *None*

Funding Source: *None*

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Authors Contribution

AA: Conceptualization of Project

AA, FA: Data Collection

M, SJ: Literature Search

SI, FH: Statistical Analysis

M: Drafting, Revision

AA: Writing of Manuscript