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Original Research Article

Neutrophil-lymphocyte ratio as a prognostic tool for the evaluation of laryngeal carcinoma

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ABSTRACT

Background: The objective of the study was to review the neutrophil lymphocyte ratio (NLR) as a prognostic tool in carcinoma larynx.
Methods: Patients who were fulfilling inclusion criteria after screening were selected for study. On the basis of cutoff pretreatment NLR (<3 or >3) divided into two groups high pretreatment NLR and low pretreatment NLR. Patient undergo chemo or radiotherapy and at the end of follow up these two group NLR were compared with tumor negative prognostic score, survival at the end of follow up, resolving of symptoms, staging change, tumor regression and overall prognosis at the end of follow up were assessed.
Results: Mean value of tumor negative prognostic score of early carcinoma with low NLR, early carcinoma with high NLR, late carcinoma with low NLR and late carcinoma with High NLR were 13.833±2.80, 24.04±4.5538, 37.833±8.68 and 55.33±6.429 respectively. 10 (17.5%) patients with high NLR show more than 50% tumor regression while 17 (29.82%) with high NLR show <50% tumor regression. 26 (45.61%) patients with low NLR show >50% tumor regression and 4 (7.01%) show <50% tumor regression.
Conclusions: It was concluded in our study that pretreatment NLR is an acceptable prognostic tool in carcinoma larynx. High NLR was associated with poor prognosis and low NLR was associated with better prognosis.

Keywords: Neutrophil/lymphocyte ratio, Laryngeal carcinoma, Tumor negative prognostic score

INTRODUCTION

Laryngeal carcinoma is the frequent site of malignancy in the region of head and neck. It has a high incidence among head neck cancer. Laryngeal tumours usually presents itself in old age group. Its incidence now rise due to increase addiction of smoking which is one of the predisposing factor. Other etiological factors associated with laryngeal carcinoma are addiction of alcohol, occupational exposure, previous radiation for other head neck cancer. Various prognostic factors are routinely used such as gender of patients, age, addiction of tobacco, smoking, cartilage of larynx invasion, staging, positive surgical margins for predicting disease progression. The variant which encountered most is squamous cell carcinoma. Prognosis can be commented by knowing variant of carcinoma, grade, size, staging, cartilage invasion, metastasis but evaluation of these are not easy, cheaper and repeatable so there is a need of spotting of new tumor marker which give us fair clue about prognosis even before the commencement of intervention.

Objective

In this study, it was aimed to review the neutrophil lymphocyte ratio (NLR) as a prognostic tool in carcinoma larynx and to evaluate the correlation of NLR with TNM staging of carcinoma larynx. Prognosis and its correlation (if any) with other prognostic factors.

METHODS

The proposed study was Hospital based prospective study and was conducted in the department of ENT, GSVM Medical College and LLR associated Hospitals from January 2019 to October 2020 on patients of laryngeal carcinoma admitted in OPD and causality department. Study was conducted on 65 patients of diagnosed carcinoma larynx showing clinical symptoms which affect quality of life.

Patient after screening were selected for study and divided into two groups on the basis of pretreatment cutoff (>3 (n=35) or < 3 (n=30)) NLR ratio then patient undergo chemo or radiotherapy and at the end of follow up compare these pretreatment NLR value with quality of life score (Tumor negative prognostic score), survival at the end of follow up, staging change (Early carcinoma include stage I and II while Late carcinoma include stage III and IV), resolving of symptoms, tumor regression on the basis of CT scan finding (>50% regression is significant), overall prognosis.

Study period

About 22 months from January 2019 to October 2020, including development of study tools, collection of data, analysis and presentation.

Study design

Comparative, prospective hospital based observational study.

It is a hospital based observational study conducted over patients of diagnosed laryngeal carcinoma. Detailed history was taken, clinical examination was performed, histopathological examination was done, relevant laboratory and radiological investigations were done and data was recorded on the case sheet.

Ethical approval

The Ethics committee GSVM Medical College approves the above mentioned study.

Inclusion criteria

Clinically diagnosed patient of squamous cell carcinoma of larynx.

Exclusion criteria

Critically ill /terminal patient. Histopathological variants of carcinoma larynx. Synchronous primaries present.

Questionaire was develop to assess tumour negative prognostic score.

Four point scale

(3) Extremely troubled (severe)
(2) Moderately troubled (moderate)
(1) Somewhat troubled (mild)
(0) Not troubled

Table 1: Questionnaire to asses tumour negative prognostic score.

	Not trouble	Somewhat trouble	Moderately trouble	Extremely trouble
Swallowing problem Pain	0	1	2	3
Vomiting	0	1	2	3
RT feed	0	1	2	3
Change in voice Hoarseness	0	1	2	3
Voice fatigue	0	1	2	3
Cannot speak due to tracheostomy	0	1	2	3
Breathing problem Mild dyspnea	0	1	2	3
Dyspnea during passive work	0	1	2	3
Dyspnea during active work	0	1	2	3
Dyspnea at rest	0	1	2	3
Pain Affected	0	1	2	3
Disturbing	0	1	2	3
Hamper in daily activity	0	1	2	3
Sleep problem Lack of sleep	0	1	2	3
Wake during night Difficulty getting to sleep	0	1	2	3

Continued.

	Not trouble	Somewhat trouble	Moderately trouble	Extremely trouble
Activity limitation Physical	0	1	2	3
Social	0	1	2	3
Occupation	0	1	2	3
Emotional function Irritable	0	1	2	3
Frustrated	0	1	2	3
Restless	0	1	2	3
Embarrassed	0	1	2	3
Practical problems Fatigue	0	1	2	3
Tiredness	0	1	2	3
Poor concentration	0	1	2	3
Reduce productivity	0	1	2	3
Headache	0	1	2	3

Disease severity

Grade I (0-21) - Mild
Grade II (22-42) - Moderate
Grade III (43-63) - Severe
Grade IV (64-84) - Very severe

Statistical analysis

The data obtained from the case sheet was recorded and tabulated on MS excel work – sheet and were analyzed using appropriate statistical tools (average, standard deviation, percentages, test such as chi- square, paired and unpaired t test) obtained were compared with the previously published authentic study and inferences were drawn accordingly.

RESULTS

10 (17.5%) patients with high NLR show more than 50% tumor regression while 17 (29.82%) with high NLR show <50% tumor regression. 26 (45.61%) patients with low NLR show >50% tumor regression and 4 (7.01%) show <50% tumor regression, on applying Chi-Square test association is considered to be statistically significant (Table 1). Out of 65 patients, 57 (87.69%) patients survive while 8 (12.3%) patients died.

Table 2: Relationship between pretreatment NLR and tumour regression.

	High NLR	Low NLR
Tumour regression present (>50%)	10 (17.54%)	26 (45.61%)
Tumour regression (<50%)	17 (29.82%)	4 (7.01%)

After applying chi square test (12.98 with 1 degree of freedom) between tumor regression and NLR value, the association is considered to be stastiscally significant.

Table 3: Relationship of NLR with QOL at the end of follow up.

	Low NLR	High NLR	P value
QOL Score	17.466±6.027	40.259±13.25	<0.0001

On comparing QOL score in high and low NLR the difference comes out to be significant (p <0.0001) on applying T test.

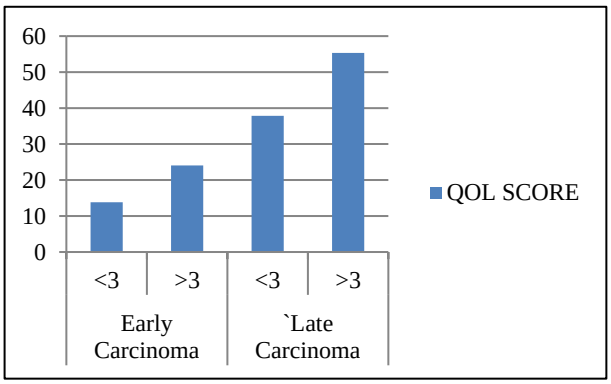

Figure 1: Relationship of QOL score with NLR and staging of laryngeal carcinoma.

On comparing QOL score in low NLR range of early and late carcinoma the difference comes out to be significant (p<0.0001) on applying T-test. On comparing QOL score in high NLR range of early and late carcinoma the difference comes out to be significant (p<0.0001) on applying T-test.

Mean±SD of high NLR group was found 6.31±3.34 while Mean±SD of low NLR group was found 2.227±0.625. 30 (100 %) patients with low NLR who took part in the study survive at the end of the follow up while only 77.14% patients with high NLR survive at the end. Mean value of QOL score (tumor negative prognostic score) of low NLR and high NLR were 17.466±6.027 and 40.259±13.25 respectively (Table 2). At the end of follow up, early carcinoma (stage 1 and stage 2) comprises 73.84% patients while late carcinoma (stage 3 and stage 4) comprises

13.84% patients and 12.30% patients died during follow up. Mean Value of QOL Score of early carcinoma with low NLR, early carcinoma with high NLR, late carcinoma with low NLR and late carcinoma with high NLR were 13.833±2.80, 24.04±4.5538, 37.833±8.68 and 55.33±6.429 respectively (Figure 1). 73.84% patients of high NLR group show addiction of smoking while only 9.23% patients of low NLR group show positive history of addiction of smoking. On applying Chi-Square test (p value=0.0031) the association between Smoking and NLR value is considered to be statistically significant (Figure 2). 55.38% Patients of high NLR group show addiction of alcohol while 9.23% patients of Low NLR group show addiction of alcohol. On applying Chi-Square Test the association between alcohol intake and NLR value is considered to be statistically significant.

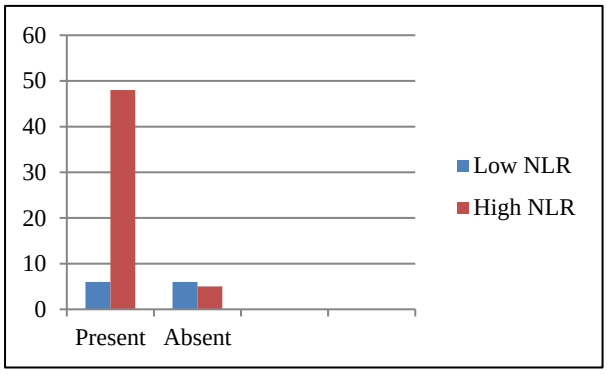

Figure 2: Relation of NLR with smoking of study subjects.

On applying Chi-Square test (p value=0.0031) the association between smoking and NLR value is considered to be statistically significant.

DISCUSSION

Many markers are used in laryngeal carcinoma as a prognostic factor. Eskiizmir et al studied neutrophil lymphocyte ratio and derived neutrophil lymphocyte ratio were predictive factors for stage, lymph node metastasis, and distant metastasis.[1] Patients with high neutrophil lymphocyte ratio value (≥4) had a poor prognosis when compared with patients with low neutrophil lymphocyte ratio value (5 year, overall survival: 69.0% versus 31.1%, p<0.001;5 year, disease free survival: 70.0% versus 32.7%, p<0.001; 5 year, locoregional recurrence free survival: 69.7% versus 32.0%, p<0.001). Furthermore, neutrophil lymphocyte ratio was an independent prognostic factor for 5 year: overall survival (HR=2.396; 95% CI 1.408-4.077; p=0.001), disease free survival (HR=2.246; 95% CI 1.322-3.816; p=0.006) and locoregional recurrence free survival (HR=2.210; 95% CI 1.301-3.753; p=0.003).

Yilmaz et al observe the relationship of NLR with the degree of differentiation of tumor, significant results were find.[2] 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 When NLR was compared with clinical stage, it was found to be significantly higher in stage IV laryngeal cancer than stage III.

Duzlu et al take 65 cases in the study and 42 cases in control group meeting inclusion criteria. In general a non-significant increase in N/L ratio was observed with increasing tumor size and stage (p>0.05) in larynx carcinoma.[3] The N/L ratio was found to be significantly higher in larynx carcinoma compared to control group (p=0.004).

Tu et al The optimal cutoff value of the NLR was 2.17. In the NLR ≤2.17 group, the 1-, 3-, and 5-year DFS rates were 88.2, 73.9 and 69.1 %, respectively, while in the NLR >2.17 group, the DFS rates were 83.0, 54.6 and 49.2 %, respectively.[4] Correspondingly, the 1-, 3-, and 5-year OS rates were 98.9, 85.1 and 77.4 % in the NLR ≤2.17 group and 97.9, 63.8 and 53.3 % in the NLR >2.17 group, respectively. The multivariate Cox proportional hazard model analysis showed that NLR >2.17 was a prognostic factor for both DFS [hazard ratio (HR)=1.869; 95 % confidence interval (CI) 1.078–3.243; p=0.026] and OS (HR=2.177; 95 % CI 1.208–3.924; p=0.010 showed that elevated preoperative NLR was an independent predictor of poor prognosis for patients with LSCC after surgical resection.

Zeng et al studied the median (range) follow-up of 45 months, the median neutrophil-to-lymphocyte ratio was 3.02.[5] The high neutrophil-to-lymphocyte ratio group (neutrophil-to-lymphocyte ratio >3.0) contained 69 patients and the low neutrophil-to-lymphocyte ratio group (neutrophil-to-lymphocyte ratio <3.0) contained 46 patients. The low neutrophil-to-lymphocyte ratio group patients had a significantly higher chemoradiotherapeutic disease control rate (86.96 versus 69.57%, p=0.031). Forty-six patients had a low neutrophil-to-lymphocyte ratio (<3.0) before chemoradiotherapy and their progression-free survival and 75% overall survival were significantly better than that of the high neutrophil-to-lymphocyte ratio patients (p=0.015, p=0.045). Multivariate analysis showed that neutrophil- to-lymphocyte ratio and N stage were independent prognostic indicators for progression-free survival (with a hazard ratio of 1.79, p=0.003 and a hazard ratio of 1.28, p=0.034) and overall survival (with a hazard ratio of 1.51, p=0.029 and a hazard ratio of 1.21, p=0.043), respectively.

Fu et al take Four-hundred twenty patients in this study. Patients with an NLR _2.59 showed a significantly lower CSS (P¼.014) and OS (P¼.032) than patients with an NLR <2.59.[6] The Cox proportional multivariate hazard model showed that a higher preoperative NLR was independently correlated with a poor CSS and OS, with hazard ratios of 1.42 (95% confidence interval [CI] 1.06–1.91, P¼.018) and 1.31 (95% CI 1.00–1.71, P¼.046), respectively. The

NLR may be an independent prognostic marker for CSS and OS in patients with advanced LSCC undergoing TL.

Kum et al studied retrospective study was performed on 209 patients admitted to a tertiary referral center with laryngeal lesions and undergoing biopsies to establish their histopathological diagnosis.[7] We reviewed the patient files for their clinical, histopathological and laboratory data. The patients were divided into three groups according to their histopathological findings, as BLL, PLL and LSCC groups. The patients in the PLL group were also divided into three subgroups as mild, moderate and severe dysplasia/ carcinoma in situ (CIS) subgroups. The groups were compared for NLR and the other laboratory data. The mean NLRs of the BLL, PLL and the LSCC groups were 2.12±0.86, 2.32±0.68 and 3.46±1.51, respectively, and the difference was statistically significant (p=0.001). The mean NLRs of the patients with PLL and LSCC were significantly higher than the patients with BLL (p=0.031 and p=0.001, respectively). The mean NLRs were similar among mild dysplasia, moderate dysplasia and severe dysplasia / CIS groups (p>0.05).

Hsueh et al studied 979 patients with LSCC were enrolled in our study. Preoperative neutrophils, platelets, lymphocytes, monocytes, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were analyzed.[8] Besides well-established clinicopathological prognostic factors, we evaluated the independent prognostic relevance of these hematological parameters by Cox regression models in disease-free survival (DFS) and cancer-specific survival (CSS). We found patients in the highest tertile of NLR (>2.40), PLR (>111.00) were at significantly higher risk of DFS and CSS (p<0.05) compared with those in the lowest tertile after multivariate analysis, whereas presenting significantly higher risk in the lowest tertile of lymphocytes (<1.60×109/l) and LMR (<3.50). Additionally, the tertile category of NLR as well as PLR increased and lymphocytes as well as LMR decreased in shorter DFS and CSS by the Kaplan-Meier method and the log-rank test.

In our study, NLR could be used as a prognostic factor in laryngeal carcinoma. when results were analyzed, significant relationships were monitored between NLR and many prognostic factors.

In our study, When NLR group compare to tumour regression at the end of follow up, Low NLR group show high tumour regression than High NLR.

When the relationship of Tumor negative prognostic score (QOL) with the NLR group was examined, significant results were observed. QOL was significantly higher in patients with High NLR group. This finding is very important. Because NLR is easily available from laboratory test, not costly and a universal biomarker.

In our study, When the relationship of NLR group with the percent of patients survive at the end of follow up, significant results were observed. All 30 patients of Low NLR group survive while 8 patients out of 35 of high NLR died at the end of follow up.

NLR was significantly higher in people who were smoker and alcohol users. The significant correlation of NLR with all these prognostic factors supposed that NLR can be used in laryngeal cancer as a prognostic factor due to the significant correlation of NLR with all these prognostic factors.

Limitations

This study had some limitations, the questionnaire for assessment of QOL was self-designed and need to be standardized. The eight domains of QOL questionnaire cannot practically assessed the severity of symptoms individually on same 4-point Likert scale. While filling the questionnaire the possibility of subjective and interviewer bias cannot be ruled out completely. The study is of short term and Long term study is required for better assessment of result statistically.

CONCLUSION

It was concluded that pretreatment NLR is a acceptable prognostic tool in carcinoma larynx. High NLR was associated with poor prognosis and low NLR was associated with better prognosis. Patients with High NLR show less tumor regression (50%) as compare to Low NLR. It was also concluded in our study that patients with pretreatment high NLR show high mortality. QOL score (Tumor negative prognostic score) is high in high NLR. Patients having high NLR also have addiction of smoking and alcohol. It was concluded in our study that patient with late carcinoma and high NLR have more QOL (Tumor negative prognostic score) as compare to early carcinoma and high NLR while patients with late carcinoma and low NLR have more QOL as compare to patient with early carcinoma and low NLR.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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