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Assessment of Neutrophil-to-Lymphocyte Ratio as A Prognostic Marker in Locally Advanced Head and Neck Cancer Treated with Concomitant Chemoradiation

Research Article

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Abstract: **Background:** Various experimental and epidemiological studies have been conducted to find the relationship between hematologic parameters like neutrophil-to-lymphocyte ratio (NLR) and prognosis in numerous solid malignancies. We conducted a similar study to assess the role of NLR as a prognostic marker in locally advanced head and neck cancer (HNC) treated with chemoradiation.

Patients and methods: A total of 60 patients of histopathologically proven, previously untreated, locally advanced HNC were included in this randomized, prospective study. They were stratified into five groups according to their NLR values (<2, 2–3, 3–4, 4–5, and >5). All 60 patients received the same concurrent chemoradiation with a radiation dose of 66 Gy in 33 fractions over 6.5 weeks with injection cisplatin 40 mg/m^2 weekly. Treatment-related toxicities were assessed weekly. Association of NLR was assessed with the outcomes as per the World Health Organization (WHO) response criteria. Informed consent was taken from all patients, and approval of institutional ethical committee was obtained.

Results: Complete response was observed to be maximum in patients with low NLR value of <2 (73% of patients). Higher percentage of treatment-related toxicities was also observed in groups with higher NLR values, that is, NLR 4–5 and >5. The association of NLR with treatment response was statistically significant on Pearson's chi-square test ($P = 0.019$).

Conclusion: Our study was able to establish the relationship between NLR and treatment outcome in HNC patients treated by concurrent chemoradiation. Higher pretreatment NLR values were associated with poorer survival outcomes and increased treatment-induced toxicities.

Keywords: *Chemoradiation • cisplatin • head and neck cancer • neutrophil-to-lymphocyte ratio • prognosis*

1. Background

Incidence of head and neck cancer (HNC) is on an increasing trend, particularly in selected parts of world where smoking and other risk factors are prominent[1-2]. According to Global Cancer Statistics 2020, HNC, combining all major subsites, comprises the highest newly diagnosed cases in India among all cancer cases[3]. This high prevalence of HNC in India is in tune with several lifestyle factors, including but not limited to smoking, alcohol intake, human papilloma virus (HPV), and other infections[4].

HNCs can be treated by surgery, chemotherapy, radiotherapy, immunotherapy, or a combination of all these modalities[5-6]. Surgery and radiotherapy have comparable results in early stages (stage I and II) for most of the squamous cell carcinomas (SCCs) of the head and neck region, whereas in locally advanced cases (stage III onward), radiotherapy along with chemotherapy is the more preferred approach[7-9]. However, it is worthy to mention that the choice of definitive treatment in head and neck SCC (HNSCC) depends on a lot of factors, which include primary site of the disease, type and stage of cancer, patient willingness, general condition of the

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patient, and many more. Concomitant chemoradiation (CCRT) is now the standard of care in most locally advanced HNCs[5, 10]. The conclusion of a large-scale meta-analysis (meta-analysis of chemotherapy in HNC[MACH-NC]) demonstrated that CCRT improved patient treatment outcomes and increased absolute survival by 6.5% in 5 years[11]. Although platinum-based CCRT has become the state-of-art therapy for locally advanced HNC, complete relief for a long duration is still limited and more than one-third of the patients continue to have tumors[5, 10, 12]. Furthermore, a greater number of initially cured patients experience recurrence and distant organ spread within a short time[13]. This has led researchers to pay attention to associated factors that contribute to disease outcome, that is, to identify prognostic and/or predictive markers which have an impact on treatment.

A lot of hematologic and biochemical parameters have been assessed in recent times as prognostic markers in HNSCC[14-15]. Some of them have shown reasonable association with respect to disease progression and treatment outcome. Recently, elevated peripheral blood neutrophil-to-lymphocyte ratio (NLR) before starting the treatment has been introduced as an independent prognostic factor associated with poor survival in different solid tumors, including colon cancer, esophageal cancer, gastric cancer, and breast cancer[16-20]. Similar studies have also been conducted in HNC patients to assess the prognostic effect of NLR; however, data in regard to Indian population is limited[21-24].

With this background, we conducted this study to determine the role of pretreatment NLR as a prognostic marker in locally advanced HNC patients of North Indian origin treated by CCRT.

2. Patients and Methods

The study was conducted on previously untreated, biopsy-proven patients of HNC receiving concurrent chemoradiation. The pretreatment evaluation in all patients was done with help of a detailed history, general physical examination, and complete systemic examination. Radiological imaging like contrast-enhanced computed tomography (CECT) of face and neck, X-ray of chest, and ultrasonography of abdomen were done routinely in all patients. Based on the clinical examination and radiological findings, all the patients were staged according to the American Joint Committee on Cancer (AJCC) 2017 staging system. The inclusion criteria for the study were as follows: i) histologically proven SCC, ii) locally advanced malignancy, that is, AJCC stage III and IVA tumor, and iii) a fair general condition, that is, Karnofsky Performance Status (KPS) 70 or above, to tolerate the radical treatment protocol. Distant metastasis and any previous treatment (surgery, chemotherapy, or radiation therapy) for the same malignancy and associated comorbidities, which can affect treatment and survival, were the primary exclusion criteria; pregnant and lactating women were also excluded from the study to avoid the adverse effect of chemoradiation.

Pretreatment hematologic assessment was done by complete hemogram including hemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), and platelet count, whereas biochemical analysis involved serum creatinine and blood urea (kidney function) and transferase enzyme assay (liver function). Blood cell count was analyzed by volume conductivity scatter parameter method, and NLR, the ratio between the absolute neutrophil count and the absolute lymphocyte count, was obtained by dividing the neutrophil count by the lymphocyte count. All patients were stratified into five groups according to pretreatment NLR value as less than 2, 2–3, 3–4, 4–5, and more than 5.

All the patients received the same schedule of therapy, that is, concurrent chemoradiation: radiation in a dose of 66 Gy in 33 fractions over 6.5 weeks (5 days/week with 2 Gy per fraction) and injection cisplatin 40 mg/m^2 weekly for six cycles. Radiotherapy was delivered by cobalt-60 teletherapy machines with shrinking field technique. Pretreatment NLR was calculated for each patient as defined earlier, and the differences in the results were assessed statistically.

During treatment, routine hematologic and biochemical parameters encompassing complete blood count and liver and kidney functions were assessed weekly in all patients. Detailed clinical examination for chemoradiation-induced side effects was done and graded as per the Radiation Therapy Oncology Group (RTOG) toxicity criteria.

All patients were examined at 15 days after treatment completion for any radiation- or chemotherapy-induced toxicity and then were kept on regular monthly follow-up for 6 months after the treatment. At each visit, every patient was assessed for any evidence of residual disease and distant metastasis and, in case of any suspicion, relevant investigations were done. To evaluate the local disease control, local examination using inspection, palpation, and indirect laryngoscopy was done at each follow-up and the response was assessed. Follow-up CECT scan was done for each patient at 3 months after treatment to assess the response as per the World Health Organization (WHO) response criteria.

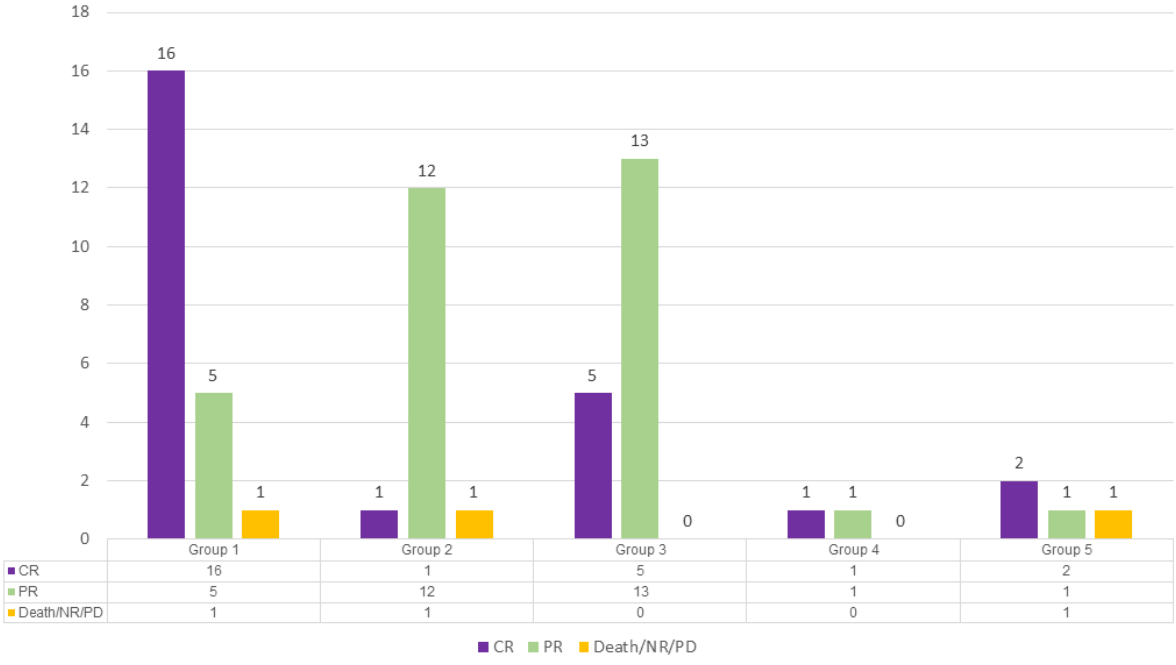


Figure 1: Response rate at 6-month follow-up in head and neck cancer patients.
CR: Complete response; NR: No response; PD: Progressive disease; PR: Partial response.

In all the groups mentioned earlier, association of NLR was seen with reference to outcome.

The data thus obtained was entered in Microsoft Excel (version 2019) and percentage proportion was calculated. Pearson's chi-square test, unpaired *t*-test, and paired *t*-test were applied to test the significance of the results using Statistical Package for Social Sciences (SPSS) software version 26. P <0.05 was considered significant.

The purpose of the study was explained to each patient and a signed written consent was taken. The clearance from institutional ethical committee for the study was obtained.

3. Results

A total of 60 patients fulfilling the inclusion criteria were enrolled in the study. Mean age of the enrolled patients was 55.1 years (range 36–77 years). There was a high male predominance in the study population, with male to female ratio being 4:1. Majority of the patients were from rural background and were chronic smokers. Details of baseline patient characteristics are presented in Table 1.

Overall, oropharynx was the most common site of primary tumor, and the most common histopathologic subtype seen in the patients was moderately differentiated SCC. Majority of the patients belonged to stage IVA. All patients had baseline hematologic and biochemical parameters in normal range.

All the patients in the study cohort completed the intended treatment. Each of the patients developed radiation-induced reactions, especially skin and mucosal reaction, during radiotherapy; hematologic and other toxicities (nausea, vomiting, deranged urea and creatinine) also occurred in majority of patients. However, no grade 4 toxicity was observed in any of these categories.

All patients, except one, completed the mandatory 6-month follow-up. Disease status at 6 months after treatment completion is shown in Figure 1. The greatest percentage (73%) of complete response (CR) was observed in group 1 patients having NLR <2. The association of treatment outcome at the sixth month with respect to NLR among the study groups was statistically significant (P < 0.05).

Table 1: Baseline characteristics of patients and tumor of head and neck cancer patients

Characteristics	Group 1	Group 2	Group 3	Group 4	Group 5
Age	<40: 1 40-49: 3 50-59: 7 60-69: 8 ≥70: 3	<40: 1 40-49: 4 50-59: 6 60-69: 3 ≥70: 0	<40: 3 40-49: 5 50-59: 6 60-69: 4 ≥70: 0	<40: 0 40-49: 1 50-59: 0 60-69: 1 ≥70: 0	<40: 1 40-49: 0 50-59: 2 60-69: 1 ≥70: 0
Gender	M: 20 F: 2	M: 14 F: 0	M: 13 F: 5	M: 1 F: 1	M: 3 F: 1
Background	R: 19 U: 3	R: 12 U: 2	R: 12 U: 6	R: 1 U: 1	R: 3 U: 1
Smoker	Y: 16 N: 6	Y: 14 N: 0	Y: 11 N: 7	Y: 0 N: 2	Y: 3 N: 1
Alcohol intake	Y: 14 N: 8	Y: 9 N: 5	Y: 9 N: 9	Y: 0 N: 2	Y: 2 N: 2
KPS	70: 6 80: 6 90: 10	70: 4 80: 7 90: 3	70: 4 80: 8 90: 6	70: 1 80: 1 90: 0	70: 1 80: 1 90: 2
Primary site	OC: 2 OP: 16 HP: 0 L: 4	OC: 0 OP: 12 HP: 1 L: 1	OC: 1 OP: 9 HP: 5 L: 3	OC: 0 OP: 2 HP: 0 L: 0	OC: 1 OP: 3 HP: 0 L: 0
Histology	MDSCC: 12 PDSCC: 2 WDSCC: 8	MDSCC: 8 PDSCC: 2 WDSCC: 4	MDSCC: 6 PDSCC:4 WDSCC: 8	MDSCC: 2 PDSCC: 0 WDSCC: 0	MDSCC: 2 PDSCC: 1 WDSCC: 1
Stage	III: 6 IVA: 16	III: 1 IVA: 13	III: 1 IVA: 17	III: 0 IVA: 2	III: 0 IVA: 4

F: female, HP: hypopharynx, KPS: Karnofsky Performance Status, L: larynx, M: male, MDSCC: moderately differentiated squamous cell carcinoma, N: no, OC: oral cavity, OP: oropharynx, PDSCC: poorly differentiated squamous cell carcinoma, R: rural, U: urban, WDSCC: well-differentiated squamous cell carcinoma, Y: yes

4. Discussion

NLR is a well-known inflammatory marker. Several cytokines and angiogenic factors can be produced by neutrophils, and these agents play important roles in promoting tumor development, while lymphocytes are associated with immune surveillance and act by eliminating cancer cells[25-27]. A decreased lymphocyte level is hence related to poorer ability to eliminate cancer cells[28]. In cancer patients, a high pretreatment NLR is associated with poorer survival outcomes[29]. Significant variation in the magnitude of this association has been observed between studies, but sources of this variation are poorly understood.

Various experimental studies have been conducted to find the relationship between NLR and prognosis in HNC patients. Tu et al estimated the prognostic significance of preoperative NLR in surgically treated laryngeal SCC patients. This retrospective evaluation marked down increased preoperative NLR as an important prognostic marker for worse survival outcome in these patients[30]. In a similar fashion, elevated pretreatment NLR was found to be associated with poor prognosis in locally advanced carcinoma larynx patients treated with concurrent platinum-based chemoradiation[31]. Outcome of these two backward-driven analyses is that high pretreatment NLR is an independent bad prognostic marker for SCC of larynx, irrespective of the treatment modality (surgery or chemoradiation). Similarly, another study from China revealed young patients of oral SCC had comparatively low NLR than older patients, and thus had better recurrence-free and disease-specific survival (DSS). This analysis summed up a strong association between NLR and DSS in oral SCC patients of young age group[32]. Analysis of a meta-analysis on patients of nasopharyngeal carcinoma revealed an identical outcome, that is, elevated NLR was associated with decreased overall survival, both in metastatic and nonmetastatic cases. The authors marked NLR as a significant marker for prognostication in carcinoma nasopharynx[33].

A large-scale meta-analysis, including 19 studies and more than 5000 patients of HNC, was conducted to assess the effect of NLR on these patients. Overall survival was found to be significantly low in patients having high NLR. Other survival parameters like disease-free survival, recurrence-free survival, progression-free survival, and many more were also found to be related to the NLR value; higher NLR value resulted in poor survival. Patients having high pretreatment NLR were more prone for local recurrence as well as distant spread. Although having a few limitations, this broad-

scale meta-analysis proved the correlation between pretreatment NLR and outcome in HNC patients[34]. Another retrospective survey on HNC patients from Korean background concluded elevated pretreatment NLR was associated with poor treatment outcome in respect to overall and progression-free survival. All patients were treated with definitive radiotherapy with or without chemotherapy (concurrent, induction, or both) and patients having high NLR were found to be having more aggressive tumor[35].

A small cohort of Iranian HNC patients of different primary, treated with platinum-based combination chemotherapy regimen, was prospectively analyzed for the association between pretreatment NLR and response to chemotherapy. Result from this survey concluded that although there was no relation between pretreatment NLR and chemotherapy-induced toxicities in these patients, pretreatment NLR could predict chemotherapy response, with low NLR favoring good response[36]. In a retrospective single-institution analysis conducted by Gorphe et al, patients of carcinoma larynx were treated with induction chemotherapy as a part of laryngeal preservation protocol. Pretreatment high NLR and low hemoglobin, that is, anemia, both were categorized as being associated with less overall and disease-free survival in this cohort of patients[37].

A retrospective analysis was done in the western part of India on patients of SCC oral cavity to evaluate the impact of NLR on survival. Survival was lower in all patients of high NLR group, but it was more pronounced in patients receiving adjuvant chemoradiotherapy. The researchers also evaluated the role of platelet-to-lymphocyte ratio (PLR) in association with survival of these patients, which was found to be more significant in predicting the adverse outcomes in this group of patients. However, high NLR, that is, NLR >5, was strongly associated with aggressive tumor characteristics as well as lower survival[23]. Another study from the eastern part of India also supported NLR as a potential predictive marker for HNC patients treated with radiotherapy, either definitive or adjuvant. Although this analysis included less number of patients, the authors combined all subsites of head and neck, thus increasing the significance of their result[24].

In our study, all patients developed radiation-induced skin and mucosal reactions during the treatment course. By week 6, maximum number of patients had grade 2 skin toxicity and the number of patients developing grade 2 skin reactions was 32%, 64%, 33%, 50%, and 75% in group 1, group 2, group 3, group 4, and group 5, respectively. At the completion of radiation therapy, grade 3 reactions were seen in 5% and 14% of patients in group 1 and group 2, respectively. Grade 2 mucosal reaction was observed in 68%, 57%, 56%, 100%, and 75% patients, respectively, at the end of the treatment. We observed greater percentage of mucosal reactions (grade 1 and grade 2) in group 4 and group 5 patients, that is, in patients with a higher range of NLR. No patient developed grade 4 hematologic and biochemical toxicity during treatment. No deaths were observed during the treatment period.

CR was observed to be maximum (in 73% patients) in the group with a lower NLR value, that is, group 1 with NLR value <2. A patient was found to have died in the first-month follow-up period in group 5 (with NLR >5) with pretreatment NLR value 8.5, complementing the previously reports that increasing value of NLR leads to increasing trend of mortality, but we could not establish if the death was due to the treatment-related toxicities or other unknown causes. However, this study strongly concludes the association of NLR with treatment response as well as with treatment-induced toxicity in locally advanced HNSCC treated by concurrent chemoradiation.

There are certain limitations of our study. Most important of them are the small sample size, that is, only 60 patients, and very short follow-up time, that is, only 6 months. However, after the initial results were found to match with other studies, more patients are recruited and all patients are evaluated for further follow-up. Future analysis with a large sample size and longer follow-up is on the way. The interesting fact of our study is its prospective nature and combining all major subsites of the head and neck region.

5. Conclusion

Thus, this study concludes the association of pretreatment NLR with treatment response in locally advanced HNC treated by radical chemoradiation. Low NLR, preferably <2, was associated with a good response compared to high NLR. This can be used as an easily available and low-cost marker for pretreatment prognosis assessment of these cohorts of patients, especially in low-resource setting countries like ours. Large-scale prospective studies with bigger sample size from our institution as well as from other parts of the nation and the world will give more promising results about the role of NLR as a pretreatment prognostic marker in locally advanced HNC treated by radical chemoradiation.

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