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Impact of Pretreatment Inflammatory Markers in Locally Advanced Head and Neck Cancer Treated with Concurrent Chemoradiotherapy

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Abstract

Background: Inflammation, when associated with cancer, has been shown to correlate with a worse prognosis. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) serve as markers of inflammation. This study aims to investigate the influence of pretreatment NLR, PLR, and MLR on treatment outcomes and their correlation with sarcopenia in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) undergoing definitive chemoradiotherapy.

Method: In this retrospective study, 240 LA-HNSCC patients who received a radiotherapy dose of 70 Gy/35 fractions over 7 weeks in conjunction with chemotherapy were enrolled. Pretreatment NLR, PLR, and MLR were determined. Sarcopenia was evaluated by measuring skeletal muscle mass at the C3 level using radiotherapy planning computed tomography scans. The impact of NLR, PLR, and MLR on complete response rate and disease-free survival was calculated. The median follow-up duration for patients was 26 months.

Results: Inflammatory markers were notably higher in elderly patients, females, and those with laryngeal primary tumours. Patients achieving a complete response exhibited lower values than those who did not. Patients with significant sarcopenia demonstrated elevated mean values of inflammatory markers. Patients with NLR<3, PLR<145, and MLR<0.4 experienced more favorable outcomes regarding complete response rate and disease-free survival.

Conclusion: Inflammatory markers such as NLR, PLR, and MLR are independent prognostic factors in HNSCC patients. Elevated values are associated with sarcopenia and inferior treatment outcomes, indicative of more aggressive tumour behavior. These markers are straightforward to calculate and should be routinely employed for early prognosis assessment.

Keywords: Inflammatory markers, Neutrophil-lymphocyte ratio, Head and neck neoplasms, Radiotherapy, Prognosis

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Introduction

Head and neck squamous cell carcinomas (HNSCC) are the 2nd most common cancer in India.[1] The general treatment modality for locally advanced HNSCC (LA-HNSCC) includes radical radiotherapy in combination with concurrent chemotherapy.[2, 3] The sub-sites include oropharyngeal, laryngeal, and hypopharyngeal primary squamous cell carcinomas. There are multiple prognostic factors which determine the outcome of the patient. These include a combination of the patient (host), disease (tumour), and treatment-related factors. Some of them are the patient's age, performance status, comorbidities, clinical stage, poorly-differentiated tumours, presence of extracapsular spread, perineural invasion, human papillomavirus (HPV) status, weight loss before and during treatment, sarcopenia, gap during treatment and number of concurrent chemotherapy cycles given.[4-7]

The relationship between inflammation and cancer is well known. Inflammation is associated with the development and progression of cancer.[8] The first link between inflammation and cancer was first observed by Rudolf Virchow, who detected leukocytes within tumours and hypothesized that inflammation increased cellular proliferation.[9]

There is mounting evidence that the tumour microenvironment plays a crucial role in tumour proliferation, invasion, metastases, and even resistance. Inflammation plays a crucial role in cancer progression.[10] It has been suggested that caner-related inflammation (including local and systemic inflammation) is associated with treatment response and survival in various solid tumours.[11,12] The tumour cells have been shown to release cytokines. Once inflammation occurs, it activates the innate immune system and recruits primitive immune cells, such as neutrophils, to the tumour site, thus increasing the neutrophil level compared with lymphocytes.[13] Neutrophils release certain factors which promote tumorigenesis and cancer progression. Inflammatory cascade can lead to capillary leakiness, which promotes tumour angiogenesis and increases the metastatic potential.[14] This makes neutrophil lymphocyte ratio (NLR) a simple biomarker for systemic inflammation. NLR has already been proven to be a prognostic marker in several solid cancers like prostate, renal, gastric cancer, and head and neck cancer.[15-18] Platelets secrete pro-inflammatory mediators such as cytokines, which increase the inflammatory microenvironment in and around the tumours, making platelet lymphocyte ratio (PLR) another notable marker. It is suggested that high neutrophil and platelet counts and low lymphocyte counts provide an environment conducive to tumour growth. Another marker of inflammation in this regard is the monocyte-lymphocyte ratio (MLR), as monocytes are also recruited in the tumour microenvironment.

This study aims to determine the impact of pretreatment NLR, PLR, and MLR on treatment outcome, disease-free survival (DFS), and its correlation with sarcopenia in LA-HNSCC patients treated with definitive concurrent chemoradiotherapy.

Material and Methods

A retrospective analysis was conducted on a cohort of 240 patients diagnosed with LA-HNSCC who received treatment between January 2016 and December 2019. Ethical clearance for this study was obtained from Action Cancer Hospital (Code: EC207). The inclusion criteria encompassed patients with histologically confirmed cases of locally advanced oropharyngeal, hypopharyngeal, and supraglottic larynx carcinomas at stage III or IV who underwent curative-intent treatment with concurrent chemoradiation. Patients who underwent upfront surgery or neoadjuvant chemotherapy, as well as those with poor performance status or metastatic disease, were excluded from the study.

Radiotherapy was administered utilizing intensity-modulated radiotherapy (IMRT), volumetric arc radiotherapy (VMAT), or image-guided radiotherapy (IGRT) techniques, delivering a total prescribed dose of 70 Gy in 35 fractions over 7 weeks, using a linear accelerator (Clinac iX or TrueBeam STx - Varian Medical System).

Table 1. Baseline characteristics of the patient cohort

Parameter	Value
Mean age/ Median age	60.5 years/ 61 years
Males: Females	8.6: 1
Smokers	216 patients (90%)
Comorbidities	48 patients (20%)
Stage III and IV disease	48 patients (20%) and 192 patients (80%)
Subsite (oro/ supra/ hypo)	66%/ 17.3%/ 16.7%
Median radiotherapy dose	70Gy/35# @ 2Gy per fraction
Median chemotherapy cycles	6

Concurrent chemotherapy was administered weekly, with the choice of cisplatin or carboplatin determined by the medical oncologist.

Analysis of NLR, PLR, and MLR

Blood counts, as part of a complete blood hemogram, were obtained within 2 weeks prior to the initiation of treatment. Hydrodynamic focusing was employed as the method for blood sample analysis. Absolute values of neutrophils, lymphocytes, and platelets were documented. The NLR was calculated as the total neutrophil count divided by the total lymphocyte count, while the PLR was determined by dividing the total platelet count by the total lymphocyte count. The MLR was calculated using a similar approach. Patients with a history of previous steroid usage were excluded from the analysis.

Assessment of sarcopenia and skeletal muscle index (SMI) calculation

The height and weight of the patients recorded on the day of computed tomography (CT) simulation for radiotherapy planning were used for assessment purposes. The presence of sarcopenia was assessed using SMI, a validated method for calculating sarcopenia using CT images. The details on sarcopenia and its impact on outcomes in head and neck cancer patients treated with radiotherapy have been published previously by the authors.[18]

A strong correlation exists between skeletal muscle mass at L3 vertebrae and skeletal muscle mass at C3 vertebrae. This study obtained CT images of the head and neck region during external beam radiotherapy simulation. A CT slice at the level of the C3 vertebrae showing the entire vertebral arc was used as a standard while contouring for the cross-sectional area (CSA).[17] This CSA at the level of C3 was used to estimate the CSA at L3 using a validated algorithm, which was described by Swartz as shown in equation 1.[19]

$$\text{CSA at L3 } (cm^2): \quad 27.304 + 1.363 \times \text{CSA at C3 } (cm^2) - 0.671 \times \text{age (years)} + 0.640 \times \text{weight (kg)} + 26.442 \times \text{sex (sex = 1 for female and 2 for male)}$$

$$\text{Lumbar SMI } (cm^2 / m^2): \quad \text{CSA at L3 } (cm^2) / \text{height}^2 \ (m^2)$$

Outcome measurements

The outcome measurements encompassed treatment response, quantified through complete response rates (CRR) and DFS evaluation, employing direct laryngoscopy and subsequent confirmation via positron emission tomography-CT imaging. Complete response (CR) was defined as the complete disappearance of all clinical manifestations of the disease. DFS was defined as the duration from the conclusion of primary treatment to when the patient remained free from any discernible signs or symptoms of the cancer. The median follow-up duration for the patient cohort amounted to 26 months.

Statistical analysis

Descriptive statistics were employed, with continuous variables represented as the mean or median and discrete variables presented as frequencies and percentages. The statistical analysis was conducted using SPSS software, version 22 (Corp, Armonk, NY, USA). The assessment of the association between NLR, PLR, and MLR with various clinical and pathological parameters was executed. Correlation analysis and odds ratio calculations were performed to ascertain the correlation between NLR, PLR, SMI, and treatment outcomes. Receiver operating characteristic (ROC) curves were constructed to

Table 2. Mean NLR and PLR values based on demographic and clinical profile

Characteristic	NLR	PLR	MLR
Mean value	4.15	176.14	0.48
Age < 60 years	3.51	162.87	0.43
Age > 60 years	4.77	188.97	0.51
Male	4.10	170.06	0.46
Female	4.55	228.21	0.61
Larynx	6.13	199.50	0.63
Oropharynx	3.46	165.77	0.42
Hypopharynx	3.91	182.17	0.49
Complete response	2.90	142.19	0.39
Without complete response	5.30	209.8	0.56

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MLR: Monocyte lymphocyte ratio

determine optimal cut-off values for various variables, ensuring appropriate sensitivity and specificity. The relationship between NLR, PLR, MLR, and DFS was assessed using Kaplan-Meier plots. A *P*-value of < 0.05 was deemed statistically significant.

Results

A total of 240 patients with LA-HNSCC, who were treated between 2016 and 2019, were included in this study. Table 1 presents the baseline characteristics of the patient cohort. The mean age of the patients was 60.5 years, and all of them exhibited a good performance status, with an Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 0 or 1. Among the patients, 192 (80%) had stage IV disease, while 48 (20%) had stage III disease. The most prevalent subsite was the oropharynx (66%), followed by supraglottic laryngeal carcinomas (17.3%) and hypopharynx (16.7%).

All patients received concurrent chemoradiotherapy, with a median dose of 70 Gy delivered in 35 fractions using IMRT/VMAT/IGRT techniques on a Linear Accelerator (Clinac iX or TrueBeam STx - Varian). Additionally, all patients received concurrent chemotherapy along with radiation therapy, with a median number of chemotherapy cycles administered being 6 (range: 3-7 cycles). The drugs used included concurrent cisplatin (92%) and carboplatin (8%), administered under the supervision of the medical oncology department.

The mean NLR, PNR, and MLR were 4.15 (range: 0.4 to 20.34), 176.14 (range: 31.44 to 673.87), and 0.48 (range: 0.04 to 5.06), respectively. Table 2 displays the analysis of NLR, PLR, and MLR about the demographic profile of the patients. In elderly patients (>60 years) and females, all three parameters were significantly higher. Among the subsites, laryngeal primaries had the highest values, followed by hypopharynx and oropharynx (Table 2). No significant correlation was found in patients with comorbidities.

The median follow-up of the patients was 26 months (6 to 48 months). At the time of analysis, 132 patients had no evidence of disease, 54 had residual disease after completion of treatment, 11 developed local recurrence disease, 15 had primary controlled but had regional recurrence, 24 developed metastatic disease, and 4 developed 2nd primary in head and neck region. Patients with complete response had lower mean NLR, PLR, and MLR values than those without complete response (2.9/ 142.19/0.39 vs. 5.3/ 209.8/0.56). There was a significant positive correlation amongst all these three inflammatory parameters (correlation coefficient: 0.773 with $P < 0.001$). Interestingly, patients who developed metastases also had a higher value in all the inflammatory markers (4.5, 220, and 0.54, respectively)

The average SMI of the entire patient cohort was 31.9 cm^2/m^2. Various SMI parameters are depicted in table 3. The previous study showed that patients with SMI of >32 cm^2/m^2 fared better than those with SMI<32 cm^2/m^2. In patients with SMI > 32 cm^2/m^2, the complete response rate was 68.7% as compared with 36.3% in those

Table 3. SMI parameters for various subgroups

Parameter	Value
SMI healthy volunteers (N=20)	43.16 cm^2/m^2
SMI healthy males | Females	44.69 cm^2/m^2 | 37.06 cm^2/m^2
SMI patient cohort	31.9 cm^2/m^2
SMI patient cohort - Males | Females	32.78 cm^2/m^2 | 26.19 cm^2/m^2

SMI: Skeletal muscle index

patients with SMI < 32 cm^2/m^2.[18]

Patients with significant sarcopenia (SMI< 32 cm^2/m^2) had higher mean NLR, PLR, and MLR values than those with SMI>32 cm^2/m^2, as shown in table 4. The ROC curve cut-off values for NLR, PLR, and MLR were 3, 145, and 0.4, respectively (based on sensitivity and specificity of 70%). The odds of having sarcopenia, if NLR, PLR, or MLR were above the cut-off value, was 1.2 but was not statistically significant. There was a negative correlation between NLR and SMI; however, it was not statistically significant (P = 0.127). On the contrary, there was a significant negative correlation between PLR and SMI (correlation coefficient -0.235, P = 0.001) and between MLR and SMI (P = 0.021).

Patients with lower NLR and PLR values had significantly better complete response rates. These

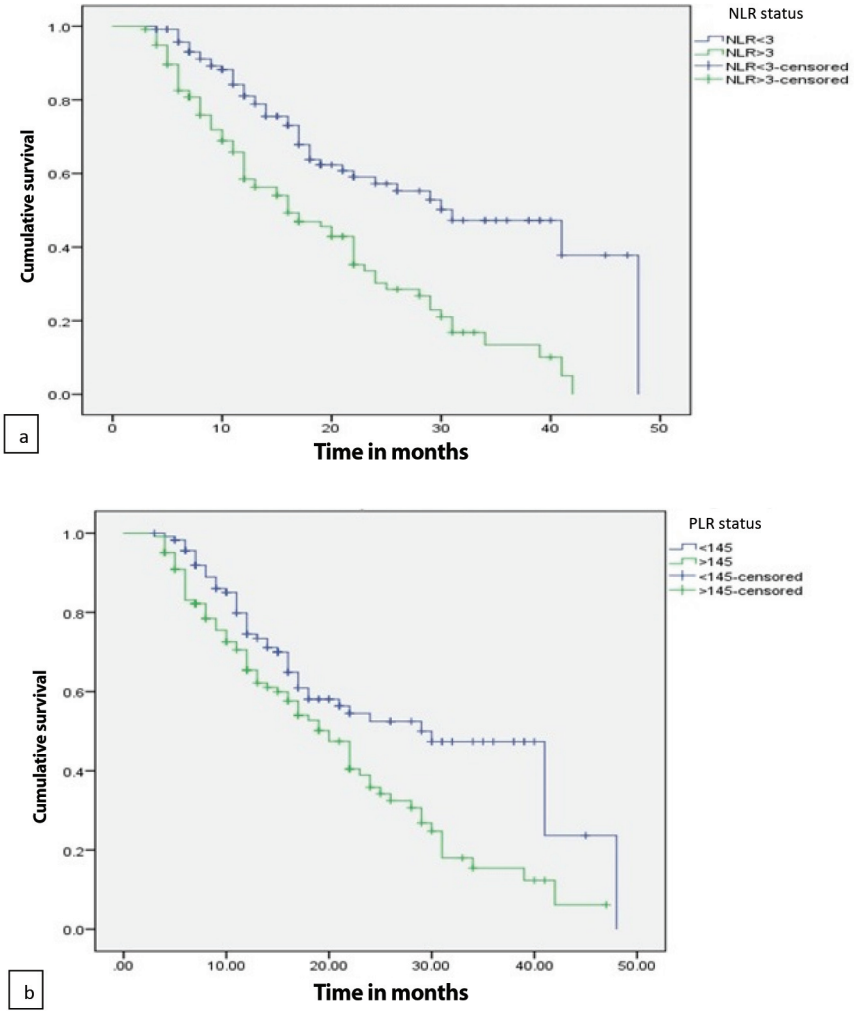

Figure 1. This figure depicts: a) the DFS of two groups - NLR < 3 (in blue) and NLR > 3 (in green); b) the DFS of two groups - PLR < 145 (in blue) and PLR > 145 (in green).

DFS: Disease-free survival; NLR: Neutrophil lymphocyte ratio; PLR: platelet-lymphocyte-ratio

Table 4. Relationship between NLR, PLR, and SMI based on SMI cut-off values

SMI	NLR	PLR	MLR
< 32 cm^2/m^2	4.73	191.08	0.53
> 32 cm^2/m^2	3.50	159.76	0.42

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MLR: Monocyte lymphocyte ratio; SMI: skeletal muscle index

patients also had a higher value of SMI, as depicted in table 5.

Patients with NLR < 3 had a higher SMI index and a better complete response rate. The odds ratio of getting a complete response in a patient with NLR < 3 as compared to with NLR > 3 was 3.55 (confidence interval (CI): 2.08 - 6.06). Similarly, the odds ratio of getting a complete response in a patient with PLR < 145 as compared to with PLR > 145 was 2.22 (CI: 1.86 - 3.85), and for MLR < 0.4 as compared to MLR > 0.4, it was 2.24 (CI: 1.33 - 3.77).

DFS at the end of one year was 56.7%. DFS was higher in patients with lower NLR (NLR < 3 vs. NLR > 3) (20 months vs. 14 months), as shown in figure 1a. Similarly, DFS was higher in patients with lower PLR (PLR < 145 vs. PLR > 145) (18 months vs. 15 months) (Figure 1b) and with lower MLR (MLR < 0.4 vs. MLR > 0.4) (17 months vs. 15 months) with a significant *P* value.

Discussion

The three primary inflammatory markers, NLR, PLR, and MLR, calculated using one of the simplest and cheapest blood investigations, complete blood count, were studied. It was found that these markers can be used as prognostic factors in treating LA-HNSCC treated with concurrent chemoradiotherapy. Higher values of these markers indicated a poor treatment response to poor DFS and were associated with sarcopenia.

All three parameters had a higher value in elderly patients, female gender, and larynx primary. Similar findings were observed in a study by Yeona Cho et al.[20] These biomarkers significantly impacted response rates and DFS. Patients with NLR < 3, PLR < 145, and MLR < 0.4 had improved complete response rates and higher DFS, which was statistically significant. Similar results were found in a study done by Ping Ng in 848 patients. They found that pre-treatment NLR (< 3) is an independent prognostic factor in patients of oropharyngeal cancer regardless of HPV status.[17] Haddad et al. also showed that pretreatment NLR > 5 was prognostic for mortality.[21] Jun Ma found that high NLR was associated with substantial disease burden, poor performance status, and worse survival.[22] In an Indian study by Malik et al., the role of NLR and PLR were both studied in 400 patients of oral cancers. Similar results were obtained, with NLR > 5 and PLR > 200 associated with poorer outcomes.[23]

Sarcopenia, characterized by a decline of skeletal muscle plus low muscle strength and/or physical performance, has emerged to be an important prognostic factor for advanced cancer patients. In a study previously published by the authors, sarcopenia in HNSCC patients receiving definitive chemoradiotherapy was shown to be an independent prognostic factor and was associated with worse treatment outcomes, more toxicities, and treatment interruptions. In that study, patients with SMI < 32 cm^2m^2 fared worse than those with SMI > 32 cm^2m^2.[18] In this study, the objective was to determine whether these three biomarkers were associated with sarcopenia. The study found that patients with SMI < 32 cm^2m^2 had higher mean NLR, PLR, and MLR values than those with SMI > 32 cm^2m^2. A clear and distinct association between sarcopenia and inflammation in cancer was observed.

Inflammatory cytokines have been implicated in causing muscle waste, protein catabolism, and suppression of muscle synthesis. This is part of the cancer cachexia syndrome, which is characterized by involuntary loss of muscle and adipose tissue in patients with cancer or chronic inflammatory disease, which strongly affects the treatment outcome.[24]

All these findings correlated well with each

Table 5. Relationship between NLR, CRR, and SMI based on NLR and PLR cut-off values

Parameter	SMI	CRR
NLR < 3	34.5	62%
NLR > 3	30.3	38%
PLR < 145	32.9	59.5%
PLR > 145	31.3	39.6%
MLR < 0.4	31.6	52.4%
MLR > 0.4	31.9	43.6%

NLR: Neutrophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; MLR: Monocyte lymphocyte ratio; SMI: Skeletal muscle index; CRR: Complete response rates

other. Patients with a high inflammatory burden (high NLR, PLR, and MLR) tend to have more muscle wasting (sarcopenia), and this, in turn, had a significant impact on treatment response and DFS.

Previous studies have suggested that HPV co-infection might affect the distribution of white blood cell count components and alter inflammatory responses in patients with oropharyngeal cancer.[25] It is suggested that HPV-positive oropharyngeal tumours should have a lower NLR value as compared with HPV-negative counterparts.[26]

The study has a few limitations. Firstly, it is retrospective. Secondly, the impact of HPV infection (p16 analysis) with these inflammatory markers and sarcopenia was not studied. The study's major strength was the ability to prognosticate the patient at the time of presentation to the clinic based on a simple blood investigation. However, large-scale prospective studies need to be done to confirm this finding.

Conclusion

NLR, PLR, and MLR represent three inflammatory biomarkers that can be readily assessed through the primary and cost-effective complete blood count test. Research has consistently demonstrated their utility as independent prognostic indicators. Elevated values of these markers are indicative of an unfavorable treatment response, diminished DFS, and a correlation with sarcopenia. Adopting a classification system based on pretreatment hematologic markers is recommended to identify patients at a heightened risk of recurrence and diminished survival in cases of HNSCC. This approach will facilitate the early implementation of more aggressive interventions for such patients, allowing for better clinical management.

Conflicts of Interest

None declared.

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