Original Article

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Correlation between Nutritional Status and Neutrophil/Lymphocyte Ratio in Patients being Treated for Head and Neck Cancer- A Prospective Observational Study

Oncology Section

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ABSTRACT

Introduction: It is a well known fact that diverse nutritional issues are associated with advanced Head and Neck Squamous Cell Cancer (HNSCC). In addition to poor nutrition, varying degrees of immunocompromisation has been noted in these patients and hence is important to study malnutrition and systemic immunity together.

Aim: To determine correlation between nutritional status and systemic immunity in patients being treated for HNSCC.

Materials and Methods: A prospective observational study was conducted at Cancer Research Institute, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, Uttarakhand, India for a period of 30 months (December 2018 and June 2021). A total of 159 HNSCC patients planned for treatment, were enrolled in the study. Data was collected pre and post-treatment for disease based on the parameters- Performance Status (PS), nutritional status (weight, Body Mass Index (BMI), Mid Upper Arm Circumference (MUAC) and haemoglobin. Subjective Global Assessment (SGA) Score and systemic immunity {Neutrophil/Lymphocyte Ratio (NLR)} were measured too. Analysis was planned for node negative (N-) and node positive (N+) groups. One-sample Kolmogorov-Smirnov test was used to check for normality of data, parametric and non parametric tests were used for association, Cochran's and Mantel-Haenszel Statistic was used to calculate Risk Ratio (RR), Pearson's and Spearman's coefficient test was used to assess the correlation. A p-value <0.05 was considered significant.

Results: Total 159 patients were analysed, 72 in N- and 87 in N+ group. Mean age was 56.3±13.27 years, 142 (89.3%) patients were males, 57 (35.8%) patients were cT1/2, 97 (61%) cT3/4 and 5 (3.2%) cTx stage, 146 (92%) were PS 0-2 and 104 (65.4%) received multimodality treatment. In pretreatment, malnutrition was found in 75 (47.2%) patients and median NLR was 3 (range 1-37). In N+ patients, median NLR was significantly higher in patients with ≥10% pretreatment weight loss, low MUAC and high SGA score pretreatment; in N- patients this association was present with only PS. A mild but statistically significant linear correlation was found for NLR with % pretreatment weight loss, BMI, haemoglobin; moderate correlation with weight, MUAC and SGA score in N+ group, but not in N- group.

Conclusion: Poor nutritional status was significantly associated with raised NLR in node positive HNSCC patients with mild to moderate correlation, but this was not found in the node negative group.

Keywords: Head and neck neoplasms, Immunity, Neoplasm, Neutrophil-to-lymphocyte ratio

INTRODUCTION

Worldwide, in the year 2018, HNSCC was found to be the sixth most commonly occurring cancer; in that year there were 890,000 new HNSCC cases with 450,000 deaths from HNSCC reported [1,2]. In India, 219,722 new cases of HNSCC were diagnosed with 121,096 deaths from HNSCC in the year 2020 (GLOBOCAN 2020) [3]. HNSCC is a particularly significant problem in India as it accounts for as many as one-third cancer cases, as compared to developed countries where HNSCC accounts for only ~4-5% cancer cases. Another difference from West, being that >70% HNSCC patients present in locally advanced stage (i.e., stage III or IV) are in India [3]. Nutritional issues associated with advanced HNSCC are important and multifactorial. Prolonged symptoms (pain, odynophagia, burning, halitosis, bleeding, dysphagia, aspiration and trismus) and bulky tumours obstructing the upper aerodigestive tract in patients with advanced HNSCC may all contribute to nutritional deterioration. In addition, oncological treatments like surgery, chemotherapy and radiotherapy have significant side-effects that also contribute to poor nutritional intake in these patients [4]. The immune system in HNSCC patients is affected by the immunosuppressive mediators that are secreted in the tumour microenvironment [5-7]. Varying degrees of compromised immunity have been noted in malnourished patients; in particular, reduction in the cell mediated immune response may occur. In some studies, the degree of malnutrition was found to be associated with disease burden and poor outcomes; the immunesuppression that was found in patients with poor nutrition was linked to unchecked tumour expansion [8]. In India, majority of HNSCC patients are diagnosed when in locally-advanced stage and they are found to have associated with higher degree of malnutrition and impairment in systemic immune response [9]. There may be some correlation between the nutritional status of a patient and the systemic immunity as was demonstrated in various studies performed on West population [10-14]. The data regarding association of malnutrition and immunity in Indian HNSCC patients is limited and needs to be explored. The aim of the present study was to determine the correlation between the nutritional status and systemic immunity in patients being treated for HNSCC. The null hypothesis of the study was that there is no correlation between nutritional status and systemic immunity in patients with HNSCC. The alternate hypothesis of the study was that there is positive correlation between nutritional status and systemic immunity in patients with HNSCC.

MATERIALS AND METHODS

The present prospective observational study was carried out at the Cancer Research Institute, Himalayan Institute of Medical Sciences,

Swami Rama Himalayan University, Dehradun, Uttarakhand, India for the period of 30 months from December 2018 and June 2021. Ethics committee permission was obtained prior to starting the planned study (SRHU/ETHICS/2018/115). The patients meeting the inclusion and exclusion criteria were enrolled in the study after obtaining a written informed consent.

Inclusion criteria: Patients diagnosed with HNSCC and planned for treatment at the Institute were included in the study.

Exclusion criteria: Patients who had any previous treatment for HNSCC, evidence of distant metastasis at the time of diagnosis, patient unwilling to enroll in the study, patients below the age of 18 years were excluded from the study.

Sample size calculation: The correlation coefficient between nutritional parameters and NLR was assumed at 0.5 (unknown), α of 0.05, β of 90%, design effect of 1.5, sample size was calculated to be 55 each in N- and N+ groups. Assuming the loss to follow-up rate to be 20%, final sample size was planned for 66 in each group (total 132 patients).

Study Procedure

A total of 190 patients were evaluated for eligibility, 11 patients were excluded as they were found to have distant metastasis, 18 patients excluded as they did not undergo the planned treatment and two patients excluded for incomplete data, a total of 159 patients were included in the final study, 72 in node negative and 87 in node positive groups. The planned oncological treatments were surgery, radiotherapy or concurrent chemoradiotherapy, either single or multimodality. The baseline data for the patient's disease status and oncological treatment were collected. The following variables were noted pre and post-treatment; Eastern Cooperative Oncology Group (ECOG) PS was assessed [15], nutritional status- weight, BMI (<18.5 underweight) [16], pretreatment percentage weight loss, SGA score [17], MUAC, haemoglobin, presence of bitot spots; systemic immunity using peripheral venous blood- Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC) to calculate the NLR.

The primary tumour subsites included oral cavity, sinuses, oropharynx, hypopharynx and larynx. For disease status TNM staging "American Joint Committee on Cancer" edition 8 schema was used for each subsite at the time of diagnosis [18]. Weight was measured using "Salter machine (unit 9069 PK3R-2914, d=0.1kg)" in the standing position. The peripheral total and differential counts were measured using 10 mL of venous blood in Ethylene Diamine Tetraacetic Acid (EDTA) tube, LH 750 Coulter machine (Beckman Coulter) used volume conductivity and scatter method for obtaining the TLC and the absolute DLC in addition to Leishman's-stained peripheral blood smear method. NLR was obtained by dividing absolute neutrophil and lymphocyte counts. To take care of biases, data collection was performed by trained investigator, using the same instruments. Data collection and analysis was planned for two patient groups based on presence or absence of lymph node metastasis (diagnosed with either cytology or biopsy) as systemic immunity may be affected to a greater degree in node positive patients:

N- No nodal disease at the time of diagnosis.

N+ Nodal metastasis at the time of diagnosis.

STATISTICAL ANALYSIS

Microsoft excel 2010 was used for the initial raw data entry. The data was organised into categories. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22.0. The data was checked for normality using "one-sample Kolmogorov-Smirnov Test". Parametric tests were used for normally distributed data, non parametric tests for non normally distributed data and Chi-square test to check for association in the categorical data. The level of significance was p<0.05. "paired-sample t-test" and "unpaired student t-test" were used to test for difference in mean, non parametric tests used were: Related-Samples Wilcoxon Signed Rank Test, Related-samples Marginal Homogeneity Test, Independent-Samples Mann-Whitney U Test and Independent-Samples Kruskal-Wallis Test. "Cochran's and Mantel-Haenszel Statistic" was used to calculated RR. Correlation was tested with "Pearson's and Spearman's coefficient". A p-value <0.05 was considered as statistically significant.

RESULTS

Descriptive data: Total 159 patients were enrolled in the study, 142 (89.3%) were males with a mean age of 56.3±13.27 years, 49 (30.8%) patients were less than 50 years of age. A total of 57 (35.8%) patients were cT1/2 stage, 97 (61%) cT3/4 stage and 5 (3.2%) cTx stage; 72 patients were node negative and 87 node positive. The commonest primary subsite was oral cavity 55 (34.6%) followed by larynx 37 (23%) and oropharynx 37 (23.3%) and hypopharynx 19 (11.9%). ECOG PS was 0-2 in 146 (92%) patients, 55 (34.6%) patients received single modality treatment and majority received multimodality treatment [Table/Fig-1]. No patients were lost to follow-up, data collection was completed for all the variables. Patients were followed-up until completion of treatment.

Variables		Number of patients n (%)
Gender	Male	142 (89.3)
	Female	17 (10.7)
Age (years)	<50	49 (30.8)
	≥50	110 (69.2)
Stage	cT1/2	57 (35.8)
	cT3/4	97 (61)
	cTx	5 (3.2)
Primary subsite	Oral cavity	55 (34.6)
	Larynx	37 (23.3)
	Oropharynx	37 (23.3)
	Hypopharynx	19 (11.9)
	Other	11 (6.9)
PS	0-2	146 (92)
	>2	13 (8)
Treatment	Single modality	55 (34.6)
	Multiple modality	104 (65.4)

[Table/Fig-1]: The baseline parameters of patients (N=159).
PS: Performance status

Outcome data: The baseline nutritional parameters of the patients are detailed in: [Table/Fig-2]. The mean weight and BMI was 57.75 kg (±11.8 SD) and 21.58 (±4.2 SD) respectively; median % pretreatment weight loss was 4% (range- 0 to 36%); mean haemoglobin was 13.4 gm/dL (±1.8 SD); mean MUAC was 24.7 cm (±3.8SD) and median SGA score was 39 (range- 26 to 65). As depicted in [Table/Fig-3] weight less than 50 kg was found in 45 (28.3%) patients, ≥10% pretreatment weight loss in 35 (22%) patients, BMI <18.5 in 37 (23.3%) patients, MUAC <21 cm in 16 (10.1%) patients, SGA score ≥40 in 75 (47.2%) patients, bitot spots in 19 (11.9%) patients and moderate to severe anaemia in 10 (6.3%) patients. Pretreatment, mean TLC

Variables	Mean±SD	Median	Range
Weight (kg)	57.75±11.8	56	30-97
BMI (kg/m^2)	21.5822±4.2	21	12.84-37.02
Percentage weight loss within six months	6.26±8.1	4	0-36
Haemoglobin (gm/dL)	13.4213±1.8	13.41	7.0-18.0
MUAC (cm)	24.711±3.8	25	16-49
SGA score	40.11±10.3	39	26-65

[Table/Fig-2]: Nutritional parameters before starting treatment.
BMI: Body mass index; SGA: Subjective global assessment; SD: Standard deviation

was 8550.8±2556 cumm SD, mean absolute neutrophil count 5688.1±2331 cumm SD, mean percentage neutrophil 65.12%±11 SD, mean absolute lymphocyte count 1973.8±890 µL SD, mean percentage lymphocyte 23.9%±9.3 SD, mean NLR was 3.83±4.42 SD, median being NLR 3 (range 1.0-37.0).

Variables		Number of patients n (%)
Weight (kg)	<50	45 (28.3)
	≥50	114 (71.7)
% Pretreatment weight loss	<10%	124 (78)
	≥10%	35 (22)
BMI (kg/m²)	<18.5	37 (23.3)
	≥18.5	122 (76.7)
MUAC (cm)	<21	16 (10.1)
	≥21	143 (89.9)
SGA score	<40	84 (52.8)
	≥40	75 (47.2)
Bitot spots	Present	19 (11.9)
	Absent	140 (88.1)
Anaemia	None/mild	149 (93.7)
	Moderate/severe	10 (6.3)

[Table/Fig-3]: Nutritional parameters before starting treatment.
BMI: Body mass index; MUAC: Mid-upper arm circumference; SGA: Subjective global assessment

Nutritional parameters and NLR: Median NLR was compared in patients with poor versus good nutritional status using non parametric tests- Independent-Samples Mann-Whitney U Test and Independent-Samples Kruskal-Wallis Test [Table/Fig-4]. At baseline, in node positive group the median NLR was significantly higher in patients who had ≥10% pretreatment weight loss as compared to <10% pretreatment weight loss {3.93 (2.69 IQR) v/s 2.79 (1.1 IQR), p-value=0.024}; significantly higher in patients with low MUAC as compared to normal MUAC {5.55 (3.58 IQR) v/s 2.44 (1.4 IQR), p-value=0.001}; significantly higher in patients with SGA score of 60-71 as compared to score 30-39 {4.32 (2.24 IQR) v/s 2.21 (1.03 IQR), p-value=0.022}. This association was not present in the node negative group. At completion of treatment, the median NLR was found to be significantly higher in patients with PS >2 as compared to PS 0-2 (6.339 (6.088IQR) v/s 4.674 (4.18IQR), p-value=0.004) in the overall group. Similar finding was noted in the node positive group, but it did not reach statistical significance (p-value=0.051).

Association between poor nutritional status and NLR groups (NLR ≤3, >3 ≤6, >6) was tested using Pearson Chi-square test and the test of strength of association was ascertained by calculating RR using "Cochran's and Mantel-Haenszel Statistic" at baseline [Table/Fig-5]. The proportion of patients with NLR >6 was significantly higher with PS >2 v/s 0-1 (30.8% v/s 9%, p-value=0.046, RR=2.171), pretreatment weight loss ≥10% v/s <10% (14.3% v/s 9.7%, p=0.057), Haemoglobin <13 gm/dL v/s ≥13 gm/dL (22.5% v/s 4.6%, p-value=0.003, R= -2.63) and SGA score ≥40 v/s <40 (17.3% v/s 4.8%, p-value=0.014, R=2.806).

In node negative patients, this association was seen only for PS and haemoglobin, but not for any other variable [Table/Fig-6]. In node positive patients, this association was statistically significant for pretreatment weight loss, MUAC and SGA score. NLR >6 was found in 8.1% v/s 16% patients with <10% v/s ≥10% pretreatment weight loss, respectively (p-value=0.015, RR=2.478); 20% v/s 5.3% patients with ≤21 cm v/s >21 cm MUAC (p-value=0.006, RR= -3.253); 2.7% v/s 16% patients with <40 v/s ≥40 SGA score (p-value=0.010, RR=2.935) [Table/Fig-7].

Correlation between nutritional parameters and NLR: Linear correlation was tested for nutritional parameters and NLR pre- and post-treatment using the "Pearson's correlation" (R) test for normal

		N/L ratio							
		Node negative group				Node positive group			
		At baseline		At completion		At baseline		At completion	
Variables		Median	p-value	Median	p-value	Median	p-value	Median	p-value
PS	0-2	3	0.206*	4	0.072*	3	0.175*	5.003	0.051*
	>2	7		5		3.5		6.52	
Weight (kg)	<50	4	0.567**	4	0.094**	3	0.234**	6.53	0.811**
	≥50	3		4.22		3		6	
Weight loss in past 6 months	<10%	3	0.748*			2.792	0.024*		
	≥10%	2				3.931			
Weight loss during treatment	≥10%			5	0.093**			6.339	0.276**
	<10%			3.978				5.416	
BMI (kg/m²)	≥18.5	3	0.886**	4.22	0.871**	2.33	0.067**	5.67	0.284**
	<18.5	4		5.34		4.2		7.191	
MUAC (cm)	Normal	3	0.564**	4.228	0.124**	2.443	0.001**	6.268	0.146**
	Moderate malnutrition	2		5.447		3.21		4.06	
	Severe malnutrition	NA		NA		5.549		7.167	
Haemoglobin (gm/dL)	Normal	2.891	0.695**	4.327	0.458**	2.911	0.275**	5.909	0.315**
	Anaemia	3.889		5.6		3		6.5	
Bitot spots present	No	3	0.750*	4.331	0.431*	2.8	0.208*	6.304	0.394*
	Yes	2		6.105		3.5		4.503	
SGA score	24-29	3	0.876**	NA	0.111**	2	0.022**	5.945	0.411**
	30-39	2.891		3.709		2.205		6.418	
	40-49	3		5.21		3		5.238	
	50-59	3		4.798		3		7	
	60-71	NA		5		4.316		5	

[Table/Fig-4]: Comparing median Neutrophil/Lymphocyte ratio (NLR) with nutritional parameters at baseline and at completion of treatment.
*Independent-Samples mann-whitney U Test, **Independent-Samples Kruskal-Wallis Test; N/L: Neutrophil to lymphocyte; PS: Performance status; BMI: Body mass index; MUAC: Mid upper arm circumference; SGA: Subjective global assessment

Variables (N=159)		N/L ratio value before starting the treatment				
		≤3	>3 and ≤6	>6	p-value*	RR**
Performance Status (PS)	0-2 (N=146)	98 (67.1)	35 (24)	13 (9)	0.046	2.171
	>2 (N=13)	6 (46.2)	3 (23)	4 (30.8)		
Weight (kg)	≤50 (N=45)	24 (53.3)	14 (31.1)	7 (15.6)	0.123	
	>50 (N=114)	80 (70.2)	24 (21)	10 (8.8)		
% Weight loss in last 6 months	<10 (N=124)	87 (70.2)	25 (20.1)	12 (9.7)	0.057	
	≥10 (N=35)	17 (48.6)	13 (37.1)	5 (14.3)		
Body Mass Index (BMI) (kg/m^2)	<18.5 (N=37)	19 (51.4)	12 (32.4)	6 (16.2)	0.119	
	≥18.5 (N=122)	85 (69.7)	26 (21.3)	11 (9)		
Mid Upper Arm Circumference (MUAC) (cm)	≤21(N=16)	7 (43.8)	5 (31.2)	4 (25)	0.065	
	>21 (N=143)	97 (67.8)	33 (23.1)	13 (9.1)		
Haemoglobin (gm/dL)	<13 (N=49)	28 (57.1)	10 (20.4)	11 (22.5)	0.003	-2.632
	≥13 (N=110)	77 (70)	28 (25.5)	5 (4.6)		
Bitot spots	No (N=140)	94 (67.2)	31 (22.1)	15 (10.7)	0.416	
	Yes (N=19)	10 (52.6)	7 (36.8)	2 (10.6)		
Subjective Global Assessment score (SGA)	<40 (N=84)	62 (73.8)	18 (21.4)	4 (4.8)	0.014	2.806
	≥40 (N=75)	42 (56)	20 (26.7)	13 (17.3)		

[Table/Fig-5]: Association between nutrition and Neutrophil /Lymphocyte ratio values and Risk Ratio (RR) before starting the treatment in the overall group.
*Pearson Chi-square test; **Cochran's and mantel-haenszel statistic; N/L: Neutrophil to lymphocyte; RR: Risk ratio

Variables (N=72)		N/L ratio value before starting the treatment				
		≤3	>3 and ≤6	>6	p-value*	RR**
Performance Status (PS)	0-2 (N=69)	45 (65.2)	18 (26.1)	6 (8.7)	0.031	2.203
	>2 (N=3)	1 (33.3)	0	2 (66.7)		
Weight (kg)	≤50 (N=17)	8 (47.1)	7 (41.2)	2 (11.7)	0.202	
	>50 (N=55)	38 (69.1)	11 ((20)	6 (10.9)		
% Weight loss in last 6 months	<10 (N=62)	40 (64.5)	15 (24.2)	7 (11.3)	1.000	
	≥10 (N=10)	6 (60)	3 (30)	1 (10)		
Body Mass Index (BMI) (kg/m^2)	<18.5 (N=16)	8 (50)	5 (31.3)	3 (18.7)	0.364	
	≥18.5 (N=56)	38 (67.8)	13 (23.2)	5 (9)		
Mid Upper Arm Circumference (MUAC) (cm)	≥21 (N=3)	3 (100)	0	0	0.688	
	<21 (N=69)	43 (62.3)	18 (26.1)	8 (11.6)		
Haemoglobin (gm/dL)	<13 (N=19)	9 (47.4)	5 (26.3)	5 (26.3)	0.014	-2.569
	≥13 (N=53)	38 (71.7)	13 (24.5)	2 (3.8)		
Bitot spots	no (N=69)	44 (63.8)	18 (26.1)	7 (10.1)	0.322	
	yes (N=3)	2 (66.7)	0	1 (33.3)		
Subjective Global Assessment (SGA) score	<40 (N=47)	31 (66)	13 (27.7)	3 (6.3)	0.205	
	≥40 (N=25)	15 (60)	5 (20)	5 (20)		

[Table/Fig-6]: Association between nutrition and Neutrophil/Lymphocyte Ratio (NLR) values and Risk Ratio (RR) before starting the treatment in the node negative group.
*Pearson Chi-square test; **Cochran's and mantel-haenszel statistic; N/L: Neutrophil to lymphocyte; RR: Risk ratio

Variables (N=87)		N/L ratio value before starting the treatment				
		≤3	>3 and ≤6	>6	p-value*	RR**
Performance Status (PS)	0-2 (N=77)	53 (68.8)	17 (22.1)	7 (9.1)	0.436	
	>2 (N=10)	5 (50)	3 (30)	2 (20)		
Weight (kg)	≤50 (N=28)	16 (57.1)	7 (25)	5 (17.9)	0.237	
	>50 (N=59)	42 (71.2)	13 (22.1)	4 (6.7)		
% Weight loss in last six months	<10 (N=62)	47 (75.8)	10 (16.1)	5 (8.1)	0.015	2.478
	≥10 (N=25)	11 (44)	10 (40)	4 (16)		
Body Mass Index (kg/m^2)	<18.5 (N=13)	4 (30.8)	5 (38.4)	4 (30.8)	0.313	
	≥18.5 (N=74)	54 (73)	15 (20.3)	5/74 (6.7)		
Mid Upper Arm Circumference (MUAC) (cm)	≤21 (N=30)	19 (63.3)	5 (16.7)	6 (20)	0.006	-3.253
	>21 (N=57)	39 (68.4)	15 (26.3)	3 (5.3)		
Haemoglobin (gm/dL)	<13 (N=30)	19 (63.3)	5 (16.7)	6 (20)	0.088	
	≥13 (N=57)	39 (68.4)	15 (26.3)	3 (5.3)		
Bitot spots	No (N=71)	50 (70.4)	13 (18.3)	8 (11.3)	0.092	
	Yes (N=16)	8 (50)	7 (43.8)	1 (6.2)		
Subjective Global Assessment (SGA) score	<40 (N=37)	31 (83.8)	5 (13.5)	1 (2.7)	0.010	2.935
	≥40 (N=50)	27 (54)	15 (30)	8 (16)		

[Table/Fig-7]: Association between nutrition and Neutrophil/Lymphocyte Ratio (NLR) values and Risk Ratio (RR) before starting the treatment in the node positive group.
*Pearson Chi-square test; **Cochran's and Mantel-Haenszel Statistic; N/L: Neutrophil to lymphocyte; RR: Risk ratio

data and "Spearman's correlation" (Rho) test for non normal data. At baseline a mild, but statistically significant linear correlation was found for NLR and pretreatment percent weight loss (positive correlation, Rho=0.213, p-value=0.007), BMI (negative correlation, R=-0.372, p-value <0.001) and Haemoglobin (negative correlation, R=-0.240, p-value=0.002); a moderate correlation with weight (negative correlation, R=-0.448, p-value <0.001), MUAC (negative correlation, R=-0.437, p-value <0.001) and SGA score (positive

correlation, R=0.593, p-value <0.001). Similar findings were noted in the Node positive patients but no correlation was found in the node negative patients [Table/Fig-8].

At completion of treatment, mild, but statistically significant correlation was found for MUAC (R=-0.162, p-value=0.047), Haemoglobin (R=-0.116, p-value=0.042) and SGA score (R=-0.194, p-value=0.017). Correlation was absent in the node positive group at completion of treatment, but in the node negative group mild, but statistically significant correlation was noted with weight (R=-0.30, p-value=0.015), MUAC (R=-0.314, p-value=0.010) and SGA score (R=-0.31, p-value=0.013) [Table/Fig-9].

	Neutrophil/Lymphocyteratio at baseline before starting treatment											
	Overall				Node negative group				Node positive group			
Variables	R*	p-value	Rho**	p-value	R*	p-value	Rho**	p-value	R*	p-value	Rho**	p-value
Performance status (PS)	NA		0.201	0.011	NA		0.094	0.43	NA		0.256	0.017
Weight (kg)	-0.448	<0.001			-0.067	0.58			-0.224	0.037		
% Weight loss in last 6 months	NA		0.213	0.007	NA		0.146	0.22	NA		0.311	0.003
Body Mass Index (BMI) (kg/m^2)	-0.372	<0.001			-0.116	0.33			-0.233	0.038		
Mid Upper Arm Circumference (MUAC) (cm)	-0.437	<0.001			-0.056	0.64			-0.196	0.069		
Haemoglobin (gm/dL)	-0.240	0.002			-0.170	0.15			-0.168	0.120		
Subjective Global Assessment (SGA) Score	0.593	<0.001			0.04	0.74			0.256	0.017		

[Table/Fig-8]: Correlation between nutrition parameters and Neutrophil/Lymphocyte Ratio (NLR) before starting treatment.
*Pearson's R; **Spearman Rho

	Neutrophil/Lymphocyte ratio at baseline at completion of treatment											
	Overall				Node negative group				Node positive group			
Variables	R*	p-value	Rho**	p-value	R*	p-value	Rho**	p-value	R*	p-value	Rho**	p-value
Performance Status (PS)	NA		0.235	0.004	NA		0.203	0.10	NA		0.218	0.047
Weight (kg)	-0.140	0.087	-0.095	0.245	-0.30	0.015	-0.313	0.010	0.089	0.42	0.073	0.510
Weight change (kg)	0.023	0.782			0.075	0.549			-0.037	0.74		
Weight change (%)	NA		-0.028	0.731	NA		-0.084	0.504	NA		0.015	0.892
Body Mass Index (BMI) (kg/m^2)	-0.123	0.134			-0.21	0.091			0.009	0.94		
Mid Upper Arm Circumference (MUAC) (cm)	-0.162	0.047			-0.31	0.010			-0.048	0.66		
Haemoglobin (gm/dL)	-0.166	0.042			-0.21	0.098			-0.104	0.35		
Subjective Global Assessment (SGA) Score	0.194	0.017			0.31	0.013			0.052	0.64		

[Table/Fig-9]: Correlation between nutrition parameters and Neutrophil/Lymphocyte Ratio (NLR) at completion of treatment.
*Pearson's R; **Spearman Rho

DISCUSSION

The prevalence of malnutrition has been reported to be between 35-60% in patients with HNSCC at diagnosis this was similar to the finding in the present study (47.2%) [18]. The HNSCC patients face nutrition related challenges at various stages of disease- before, during and after the completion of treatment [19]. Malnutrition or even unintentional loss of weight were linked to poor disease outcome, rise in treatment related morbidity, poor survival and Quality of Life (QoL) parameters [17]. In patients with poor nutritional status, significant immunosuppression has been noted along with unhindered growth of the tumour [20].

In the present study, mean pretreatment NLR was 3.83 (±4.42 SD, range 1.0-37.0), a recent publication in 2020 evaluated role of NLR in 153 patients with p16 negative HNSCC with unknown primary and found the mean NLR to be 3.9 (range 1.4-8.3) [14]. They found cachexia in 6.54% patients and assessed the association between that and NLR. The proportion of patients with cachexia was significantly higher in with rising NLR (1.9%, 4.5% and 18.2% patients with cachexia for NLR of 1.4-3.7, 3.7-6 and ≥6, respectively, p-value=0.008). In the present study, association between poor nutrition and NLR was tested by comparing median NLR value, proportion of malnourished patients with rising NLR (groups- ≤3, >3 and ≤6, >6) and finally calculation of parametric or non parametric correlation coefficient pretreatment as well as at completion of the treatment. In the present study, it was found that there was no difference in median NLR in patients with worse PS, low weight or low BMI. The results demonstrated a significant association between poor nutrition and raised NLR, but only in the lymph node positive patients with HNSCC.

The HNSCC patients with lymph node metastasis may experience higher degree of immunesuppression as compared to node negative patients. Some studies have evaluated at the systemic immunity changes in HNSCC patients with lymph node metastasis. It has been postulated that the immune response against the tumour is mainly mounted at the nodal level. A study published in 2009 found that there was immune-modulation at the level of nodal metastasis and HNSCC patients with lymph node metastasis with associated clinically important effects on the systemic immunity [21]. To take care of this bias, data collection and analysis for association and correlation between nutritional status and systemic immunity was planned in two separate groups- Node negative (N-) and Node positive (N+).

A recent study published in 2021 aimed to find association between and cut-off point for NLR to predict poor nutritional status in 119 cancer patients [22]. The result of the present study was- NLR ≥5 had higher proportion of patients with poor nutrition as compared to NLR <5 (73.6% v/s 37.9%, p-value=0.001). Other studies have also shown that NLR value was predictive of the nutritional status of a patient [23-25]. A study on 87 abdominal cancer patients found that raised NLR was associated with nutritional parameters- ≥10% weight loss in past six months (p-value=0.002) and raised SGA score (p-value=0.009) [26]. NLR was studied in patients with hepatocellular carcinoma and raised NLR was found to be associated significantly with poor nutrition [27]. In another study on patients with gastric cancer, inflammatory markers Platelet/Lymphocyte Ratio (PLR) and NLR were found to be significantly linked to nutritional status and even cancer stage [28]. Izuegbuna OO et al., noted that in breast cancer patients these markers (NLR and PLR) were associated with PS, similar to the finding in the present study [29].

Cancer causes in certain immune related metabolic alteration that result in an increase in response of systemic inflammation and

raised energy expenditure. Due to these metabolic and inflammatory changes the patients may have nutritional risk and resulting malnutrition [30-32]. Inflammation cannot be separated from the pathogenesis of poor nutrition, so much so that the European Society for Clinical Nutrition and Metabolism (ESPEN) has made recommendation to classify disease-related malnutrition into with or without inflammation [33]. Inflammation as already noted has multiple metabolic effects. Cytokines {Ilnterleukin-6 (IL-6 and Tumour Necrosis Factor (TNF-α)} are associated with effects like insulin resistance, reduced appetite and inhibition of entry of nutrients into the cells [34,35].

Various methods may be utilised to evaluate the nutritional status of a patient being treated for HNSCC. Anthropometric methods used in the present study like weight, BMI, MUAC have been used extensively by various studies, but their use in isolation has some limitations. They fail to reflect acute and sudden changes in the nutritional status [36]. History of significant weight loss (either ≥5% or ≥10%) along with low BMI has been traditionally used to classify cancer patients as having poor nutrition. Due to the recent obesity epidemic worldwide along with the fresh concept of significant changes in metabolism even before poor nutrition is reflected as change of weight puts a question mark of the approach based on weight-based parameters alone. Regardless of normal weight, presence history of recent anorexia or changes in appetite or changes in oral intake has been now accepted as markers indicating an increased risk for malnutrition. Thus, SGA scale utilising weight, change in weight, history of changes in oral intake along with physical examination is a dynamic tool which can be utilised for determining the nutritional status of a patients over a period of time. Various studies have used SGA as a nutritional screening tool in cancer patients [37-41]. NLR has been shown to have acceptable reliability as well as accuracy to predict systemic inflammation [42]. In addition to being a marker of systemic inflammation, NLR has been linked to prognostication of solid tumours [43] and HNSCC as well (Takenaka Y et al., 2018, Cho H et al., 2009, Zahorec R, 2001) [42,44,45].

Limitation(s)

The limitation of the present study was small sample number of subjects in the node negative group, to achieve statistical significance and to detect mild to moderate correlation coefficient a larger sample size needs to be planned.

CONCLUSION(S)

A poor nutritional status was found to be significantly associated with raised NLR in patients with HNSCC in the node positive group with mild to moderate correlation between the two parameters, but this association or correlation was not found in the node negative patients. The findings from the present study could be generalised to patients being diagnosed with HNSCC with good external validity as well.

Author contributions: AA and SS helped in conception and design of the study, provision of study materials or patients, collection and assembly of data, data analysis and interpretation and manuscript writing. SS helped in administrative support. Both the authors gave final approval of manuscript.

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