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Original Article

Prognostic Nutritional Index - A Predictive Tool for Treatment Tolerance in Head and Neck Radiotherapy

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Abstract

Background: Head-and-neck cancer (HNC) constitutes one-third of all cancers in developing countries, and the majority present in locally advanced stages. Poor nutritional status is invariably present which compromises treatment compliance, quality of life and survival outcome, posing a major treatment challenge. The aim of this study was to assess the role of pretreatment biomarkers including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) in predicting treatment tolerance. **Materials and Methods:** This prospective observational study included 82 patients receiving definitive and adjuvant radiotherapy for HNC. Utilizing baseline blood investigations, the NLR, PLR, and PNI (10 × albumin + 0.005× lymphocyte count) were calculated for each patient. The cutoff values of NLR, PLR, and PNI were based on the median values. Treatment tolerance in terms of weight loss of more than 10% during treatment, the need for feeding procedure, treatment breaks, and not completing planned treatment as per the schedule were assessed. Associations of NLR, PLR, and PNI with the treatment tolerance factors were assessed using the Chi-square test and Fisher's exact test, and a $P < 0.05$ was considered statistically significant. **Results:** Low PNI significantly correlated with feeding procedure requirement and treatment breaks, thus compromising treatment completion. NLR and PLR did not show statistically significant correlations. **Conclusion:** Low PNI is a reliable predictive factor of poor treatment tolerance. It is an accessible screening tool to identify patients at risk of poor treatment tolerance in whom early interventions can be made to aid in uneventful treatment completion.

Keywords: Head and neck cancer, predictive tool, prognostic nutritional index, radiotherapy

Introduction

Head-and-neck cancer (HNC) is the most common malignancy accounting for nearly 30% of all cancers in India.[1] In contrast to Western countries, most of the patients present in locally advanced stages in India,[1] and thus, the outcome has not considerably improved despite the advances in treatment. Radiotherapy forms the mainstay of treatment for HNC.

Malnutrition and cachexia are commonly seen among HNC patients.[2] Reduced intake and poor nutrition are mainly due to pain and dysphagia caused either by the tumor obstructing the aerodigestive tract or by treatment-induced mucositis leading to weight loss. This in turn is associated with a poor quality of

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life.[3] Therefore, nutritional compromise has to be addressed to improve treatment tolerance and outcomes.

Lymphocyte count, platelet count, albumin level, hemoglobin (Hb) level, and C-reactive protein level are the examples of circulating markers linked with nutrition and inflammation.[4,5] The prognostic nutritional index (PNI) is considered to be a surrogate marker of nutritional status and systemic inflammation, so intercepting both components.[6] The aim of this study was to assess the role of baseline neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and PNI before starting radiation in predicting treatment tolerance and treatment outcome at a median follow-up of 1 year.

Materials and Methods

This prospective observational study included 82 histologically proven HNC patients undergoing Intensity-modulated radiotherapy, either in a definitive or adjuvant setting, with or without concurrent chemotherapy between October 2018 and October 2019 following institutional ethical committee clearance (MSRMC/EC/PG-23/01-2018) and patient informed consent. The radiation dose to high risk clinical target volume was 60–66 Gray (Gy), low risk clinical target volume (LRCTV) and intermediate risk CTV (IRCTV) was 50–54 Gy in 1.8–2.2 Gy/fraction using the simultaneous integrated boost technique, delivered in five fractions per week along with or without weekly concurrent chemotherapy with either cisplatin (40 mg/m^2 body surface area (BSA)) or carboplatin AUC 2 (area under curve). Patients who completed the planned radiation dose and received ≥4 cycles of chemotherapy when indicated were considered to have completed treatment.

Complete blood count, including Hb (g/dL), total lymphocyte count (total leukocyte count cells/mm^3), differential count (percentage of total counts), platelet count (lakhs/mm^3), and albumin level (g/dL) were recorded prior to starting radiotherapy. All of the patients were started on a high protein diet prior to the start of radiation treatment and continued the same during treatment. The NLR was defined as the neutrophil count divided by the lymphocyte count, and the PLR was defined as the platelet count divided by the lymphocyte count. PNI was calculated using the formula 10 × albumin + 0.005 × lymphocyte count.[3-5] All of these values were documented at baseline, and the cutoff values of NLR, PLR, and PNI were derived based on the median values.

Treatment tolerance in terms of treatment breaks, weight loss of more than 10% during treatment, the need for feeding procedure, and not completing planned treatment as per schedule were assessed. The reasons for treatment breaks were noted. The first follow-up visit was at 2 weeks after completing treatment. Thereafter, the patients were followed up at 3-month interval for a maximum of 1 year. Any recurrence or death during the follow-up was noted. STATISTICS**:** Descriptive statistics were presented as mean/standard deviation, and median/interquartile range for continuous variables, and frequencies and percentages for categorical variables. Statistical analysis was done using the Chi-square test for group comparisons for categorical data. If the expected frequency in the contingency tables was found to be <5 for >25% of the cells, Fisher's exact test was used.

In a study by Chang *et al*.,[7] 14% of the patients did not complete radiotherapy alone (RT) alone. However, since the purpose of this study was to investigate tolerance to concurrent chemoradiation (CCRT), sepsis was taken as a predictor of tolerance, which was 27% in their study (significant P value). Based on the study by Chang *et al*.,[7] the minimum sample size required was 76 with absolute precision of 10% and 95% confidence interval.

Results

The characteristics of the patients, tumors, and treatment are shown in Table 1. Of the 82 patients, more than 50% were between 50 and 70 years of age. Most (79%) of the patients had advanced stages, and 70% were node-positive. The hematological parameters are shown in Table 2. Sixteen (19%) patients had hypoalbuminemia (<3.5 g/dL) and 35 (43%) patients were anemic (Hb <12 g/dL). The cutoff values of NLR, PLR, and PNI based on the median values were 3, 149, and 49, respectively.

Table 3 shows the associations of NLR, PLR, and PNI with various treatment tolerance parameters. Fourteen patients had treatment breaks, one due to dengue fever, one who was admitted to the intensive care unit due to aspiration pneumonia, one who developed stroke, one due to neutropenic fever, two due to personal reasons, three who had endoscopic-guided Ryle's tube placement for feeding, and five who had >Grade 3 toxicity. A low PNI was not significantly associated with the incidence of treatment breaks (P = 0.053). The patients with a high NLR and high PLR also had more treatment breaks which showed a trend toward statistical significance.

Feeding procedure was done in 13 patients who had ≥10% weight loss during treatment. Eleven patients had Ryle's tube placement and two had peg tube placement. Of the patients with a low PNI, 26% required feeding procedure, compared to only 3% of those with a high PNI, and the difference was statistically significant (P = 0.004). There were no correlations between NLR and PLR values and the need for feeding procedure.

Fourteen patients did not complete planned treatment, of whom 12 had a low PNI and only two had a high PNI (P = 0.006). High NLR and PLR also showed a similar trend, although without reaching statistical significance.

The patients with high NLR, high PLR and low PNI had twice the number of recurrences compared to those with low NLR, low PLR, and high PNI. The correlations between NLR and PLR with recurrence showed a trend toward statistical significance (P = 0.078 and 0.084, respectively).

Similarly, the patients with high PLR, high NLR, and low PNI had a higher mortality rate compared to those who had low

Table 1: Study characteristics

Patient characteristics	Frequency, *n* (%)	Tumor characteristics	Frequency, *n* (%)	Treatment characteristics	Frequency, *n* (%)
Age		T stage		Treatment given	
<40	8 (10)	1	6 (8)	Sx + RT	21 (26)
40-50	14 (17)	2	29 (35)	Sx + RT + CT	16 (19)
51-60	25 (30)	3	29 (35)	RT + CT	44 (54)
61-70	22 (27)	4	18 (22)	RT alone	1 (1)
>70	13 (16)	N stage		Number of chemo cycles	
Sex		0	25 (30)	Nil	23 (8)
Male	58 (70.7)	1	22 (27)	≤3	14 (17)
Female	24 (29.3)	2	31 (38)	≥4	45 (55)
ECOG		3	4 (5)	Radiation dose (Gy)	
0	6 (7.3)	Overall stage (AJCC 8th)		<60	7 (7.8)
1	42 (51)	I	9 (11)	60	29 (33)
2	31 (38)	II	8 (10)	66	46 (52.2)
3	3 (3.7)	III	31 (38)	Treatment breaks	
Comorbidities		IV	34 (41)	Yes	14 (17)
Nil	58 (70.7)	Treatment site		No	68 (83)
HTN	11 (13.5)	Oral cavity	35 (43)	Feeding procedure	
DM	9 (10.9)	Hypopharynx	17 (21)	Ryles tube	11 (13.4)
HTN + DM	4 (4.9)	Larynx	11 (13)	Peg tube	2 (2.4)
Albumin (g/dl)		Nasopharynx	4 (5)	No intervention	69 (84.2)
≤3.5	16 (19.5)	Oropharynx	14 (17)	Completed Rx	
>3.5	66 (80.5)	Others	1 (1)	Yes	68 (82.9)
Anaemia (g/dl)				No	14 (17.1)
≤12	35 (42.6)				
>12	47 (57.4)				

ECOG: Eastern Co-operative Oncology Group, HTN: Hypertension, DM: Diabetes mellitus, T: Tumor, N: Node, AJCC 8th edition: American Joint Committee on Cancer, Sx: Surgery, RT: Radiotherapy, CT: Chemotherapy, Rx: Treatment

Table 2: Hematologic parameters

	Mean (SD)	Median (IQR)
Hb (g/dL)	12.5 (2.1)	12 (11-14)
Total WBC count (TLC) (cells/dL)	7870 (2353)	7800 (6357-9132)
ALC (cells/dL)	1666 (838)	1758 (1108-2261)
ANC (cells/dL)	4994 (2032)	4705 (3548-5486)
Platelet count (lakhs)	2.5 (0.82)	2 (2-3)
Serum albumin (g/dL)	3.83 (0.60)	4 (4-4)
NLR	5 (5.9)	3 (2-5)
PLR	288 (447)	149 (107-230)
PNI	46 (7.9)	49 (42-52)

NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, PNI: Prognostic nutritional index, TLC: Total leukocyte count, WBC: White blood cell, Hb: Hemoglobin, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, SD: Standard deviation, IQR: Interquartile range

NLR, low PLR, and high PNI, of which the PNI correlation was statistically significant ($P = 0.024$).

The adjuvant CCRT arm was statistically significantly correlated with high PLR and low PNI compared to the adjuvant RT alone arm ($P = 0.012$ and 0.01, respectively). NLR was not significantly correlated with either arm ($P = 0.073$). NLR and PLR were not significantly correlated when the surgery plus RT arm was compared with the CCRT arm ($P = 0.137$), however, low PNI was significantly correlated ($P = 0.007$). However, none of the three parameters (NLR, PLR, and PNI) were significantly correlated when surgery + CCRT versus CCRT alone was compared ($P = 0.385$, 0.263, and 0.422, respectively).

Discussion

In this prospective observational study, we enrolled HNC patients receiving definitive and adjuvant radiotherapy and investigated the associations of pretreatment PLR, NLR, and PNI values with treatment tolerance. Similar studies have been done by Chang *et al*.,[7] Cho *et al*.[8] and Ling *et al*.[9] Chang *et al*. studied the role of PNI alone in predicting toxicity and treatment tolerance, while Cho *et al*.[8] studied the association of NLR with survival outcomes. Ling *et al*. studied various nutritional assessment tools to predict 1-year mortality, which included PNI and PLR.

We selected three markers, NLR, PLR, and PNI to study treatment tolerance, because the immunity of patients will depend on both nutritional and inflammatory status. Using anthropometric measurements such as weight and BMI as the sole markers of nutritional status may not be adequate.[10] Albumin is an indicator of malnutrition and a good predictive serum marker of mortality in hospitalized patients.[11-14] PNI is calculated based on albumin level and lymphocyte count, which are routinely done as a part of the initial assessment.[6]

Table 3: Correlation of treatment tolerance and outcomes with neutrophil lymphocyte ratio, platelet lymphocyte ratio, and prognostic nutritional index (total patients=82)

Outcome	Yes/no	NLR >3 (*n*=39), *n* (%)	NLR ≤3 (*n*=43), *n* (%)	PLR >149 (*n*=40), *n* (%)	PLR ≤149 (*n*=42), *n* (%)	PNI >49 (*n*=36), *n* (%)	PNI ≤49 (*n*=46), *n* (%)
Treatment breaks	Yes (14)	8 (20.5)	6 (14)	10 (25)	4 (9.5)	3 (8.3)	11 (23.9)
	No (68)	31 (79.5)	37 (86)	30 (75)	38 (90.5)	33 (91.7)	35 (76.1)
P		0.431		0.0631		0.053[a]	
Feeding procedure	Yes (13)	6 (15.4)	7 (16.3)	7 (17.5)	6 (14.3)	1 (2.8)	12 (26.1)
	No (69)	33 (84.6)	36 (83.7)	33 (82.5)	36 (85.7)	35 (97.2)	34 (73.9)
P		0.9121		0.691		0.004[a***]	
Completed planned treatment	Yes (68)	31 (79.4)	37 (86)	31 (77.5)	37 (88)	34 (94)	34 (74)
	No (14)	8 (20.5)	6 (13.9)	9 (22.5)	5 (12)	2 (6)	12 (26)
P		0.632		0.2022		0.006[b***]	
Recurrence	Yes (9)	7 (17.9)	2 (4.7)	7 (17.5)	2 (4.8)	3 (8.3)	6 (13)
	No (73)	32 (82.1)	41 (95.3)	33 (82.5)	40 (95.2)	33 (91.7)	40 (87)
P		0.0782		0.0842		0.7242	
Death	Died (16)	10 (25.6)	6 (14.0)	11 (27.5)	5 (11.9)	3 (8.3)	13 (28.3)
	Alive (66)	29 (74.4)	37 (86)	29 (72.5)	37 (88.1)	33 (91.7)	33 (71.7)
P		0.1821		0.0751		0.024[a***]	

***Significant at $P<0.05$, [a]Chi-squared test, [b]Fisher's exact test. NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, PNI: Prognostic nutritional index

We selected PNI as an assessment tool since it addresses both nutritional and inflammatory aspects.

The cutoff values to define high and low NLR, PLR, and PNI were chosen based on median values in our study. Chang *et al*.[7] used median value to divide PNI into high and low similar to our study, whereas Cho *et al*. and Ling *et al*. used receiver operating curve analysis to arrive at the cutoff values, which were comparable to our study. The NLR cutoff value was 2.7 in the study by Cho *et al*. and 3 in our study, and the cutoff values of PLR and PNI were 191 and 46.8 in the study by Ling *et al*.[9] compared to 149 and 49 in our study. The median PNI cutoff value in the study by Cho *et al*. was 53.1, which is slightly higher than in our study. This may be because only 54% of their patients had an advanced stage compared to 79% in the present study. Moreover, compared to patients from developed countries, our patients had a higher malnutrition at baseline. About 26% of the patients in the present study had undergone surgery, and surgery would have contributed to poor nutritional status, whereas their study included only definitive RT patients.

As in the present study, Chang *et al*. studied treatment tolerance in terms of need for feeding procedure and treatment completion. They documented a higher number of feeding procedures (50%) in the patients with a low PNI. We observed similar results, and 30% of the patients with a low PNI required feeding procedure compared to 3% in the high PNI group. In our patients, nutritional interventions such as Ryle's tube feeding were done during treatment if weight loss was more than 10% of the pretreatment value.

However, the rate of treatment completion was slightly lower in our study (74% in the low PNI group and 95% in the high PNI group) compared to their study (88.9% in the low PNI group and 97% in the high PNI group). There are many possible reasons for this finding. They studied completion of radiation treatment only, whereas we studied completion of chemotherapy and radiotherapy (CTRT) (chemoradiation). In addition, 26% of our patients had undergone surgery, whereas they had only patients treated with CTRT. Moreover, 85% of their patients had a good ECOG performance status of <2, whereas only 58% of our patients had ECOG performance status of <2.

Few other studies have documented the prognostic significance of NLR and PLR in HNC patients.[3,8,13] Cho *et al*. reported that a high NLR was strongly and independently correlated with a poorer progression-free survival and overall survival (OS) in HNC patients.[8] They studied 5-year OS and disease-free survival (DFS), however we only had 1 year of follow-up data, hence survival outcomes cannot be compared.

Ling *et al*. made a similar observation that NLR, PLR, and PNI were significantly associated with 1-year mortality and that PNI and PLR were the independent prognostic factors.[9] The 1-year mortality rate was 52% for patients with a low PNI (<46.8) and 12% for those who had PNI >46.8 in their study. In our study 28% of the patients in the low PNI (<49) group and 8% of the patients in the high PNI (>49) group died at a median follow-up of 1 year. The overall 1-year mortality rate was low in our study (19.5%) compared to their study (30%). The possible reasons for this difference may be that they only included patients with locally advanced HNC and around 82% were node-positive, whereas about 21% of our patients were early stage and only 70% were node-positive. Other tumour and treatment characteristics were similar to ours, except that 28% of the patients in their study received neoadjuvant chemotherapy. Another study by Bruixola *et al*.[15] documented a 1-year OS rate of 72% for patients with a low PNI (<45) compared to 90% for patients with a high PNI (≥45).

We did not find any correlation of these parameters with tumour recurrence, possibly because of the short follow-up period of 1 year and the low number of recurrences.

Although many studies in the recent years have analysed the role of these biomarkers in treatment outcomes in HNC, few studies have analyzed their associations with treatment tolerance. This is a comprehensive prospective study, as all three markers (NLR, PLR, and PNI) were included with their correlations with both treatment tolerance and short-term outcomes. The role of PNI is more relevant in developing countries where malnutrition is a major challenge for oncologists. To our knowledge, this is the only study of its kind from a developing country.

One of the limitations of this study is that we used medians for cut-off values of PLR/NLR/PNI, even though dichotomization has been used in similar studies. Since these are naturally continuous variables, using ROC analysis to identify the cutoff values would be ideal. The short follow-up period is another limitation of our study. We hope to continue this study and extend the follow-up period to assess the role of these markers in long-term survival outcomes.

Conclusion

Low PNI was associated with poor treatment tolerance. High NLR and PLR were associated with more treatment breaks, lesser treatment completion, more recurrences and death, but without statistical significance. Since these parameters are a part of routine work-up, they are simple and effective screening tools to identify patients at risk of nutritional compromise and treatment breaks, and hence inferior outcomes. Along with other factors, PNI should be included to predict treatment tolerance in HNC patients. This will allow for early interventions in patients undergoing definitive or adjuvant radiotherapy. Studies with a longer follow-up are needed to evaluate the prognostic significance of these parameters with survival in terms of DFS and OS.

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Conflicts of interest

There are no conflicts of interest.

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