DOI:10.31557/APJCC.2026.11.5.727

RESEARCH ARTICLE

Stage-Dependent Elevation of Platelet-Based Inflammatory Indices in Head and Neck Squamous Cell Carcinoma: A Retrospective Cohort Study

Pritanjali Singh*, Dharmendra Singh

Department of Radiotherapy, All India Institute of Medical Sciences, Patna, India.

Abstract

Introduction: To evaluate baseline hematological characteristics and stage-wise variation of platelet-based inflammatory indices, platelet lymphocyte ratio (PLR), platelet neutrophil ratio (PNR), and platelet eosinophil ratio (PER) in patients with head and neck squamous cell carcinoma (HNSCC), and to examine their association with disease stage. **Materials and Methods**: This retrospective observational study included 831 treatment-naïve HNSCC patients treated between January 2022 and December 2025. Hematological parameters were obtained from baseline complete blood counts, and PLR, PNR, and PER were calculated. As data were non-normally distributed (Shapiro–Wilk test, $p < 0.001$), results are reported as median (interquartile range), and comparisons across stages were performed using the Kruskal–Wallis test with Dunn's post-hoc analysis. Multivariable logistic regression was used to assess independent associations adjusting for age, gender, tobacco use, and tumor site. **Results**: Inflammatory indices demonstrated right-skewed distributions, with median PLR, PNR, and PER of 162.3, 48.7, and 1078.4, respectively. All indices showed significant stage-wise increases ($p < 0.001$). ROC analysis revealed that PLR had the highest discriminative ability for advanced disease (AUC: 0.741; 95% CI 0.701-0.781), followed by PER (AUC: 0.651; 95% CI 0.613-0.699) and PNR (AUC: 0.635; 95% CI 0.585-0.686). On univariate analysis, PLR, PNR, PER, tobacco use, and tumor site were significantly associated with stage. However, on multivariable regression, only PLR (adjusted OR: 1.013, $p < 0.001$) and tumor site remained independently associated with advanced-stage disease. **Conclusion**: Platelet-based inflammatory indices demonstrate significant associations with disease stage in HNSCC. These findings likely reflect underlying systemic inflammatory changes associated with tumor burden; however, their prognostic or predictive utility requires validation in prospective studies with survival outcomes.

Keywords: Platelet-to-lymphocyte ratio, Platelet-to-neutrophil ratio, Platelet-to-eosinophil ratio, Systemic inflammation

Asian Pac J Cancer Care, **11 (5)**, 727-735

Submission Date: 05/23/2026 Acceptance Date: 07/27/2026

Introduction

Head and neck cancers (HNC) represent a major global health challenge, accounting for approximately 900,000 new cases and over 400,000 deaths annually worldwide [1]. The burden of HNC is disproportionately high in South and Southeast Asia, particularly in India, where HNC constitute nearly 15% of all cancers in males and approximately 6% in females [2, 3]. According to the GLOBOCAN 2022 estimates, India alone contributes a substantial proportion of the global head and neck cancer burden, with oral cavity cancer being among the most common malignancies in the country [2]. The high prevalence is largely attributed to widespread use of tobacco in both smoked and smokeless forms, areca nut consumption, alcohol intake, and poor oral hygiene [3, 4].

Despite improvements in diagnostic and therapeutic modalities, a significant proportion of patients in India continue to present with locally advanced or metastatic disease (Stage III–IV), which adversely impacts treatment outcomes and overall survival [5]. Delayed presentation, lack of awareness, socioeconomic barriers, and limited access to specialized oncology services contribute to this advanced-stage predominance [4, 5]. Identification of reliable, cost-effective, and easily accessible prognostic markers is therefore essential,

Corresponding Author:
Dr. Dharmendra Singh
MD (Radiotherapy), Department of Radiotherapy, All India Institute of Medical Sciences, Deoghar, India.
Email: babu.dsingh.singh35@gmail.com

particularly in resource-constrained healthcare settings.

Cancer-related systemic inflammation is now recognized as a hallmark of tumor progression [6]. The tumor microenvironment interacts dynamically with host immune and inflammatory cells, promoting angiogenesis, tumor growth, invasion, and metastatic spread. Hematological parameters derived from routine peripheral blood investigations have emerged as potential surrogate markers of this systemic inflammatory response. Because complete blood count (CBC) testing is universally available and inexpensive, derived inflammatory indices may offer practical clinical value in daily oncology practice.

Among these indices, the platelet–lymphocyte ratio (PLR), platelet–neutrophil ratio (PNR), and platelet–eosinophil ratio (PER) have gained attention in recent years. These indices are calculated as Platelet–Lymphocyte Ratio (PLR) = Absolute platelet count ÷ Absolute lymphocyte count; Platelet–Neutrophil Ratio (PNR) = Absolute platelet count ÷ Absolute neutrophil count; Platelet–Eosinophil Ratio (PER) = Absolute platelet count ÷ Absolute eosinophil count.

PLR reflects the balance between thrombocytosis-associated tumor-promoting mechanisms and lymphocyte-mediated antitumor immune response. Elevated platelet counts have been linked to tumor angiogenesis, protection of circulating tumor cells, and metastatic potential, whereas reduced lymphocyte counts may indicate impaired immune surveillance [6, 7].

PNR represents the relationship between platelets and neutrophils. Neutrophils contribute to tumor progression through secretion of pro-inflammatory cytokines, growth factors, and matrix metalloproteinases, which facilitate invasion and metastasis [8]. Alterations in platelet and neutrophil dynamics may therefore reflect systemic tumor-associated inflammation.

Neutrophils play a central role in tumor progression through secretion of cytokines, growth factors, and proteolytic enzymes that facilitate invasion and metastasis [9]. The platelet–eosinophil ratio (PER), although less extensively investigated, represents a novel inflammatory index reflecting the interaction between platelets and eosinophils. Eosinophils have demonstrated context-dependent roles in cancer, including modulation of immune responses and release of cytotoxic mediators. Importantly, data on PER in head and neck cancer are scarce, particularly in large clinical cohorts, making its evaluation relevant for understanding tumor-associated systemic inflammation in this population.

We hypothesized that platelet-based inflammatory indices (PLR, PNR, and PER) are significantly elevated in advanced-stage head and neck squamous cell carcinoma and are associated with increasing tumor burden.

Several international studies have demonstrated associations between elevated inflammatory indices particularly PLR and neutrophil-related ratios and advanced stage, nodal involvement, poor response to therapy, and reduced survival in head and neck cancers [7, 10]. However, data from Indian cohorts remain limited, especially in large sample sizes examining multiple platelet-based indices simultaneously. Considering the unique epidemiological and etiological profile of head and neck cancers in India, region-specific evaluation of these biomarkers is essential. In this context, the present study was undertaken to comprehensively evaluate the baseline hematological characteristics and stage-wise distribution of inflammatory indices (PLR, PNR, and PER) in a large cohort of patients with head and neck cancer.

The present study aimed to evaluate baseline hematological characteristics and stage-wise variation of platelet-based inflammatory indices (PLR, PNR, and PER) in patients with head and neck squamous cell carcinoma, and to examine their association with disease stage at presentation.

Materials and Methods

Study Design and Setting

This was a retrospective observational study conducted at a tertiary cancer care center. The study included patients diagnosed with head and neck cancer who presented to the Department of Radiotherapy, All India Institute of Medical Sciences, Patna during the study period from January 2022 to December 2025. All eligible patients presenting during the study period were included using a consecutive sampling strategy, based on predefined inclusion and exclusion criteria.

Study Population

Patients with histopathologically confirmed head and neck malignancies were included in the analysis. Patients with incomplete baseline hematological data were excluded. Complete hematological parameters (hemoglobin, total leukocyte count, and platelet count) were available for all included patients.

Patients aged 18 years or older with histopathologically confirmed squamous cell carcinoma of the head and neck who were newly diagnosed and treatment-naïve were included in the study, provided that complete baseline hematological parameters were available at the time of diagnostic work-up. Patients with a history of prior chemotherapy or radiotherapy, those with active infection, inflammatory disease, or underlying hematological disorders at presentation, and those with incomplete clinical or laboratory records were excluded from the study.

Data Collection

Patient data were retrieved from institutional medical records and departmental databases. Records were systematically screened to identify all consecutive eligible cases, thereby minimizing selection bias. Data collected included age, gender, primary tumor site (oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx), tobacco use status, and stage at presentation. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM staging system (8th edition) applicable during the study period [11].

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25. Continuous variables were assessed for normality using the Shapiro–Wilk test. As inflammatory indices (PLR, PNR, PER) demonstrated non-normal distribution, they are presented as median and interquartile range (IQR), in addition to mean ± standard deviation for descriptive purposes. Comparisons of inflammatory indices across disease stages were performed using the Kruskal–Wallis test, followed by Dunn's post-hoc test with Bonferroni correction for multiple comparisons. Categorical variables were analyzed using the Chi-square test. To evaluate independent associations between inflammatory indices and disease stage, multivariable logistic regression analysis was performed, adjusting for age, gender, tobacco use, and tumor site. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Effect sizes for group comparisons were calculated using epsilon-squared (ε^2). A p-value of <0.05 was considered statistically significant.

Results

Patient Characteristics and Baseline Hematological Profile

Complete hematological data were available for hemoglobin (Hb), total leukocyte count (TLC), and platelet count in all patients. PLR and PNR values were available for all 835 patients, while PER data were available for 831 patients due to zero eosinophil counts in four cases. Final analysis was performed on 831 patients.

A total of 831 patients were included in the analysis of baseline hematological parameters. The median hemoglobin level was 11.3 g/dL (interquartile range [IQR]: 10.4–12.5 g/dL). The median total leukocyte count was 7,100 cells/μL (IQR: 5,400–8,600 cells/μL), and the median platelet count was 230,000 cells/μL (IQR: 200,000–290,000 cells/μL). Assessment of distribution showed near-symmetric distribution for hemoglobin (skewness = 0.268), moderate right-skewness for total leukocyte count (skewness = 0.862), and marked right-skewness for platelet count (skewness = 1.966), summarized in (Table 1).

The median platelet–lymphocyte ratio (PLR) was 162.33 (interquartile range IQR: 107.23–260.87), the median platelet–neutrophil ratio (PNR) was 48.69 (IQR: 35.44–67.90), and the median platelet–eosinophil ratio (PER) was 1078.43 (IQR: 659.72–1811.59). All indices demonstrated marked right-skewed distributions, with mean values exceeding median values. Skewness values were 4.784 for PLR, 5.586 for PNR, and 3.981 for PER, with corresponding kurtosis values of 34.811, 55.895, and 24.806, respectively (Table 2).

Gender-wise Distribution of Clinicopathological Variables

Distribution of Disease Stage Across Primary Tumor Subsites

The gender-wise distribution of clinicopathological characteristics is summarized in (Table 3). The distribution of primary tumor site did not differ significantly between males and females (p = 0.785). Oral cavity cancer was the most common subsite in both males (24.06%) and females (16.24%), followed by oropharynx, hypopharynx, larynx, and nasopharynx, with comparable proportional distribution across genders. A statistically significant association was observed between gender and tobacco use (p < 0.001). Tobacco consumption was markedly higher among males (39.59%) compared to females (8.54%), whereas a greater proportion of females reported no tobacco use (30.08%) compared to males (21.78%). The distribution of disease stage at presentation was similar between males and females, with no statistically significant difference (p = 0.274). The majority of patients in both groups presented with advanced-stage disease (Stage IVA–IVC), with Stage IVB being the most frequent stage in both males (18.29%) and females (12.51%). Similarly, the distribution of comorbid conditions did not differ significantly between genders (p = 0.147). Hypertension was the most common comorbidity in both males (19.13%) and females (14.07%), followed by diabetes mellitus and combined diabetes with hypertension, while a substantial proportion of patients in both groups had no reported comorbidity.

The cross-tabulation of primary diagnosis and

Table 1. Summary of Baseline Hematological Characteristics

	HB	TLC	Platelet
N	831	831	831
Median	11.300	7100.00	230000.000
Std. deviation	1.688	2434.848	117450.498
Skewness	0.268	0.862	1.966
Kurtosis	0.313	1.829	4.410
Percentile			
25	10.400	5400.000	200000.000
50	11.300	7100.000	230000.000
75	12.500	8600.000	290000.000

HB- Hemoglobin; TLC- Total Leucocyte Count

Table 2. Summary Statistics of Systemic Platelet-derived Inflammatory Indices

	PLR	PNR	PER
N	831	831	831
Mean	222.846	60.067	1519.139
Median	162.330	48.685	1078.431
Std. deviation	220.225	47.922	1553.235
Skewness	4.784	5.586	3.981
Kurtosis	34.811	55.895	24.806
Percentiles			
25	107.226	35.435	659.722
50	162.330	48.685	1078.431
75	260.869	67.904	1811.594

PLR- Platelet to Lymphocyte Ratio; PNR- Platelet to Neutrophil Ratio; PER- Platelet to Eosinophil Ratio

Table 3. Genderwise Distribution of Clinicopathological Variables

		Male		Female		
		Count	Table N %	Count	Table N %	P value
Diagnosis	Oral Cavity	200	24.06	135	16.24	0.785
	Oropharynx	138	16.60	76	9.14	
	Hypopharynx	91	10.95	62	7.46	
	Larynx	55	6.61	34	4.09	
	Nasopharynx	26	3.12	14	1.68	
Tobacco	Yes	329	39.59	71	8.54	<0.001
	No	181	21.78	250	30.08	
Stage	Stage I	0	0.00	0	0.00	0.274
	Stage II	37	4.45	29	3.48	
	Stage III	108	12.99	66	7.94	
	Stage IVA	111	13.35	76	9.14	
	Stage IVB	152	18.29	104	12.51	
	Stage IVC	102	12.27	46	5.53	
Comorbidity	None	287	34.53	178	21.41	0.147
	DM	37	4.45	16	1.92	
	HTN	159	19.13	117	14.07	
	DM+HTN	27	3.24	10	1.20	

DM- Diabetes Mellitus; HTN- Hypertension

stage demonstrated variability in stage distribution across different tumor subsites (Table 4). Oral cavity cancer constituted the largest subgroup (n = 336) and demonstrated a clear predominance of advanced-stage presentation, with the highest number of cases in Stage IVB (n = 111), followed by Stage IVA (n = 85) and Stage IVC (n = 55). Early-stage disease (Stage II) accounted for a relatively small proportion of cases. Oropharyngeal cancers (n = 216) also showed a predominance of advanced-stage disease, particularly in Stage IVB (n = 65) and Stage IVC (n = 43). A similar pattern was observed in hypopharyngeal cancers (n = 154), where the majority of patients presented in Stage IVB (n = 52) and Stage IVC (n = 29). Laryngeal cancers (n = 89) demonstrated a comparatively more balanced stage distribution, with fewer patients presenting with metastatic disease (Stage IVC, n = 12) relative to other subsites. Nasopharyngeal cancers (n = 40), although fewer in number, showed a relatively higher proportion of patients presenting in earlier stages, particularly Stage II (n = 12), compared to other subsites. Overall, advanced-stage disease (Stage IVA–IVC) predominated across most tumor subsites, with Stage IVB representing the most common stage at presentation (Figure 1).

Stage-wise Comparison of Inflammatory Indices

Pairwise comparisons following the Kruskal–Wallis test (with Bonferroni correction) demonstrated distinct stage-wise differences in PLR, PNR, and PER.

Platelet–Lymphocyte Ratio (PLR)

PLR values were significantly higher in Stage III compared to Stage II (adjusted p = 0.002). A progressive increase in PLR was observed with advancing stage. Compared to Stage II, PLR was significantly higher in Stage IVA, IVB, and IVC (all adjusted p < 0.001). Similarly, Stage III showed significantly lower PLR values compared to Stage IVA, IVB, and IVC (all adjusted p < 0.001). No statistically significant difference was observed between Stage IVA and Stage IVB (adjusted p = 0.054). However, Stage IVC demonstrated significantly higher PLR values compared to both Stage IVA (adjusted p < 0.001) and Stage IVB (adjusted p = 0.002). Overall, PLR showed a statistically significant increasing trend with advancing disease stage, with the highest values observed in Stage IVC, indicating greater systemic inflammatory burden in advanced disease (Figure 2).

Platelet–Neutrophil Ratio (PNR)

PNR values were significantly higher in Stage III compared to Stage II (adjusted p = 0.027). A progressive increase in PNR was observed with advancing stage.

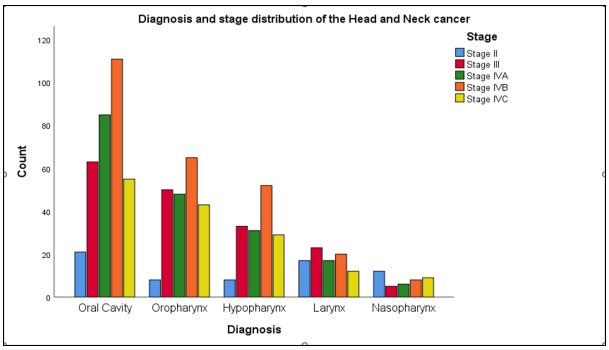

Figure 1. Distribution of disease stage across Head and Neck Cancer subsites, demonstrating a predominance of advanced-stage presentation (particularly stage IVB) across most primary tumor locations

Table 4. Distribution of Primary Site of Cancer According to Stage at Diagnosis

		Stage					Total
		Stage II	Stage III	Stage IVA	Stage IVB	Stage IVC	
Diagnosis	Oral Cavity	21	63	85	111	55	336
	Oropharynx	8	50	48	65	43	216
	Hypopharynx	8	33	31	52	29	154
	Larynx	17	23	17	20	12	89
	Nasopharynx	12	5	6	8	9	40
Total		66	174	187	256	148	831

Compared to Stage II, PNR values were significantly higher in Stage IVA, IVB, and IVC (all adjusted $p < 0.001$). Similarly, Stage IVA showed significantly higher PNR values compared to Stage III (adjusted $p = 0.030$), while Stage IVB and Stage IVC demonstrated significantly higher values than Stage III (both adjusted $p < 0.001$). No statistically significant difference was observed between Stage IVA and Stage IVB (adjusted $p = 0.747$), or between Stage IVB and Stage IVC (adjusted $p = 0.424$). However, Stage IVC demonstrated significantly higher PNR values compared to Stage IVA (adjusted $p = 0.005$). Overall, PNR showed a statistically significant increasing trend with advancing disease stage, with the highest values observed in Stage IVC, indicating an increasing systemic inflammatory response with disease progression (Figure 3) .

Platelet–Eosinophil Ratio (PER)

Due to marked right-skewness, platelet–eosinophil ratio (PER) was evaluated using raw values in regression analysis; however, interpretation should consider its wide dispersion and scale. PER was significantly associated with advanced-stage disease on univariate analysis (OR: 1.001, 95% CI: 1.000–1.001, $p < 0.001$); however, the effect size per unit increase was minimal due to the large numerical scale of PER values. For better interpretability, this corresponds to a 100-unit increase, PER corresponds to an approximate 10% increase in odds, indicating that the observed effect is scale-dependent. Due to scale dependence and high dispersion, the clinical interpretability of PER remains limited. In multivariable analysis, PER did not retain statistical significance ($p = 0.925$) (Figure 4).

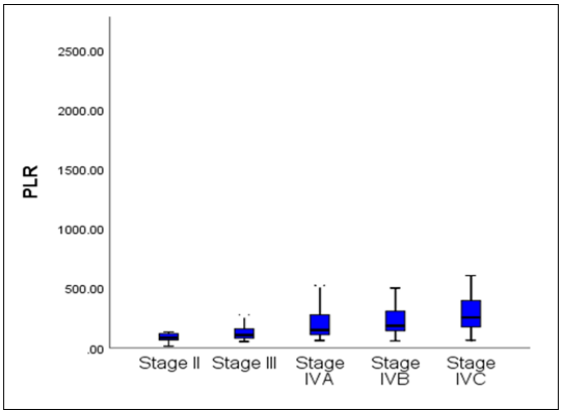

Figure 2. Box-and-Whisker plots illustrate the distribution of the PLR and stage. The box denotes the interquartile range (IQR) (25^{th}–75^{th} percentile), the horizontal line within the box indicates the median, and whiskers extend to values within 1.5 × IQR.

Receiver Operating Characteristic (ROC) Analysis

ROC analysis demonstrated that all three platelet-based inflammatory indices had statistically significant ability to discriminate advanced-stage disease ($p < 0.001$ for all). Among them, PLR showed the highest discriminative performance (AUC: 0.741, 95% CI: 0.701–0.781), followed by PER (AUC: 0.651, 95% CI: 0.613–0.699) and PNR (AUC: 0.635, 95% CI: 0.585–0.686). Based on conventional interpretation, an AUC between 0.7 and 0.8 indicates acceptable discrimination, while values between 0.6 and 0.7 reflect poor to fair discrimination. Accordingly, PLR demonstrated acceptable discriminative ability, whereas PER and PNR showed relatively modest performance. The optimal cut-off values identified were 167.41 for PLR, 57.27 for PNR, and 1127.40 for PER. PLR demonstrated high sensitivity (85.1%) with moderate specificity (60.9%), whereas PNR showed moderate specificity (68.2%) with lower sensitivity (56.1%). PER exhibited balanced but modest sensitivity (70.3%) and specificity (56.2%). These cut-off values should be considered exploratory and data-driven, derived from the present cohort, and have not been externally validated. (Figure 5).

Univariate and multivariate analysis of variables influencing the stage

Univariate logistic regression analysis demonstrated that tobacco use, tumor site, and all three inflammatory indices (PLR, PNR, and PER) were significantly associated with disease stage. Tobacco use was associated with lower odds of advanced-stage disease (OR: 0.729, 95% CI: 0.539–0.987, $p = 0.041$). Tumor site showed a significant association with staging (OR: 0.801, 95% CI: 0.708–0.906, $p < 0.001$). Among inflammatory markers, PLR (OR: 1.014, 95% CI: 1.011–1.017, $p < 0.001$), PNR (OR: 1.023, 95% CI: 1.016–1.031, $p < 0.001$), and PER (OR: 1.001, 95% CI: 1.000–1.001, $p < 0.001$) were all significantly associated with advanced-stage disease. Gender and comorbidity did not show statistically significant associations. On multivariable logistic regression analysis, after adjusting for confounding variables, only tumor site and PLR remained independently associated with disease stage. Tumor site retained a significant association (adjusted OR: 0.794, 95% CI: 0.692–0.912, $p = 0.001$),

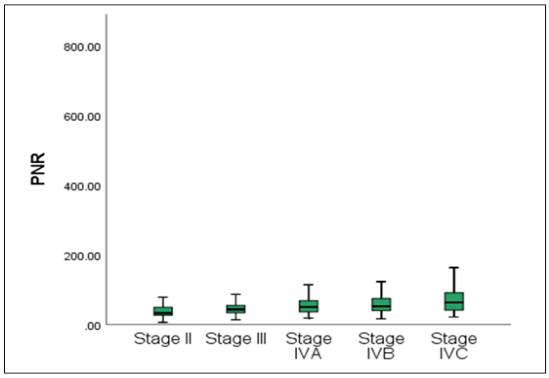

Figure 3. Box-and-Whisker plots illustrate the distribution of PNR and stage. The box denotes the interquartile range (IQR) (25^{th}–75^{th} percentile), the horizontal line within the box indicates the median, and Whiskers extend to value within 1.5 × IQR.

while PLR continued to demonstrate a strong independent association with advanced-stage disease (adjusted OR: 1.013, 95% CI: 1.010–1.017, $p < 0.001$). In contrast, tobacco use ($p = 0.116$), PNR ($p = 0.420$), and PER ($p = 0.925$) did not retain statistical significance in the adjusted model (Table 5). These findings indicate that while multiple inflammatory indices are associated with disease stage on univariate analysis, PLR remained the only inflammatory index independently associated with advanced-stage disease after adjustment.

Table 5. Univariate and Multivariate Regression Analysis

Univariate regression analysis of variables affecting staging				
	Odds ratio	p value	95% CI of Odd's ratio	
Gender	1.055	0.732	0.776	1.435
Tobacco	0.729	0.041	0.539	0.987
Tumor site	0.801	< 0.001	0.708	0.906
Comorbidity	0.828	0.635	0.381	1.803
PLR	1.014	< 0.001	1.011	1.017
PNR	1.023	< 0.001	1.016	1.031
PER	1.001	< 0.001	1.000	1.001
Multivariate regression analysis of variables affecting staging				
Tobacco	0.760	0.116	0.541	1.070
Tumor site	0.794	0.001	0.692	0.912
PLR	1.013	<0.001	1.010	1.017
PNR	1.003	0.420	0.996	1.011
PER	1.000	0.925	0.996	1.011

Discussion

In this large retrospective cohort of 831 treatment-naïve head and neck cancer (HNC) patients, we observed a progressive increase in systemic inflammatory indices (PLR, PNR, PER) with advancing disease stage, especially in metastatic (Stage IVC) disease. These findings indicate a strong association between tumor burden and systemic inflammatory response, suggesting that hematological inflammatory indices are associated with advanced stage disease.

Inflammatory Indices and Disease Stage: Our study demonstrated that PLR and PNR were significantly higher in advanced stages (IVA–IVC) compared to early stages, with the highest values in Stage IVC ($p < 0.001$). This trend mirrors evidence from multiple studies showing that elevated PLR is associated with more aggressive disease and poorer outcomes in HNSC. A recent meta-analysis of pretreatment PLR in HNSCC reported that higher PLR correlated significantly with worse overall survival (HR 1.85; 95% CI 1.23–2.80), supporting a prognostic role for PLR in advanced disease [12]. Another meta-analysis confirmed that elevated PLR is associated with reduced overall survival (pooled HR 1.64; 95% CI 1.13–2.37), reinforcing its significance across diverse HNC cohorts [13]. In addition to PLR, our findings on PNR extend the concept of inflammation in advanced HNC. While fewer studies have specifically evaluated PNR, neutrophil-related ratios such as NLR have been linked to advanced stage and worse outcomes. For example, elevated PLR and NLR were associated with a nearly three-fold increased mortality risk in HNC patients after adjusting for clinical factors, indicating the combined impact of platelet and neutrophil elevations on prognosis [14, 15].

Indian studies further validate the association between inflammatory markers and tumor burden in HNC. A study on oral squamous cell carcinoma (OSCC) reported that preoperative PLR was significantly elevated in cancer cases compared to controls (147.48 ± 61.38 vs. 101.92 ± 36.99; $p < 0.001$), and higher PLR levels were associated with advanced tumor sites and staging [16]. Another Indian cohort found that both PLR and NLR were closely associated with tumor size and stage, suggesting their role in reflecting disease severity in HNC patients [17]. These region-specific observations support the external validity of our findings in an Indian population with a high prevalence of advanced-stage HNC.

The concordance between ROC and regression analyses in this study suggests that PLR is not only capable of differentiating early from advanced disease but also independently reflects disease burden. In contrast, the loss of statistical significance of PNR and PER in the adjusted model indicates that their associations with stage may be influenced by confounding factors or shared inflammatory pathways. Overall, these findings support the relative robustness of PLR as a hematological marker associated with advanced-stage presentation, while the clinical utility of PNR and PER appears limited in comparison.

The relationship between systemic inflammatory indices and cancer stage can be explained by tumor–host interactions. Platelets promote angiogenesis, tumor growth, and metastatic spread through release of pro-tumorigenic cytokines and protection of circulating tumor cells, while lymphocytes are central to antitumor immune surveillance [18, 19, 20]. Thus, higher PLR reflects an imbalance favouring pro-tumorigenic inflammation and diminished immune response, consistent with advanced disease status. Similarly, neutrophils facilitate tumor progression by secreting proteolytic enzymes and cytokines that support

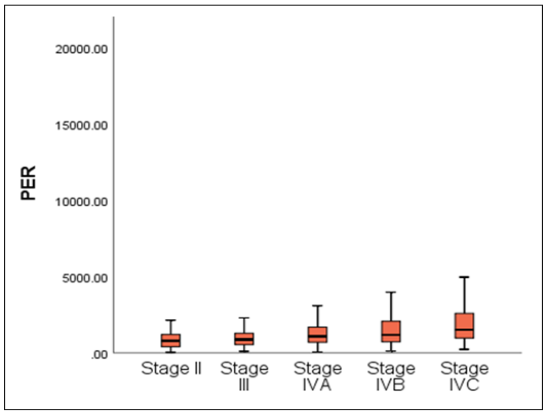

Figure 4. Box-and-Whisker plots illustrate the distribution of the PER and stage. The box denotes the interquartile range (IQR) (25th–75th Percentile), the horizontal line within the box indicates the median, and whiskers extend to values within 1.5 × IQR

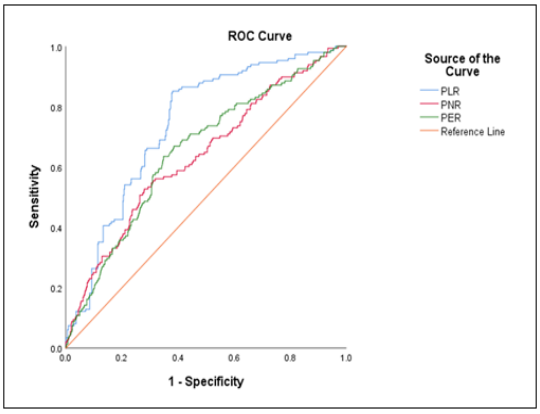

Figure 5. Receiver Operating Characteristic (ROC) Curves comparing the predictive performance of PLR, PNR, and PER for advanced stage HNSCC. The AUC values were 0.741, 0.635, and 0.651, respectively.

invasion and metastasis, explaining the association between PNR and advanced stage [21].

PER, reflecting the balance between platelets and eosinophils, showed the most pronounced stage-wise variation in our study. Although eosinophil-based indices are less studied in HNC, emerging evidence highlights that eosinophils play complex roles in the tumor microenvironment. Eosinophils can exert antitumor cytotoxic effects but also contribute to tumor-promoting inflammation depending on context [22]. In this study, PER demonstrated substantial skewness and wide dispersion, which may limit the stability and interpretability of regression estimates. The observed associations should therefore be considered exploratory. PER demonstrated significant stage-wise variation; however, its independent association with disease stage was not retained after multivariable adjustment. Given the limited and inconsistent evidence regarding eosinophil-based indices in head and neck cancer, these findings should be considered exploratory. The wide variability observed in PER further limits its interpretability, and its biological relevance requires further investigation in prospective studies.

In conclusion, the present study, platelet-based inflammatory indices, particularly PLR, demonstrated a significant association with advanced-stage disease in head and neck cancer. While all three indices (PLR, PNR, and PER) showed stage-wise variation, only PLR retained independent significance after adjustment for confounding variables. These findings suggest that PLR reflects systemic inflammatory burden associated with tumor progression. However, given the observational and retrospective nature of the study, these results should be interpreted as associative rather than indicative of clinical applicability.

Limitations

The present study has several limitations. First, its retrospective design introduces the possibility of selection bias and limits causal inference. Second, although multivariable analysis was performed, residual confounding cannot be excluded, as certain factors such as nutritional status, subclinical infections, inflammatory conditions, and medication use (e.g., corticosteroids) were not systematically accounted for. Third, the inflammatory indices demonstrated markedly skewed distributions, which may influence statistical robustness despite appropriate analytical approaches. Additionally, PER showed substantial variability, and its biological and clinical relevance in head and neck cancer remains insufficiently established. Finally, the absence of survival or outcome data limits assessment of prognostic significance. Prospective studies are required to validate these findings.

Declarations

Funding

Study was non funded.

Clinical trial registration

Not applicable.

Conflicts of interest

Authors declare that they have no conflicts of interest.

Availability of data and material

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Code availability

The custom code was used during analysis is available on request.

Authors' contributions

PS – contributed on concept, study design, manuscript preparation, data curation, and primary drafting of the study. DS – contributed in design, manuscript preparation, data collection, analysis, manuscript revision. All authors approved the final version of the submission.

Ethics approval

The local Ethics Committee of All India Institute of Medical Sciences, Patna waived ethical approval in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Consent

Not applicable.

Consent for publication

Not applicable.

Originality declaration for figures

All the figures included in this manuscript are original and have been created by the authors specifically for the purpose of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research.

Acknowledgments

The nursing staff, office staff the department of Radiotherapy, AIIMS Patna, whose invaluable assistance and compassionate care greatly supported this research project.

Declaration on generative AI and AI-assisted technologies in the writing process

No AI tool was used in this manuscript preparation.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021 05;71(3):209-249. https://doi.org/10.3322/caac.21660
2. https://gco.iarc.who.int/media/globocan/factsheets/populations/356-india-fact-sheet.pdf (accessed on February 2024)..
3. Singh K, Grover A, Dhanasekaran K. Unveiling the cancer epidemic in India: a glimpse into GLOBOCAN 2022 and past patterns. The Lancet Regional Health. Southeast Asia. 2025 03;34:100546. https://doi.org/10.1016/j.lansea.2025.100546
4. Mehrotra R, Yadav S. Oral squamous cell carcinoma: etiology, pathogenesis and prognostic value of genomic alterations. Indian J Cancer. 2006;43(2):60-6. https://doi.org/10.4103/0019-509x.25886
5. Mallath M, Taylor D, Badwe R, Rath G. The growing burden of cancer in India: epidemiology and social context. Lancet Oncol. 2014 05 15;. https://doi.org/10.1016/S1470-2045(14)70115-9.
6. Hanahan D, Weinberg R. Hallmarks of cancer: the next generation. Cell. 2011;4;144(5):646-74. https://doi.org/10.1016/j.cell.2011.02.013.
7. Templeton A, Ace O, McNamara M. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014 07 23;. https://doi.org/10.1158/1055-9965.
8. Verrico M. Role of neutrophil-to-lymphocyte, platelet-to-lymphocyte and myelocite-to-lymphocyte ratio as prognostic markers for immunotherapy response in patients with advanced solid tumors, a retrospective analysis from a single institution. J Clin Oncol. 2022;40:14529– 14529 . https://doi.org/10.1200/JCO.2022.40.16_suppl.e14529.
9. Grisaru-Tal S, Rothenberg M, Munitz A. Eosinophil-lymphocyte interactions in the tumor microenvironment and cancer immunotherapy. Nat Immunol. 2022;23(9):1309-1316. https://doi.org/10.1038/s41590-022-01291-2.
10. Abelardo E, Davies G, Kamhieh Y, Prabhu V. Are Inflammatory Markers Significant Prognostic Factors for Head and Neck Cancer Patients?. ORL; Journal for Oto-rhino-laryngology and its Related Specialties. 2020;82(5):235–244. https://doi.org/10.1159/000507027
11. Amin M, Greene F, Edge S, Compton C, Gershenwald J, Brookland R, Meyer L, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017 03 02;. https://doi.org/10.3322/caac.21388.
12. Diana R, Pierluigi M, Dardo M, Claudia A. The prognostic role of pre-treatment platelet-to-lymphocyte ratio in head and neck squamous cell carcinoma: meta-analysis and trial sequential analysis. J Evid Based Dent Pract. 2023;23(4):101898. https://doi.org/10.1016/j.jebdp.2023.101898.
13. Gu X, Gao X, Qin S, Li X. Elevated Platelet to Lymphocyte Ratio Is Associated with Poor Survival Outcomes in Patients with Colorectal Cancer. PLoS One. 2016 09 22. https://doi.org/10.1371/journal.pone.0163523.
14. Takenaka Y, Oya R, Kitamiura T. Platelet count and platelet-lymphocyte ratio as prognostic markers for head and neck squamous cell carcinoma: Meta-analysis. Head Neck. 2018;Dec;40(12):2714-2723. https://doi.org/10.1002/hed.25366.
15. Sharma R, Kalsotra G, Mahajan D, Kalsotra P, Raj D. Prognostic Significance of Pre-Treatment Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Head and Neck Malignancies. Indian J Otolaryngol Head Neck Surg. 2024;76(1):567-574. https://doi.org/10.1007/s12070-023-04213-2.
16. Uniyal A, Urs AB, Augustine J. Is assessment of platelet-lymphocyte ratio and neutrophil-lymphocyte ratio a predictor for lymph node metastasis in oral squamous cell carcinoma. Indian Journal of Cancer. 2024 07;61(3):516–522. https://doi.org/10.4103/ijc.IJC_562_20
17. Kumarasamy C, Tiwary V, Sunil K, Suresh D. Prognostic Utility of Platelet-Lymphocyte Ratio, Neutrophil-Lymphocyte Ratio and Monocyte-Lymphocyte Ratio in Head and Neck Cancers: A Detailed PRISMA Compliant Systematic Review and Meta-Analysis. Cancers (Basel. 2021 08 19;. https://doi.org/10.3390/cancers13164166.
18. Nishida A, Andoh A. The Role of Inflammation in Cancer: Mechanisms of Tumor Initiation, Progression, and Metastasis. Cells. 2025 03 25. https://doi.org/10.3390/cells14070488.
19. Aguilar-Cazares D, Chavez-Dominguez R, Marroquin-Muciño M, Perez-Medina M. The systemic-level repercussions of cancer-associated inflammation mediators produced in the tumor microenvironment. Front Endocrinol (Lausanne. 2022 08 22. https://doi.org/10.3389/fendo.2022.929572.
20. Liao K, Zhang X, Liu J. The role of platelets in the regulation of tumor growth and metastasis: the mechanisms and targeted therapy. MedComm. 2023;:4 350. https://doi.org/10.1002/mco2.350
21. Shen Y, Wang J, Hua Q, Dong M. The Predictive Value of NLR, PLR, LMR, NPAR and D-Dimer on the Efficacy and Prognosis of First-Line Immunotherapy for Extensive-Stage

Small Cell Lung Cancer. J Inflamm Res. 2025 Dec 10. https://doi.org/10.2147/JIR.S557312.
22. Ghaffari S, Rezaei N. Eosinophils in the tumor microenvironment: implications for cancer immunotherapy. J Transl Med. 2023 08;16;21(1):551. https://doi.org/10.1186/s12967-023-04418-7.