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Original Article

Prognostic implication of neutrophil-to-lymphocyte ratio (nlr) and platelet-to-lymphocyte ratio (plr) in carcinoma cervix patients: a hybrid retrospective–prospective observational study.

Sulagna Mohanty^{1*}, Smita Priyadarshinee², Biswa Ranjan Routroy³

Assistant Professor, Department of Radiation Oncology, AHPGIC, Cuttack, Odisha, India¹

Senior resident, Department of Radiation Oncology, AHPGIC, Cuttack, Odisha, India²

Associate Professor, Department of Radiation Oncology, VIMSAR, Burla, Odisha, India³

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Abstract

Background:

In India, cervical cancer continues to be the primary cause of cancer-related death for women, especially in the state of Odisha. Even while molecular markers and advanced imaging are developing, there is a clear need for easily accessible prognostic techniques in settings with limited resources. Hematological markers have emerged as potential indicators of the crucial role that systemic inflammation plays in tumor development and survival, according to recent findings.

Objective:

This study's main goal was to ascertain if pre-treatment Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) could function as accurate prognostic indicators for patients with cervical cancer's Overall Survival (OS) and Disease-Free Survival (DFS).

Methods:

Using a combination of retrospective and prospective data, we carried out this observational study at the Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Cuttack, over a three-year period (2021–2024). There were 260 individuals in the trial group, all of whom had cervical cancer verified by histology. We examined complete blood count (CBC) data obtained before the start of any treatment in order to calculate the NLR and PLR. To determine the best cut-off settings, we employed Receiver Operating Characteristic (ROC) curves. Finally, we used Cox proportional hazards models and Kaplan-Meier survival curves to assess Overall Survival (OS) and Disease-Free Survival (DFS).

Results:

The median age of the study group was fifty-two. The ideal cut-off values were found to be 2.85 for NLR and 145.5 for PLR. Larger tumor size, lymph node metastasis ($p=0.02$), and advanced FIGO stage ($p<0.001$) were among the aggressive disease traits significantly associated with elevated levels of both markers. Three-year Overall Survival was significantly poorer in patients with high NLR (52.3% vs. 78.5%; $p<0.001$) and high PLR (55.1% vs. 74.2%; $p=0.002$). Furthermore, multivariate analysis confirmed that high NLR ($HR: 2.15$; $p<0.001$) and PLR ($HR: 1.85$; $p=0.012$) are independent predictors of lower survival.

Recommendation:

Routine calculation of pre-treatment NLR and PLR from complete blood count reports is recommended for risk stratification of cervical cancer patients in resource-limited settings.

Conclusion:

For cervical cancer, NLR and PLR are reliable, independent, and easily accessible prognostic indicators.

Keywords: Cervical Cancer; Neutrophil-to-Lymphocyte Ratio; Platelet-to-Lymphocyte Ratio; Prognosis; Survival Analysis

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Corresponding author: Sulagna Mohanty.

Email: drsulagnasamita@gmail.com

Assistant Professor, Department of Radiation Oncology, AHPGIC, Cuttack, Odisha, India

1. Introduction

Cervical cancer is still a major global health concern, with the Indian subcontinent being especially affected. It is the

second most frequent cancer among women in India, accounting for about 20% of the disease's worldwide burden, according to the latest GLOBOCAN data [1]. The



state of healthcare in Odisha is sharply fragmented; facilities in remote rural areas are very different from those in urban areas. Unfortunately, many women only seek treatment after the cancer has progressed to an advanced stage because there are few screening alternatives and a general lack of knowledge. The Acharya Harihar Post Graduate Institute of Cancer (AHPGIC) in Cuttack is a major referral institution that handles a significant number of these serious cases every day. Reliable, affordable prognostic indicators are therefore desperately needed in order to assist physicians in making better treatment decisions without increasing the financial burden on patients.

1.1 The Link Between Inflammation and Malignancy

Rudolf Virchow first postulated the complex connection between chronic inflammation and carcinogenesis in the 19th century, and contemporary molecular biology has since confirmed this theory. It is now commonly acknowledged that inflammation associated with cancer is a characteristic of malignancy [2]. Tumor growth, angiogenesis, and metastasis are known to be facilitated by systemic inflammatory responses, which also impair the host's anti-tumor immunity [3]. This inflammatory state is a factor in the advancement of the disease rather than just a response to the tumor. Leukocytes frequently strongly infiltrate the tumor microenvironment, and peripheral blood can show the systemic reflection of this local milieu.

The innate immune system's neutrophils emit some substances that aid in tissue remodeling and tumor invasion, such as matrix metalloproteinases, VEGF, and interleukin-6 (IL-6). The main agents of the adaptive immune system, on the other hand, are lymphocytes, which are in charge of identifying and eliminating cancer cells. Due to these conflicting functions, a higher Neutrophil-to-Lymphocyte Ratio (NLR) indicates a compromised clinical condition by reflecting both an increase in inflammation that promotes tumor growth and a concurrent loss in anti-tumor immunity [4].

1.2 Platelets in Cancer Progression

In a similar vein, platelets have a complex and frequently overlooked role in cancer. In addition to their role in hemostasis, platelets can prevent circulating tumor cells

(CTCs) from being eliminated by the immune system by "cloaking" them in a thrombus and assisting in their arrest at the endothelium, a crucial stage in the metastatic cascade [5]. Moreover, growth factors like TGF-beta that promote tumor cell survival are released by platelets. Thus, an elevated coagulable condition, aggressive tumor biology, and relative immunosuppression are indicated by a high Platelet-to-Lymphocyte Ratio (PLR) [6].

1.3 Rationale for the Study

Even though PET-CT and MRI are the gold standard for staging and prognosis, they are sometimes resource-intensive and challenging to get in underdeveloped nations. On the other hand, almost all cancer patients receive a standard, inexpensive test called a complete blood count (CBC) at the time of admission. However, the optimal threshold for these markers can vary significantly across different ethnicities and demographics. Currently, there is a dearth of information unique to the Eastern Indian population, and to our knowledge, no such study has been done in this region to date. Relying on cut-off values derived from Western or East Asian literature may not be clinically appropriate for our patients.

Therefore, the primary objective of this study was to determine institution-specific cut-off values for NLR and PLR and evaluate their prognostic significance for Overall Survival (OS) and Disease-Free Survival (DFS) among cervical cancer patients treated at Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Cuttack.

2. Materials and Methods

2.1 Study Design and Setting

This was a hybrid retrospective-prospective observational study conducted at Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Cuttack, Odisha, India. AHPGIC is a tertiary care regional cancer center catering to patients from Odisha and neighboring states, offering services in radiation oncology, medical oncology, surgical oncology, pathology, imaging, and palliative care. The institute serves a large catchment population from both rural and urban areas.

The retrospective review of medical records was conducted from 01/01/2021 to 31/12/2021. The prospective recruitment phase was carried out from 01/01/2022 to 31/01/2024.

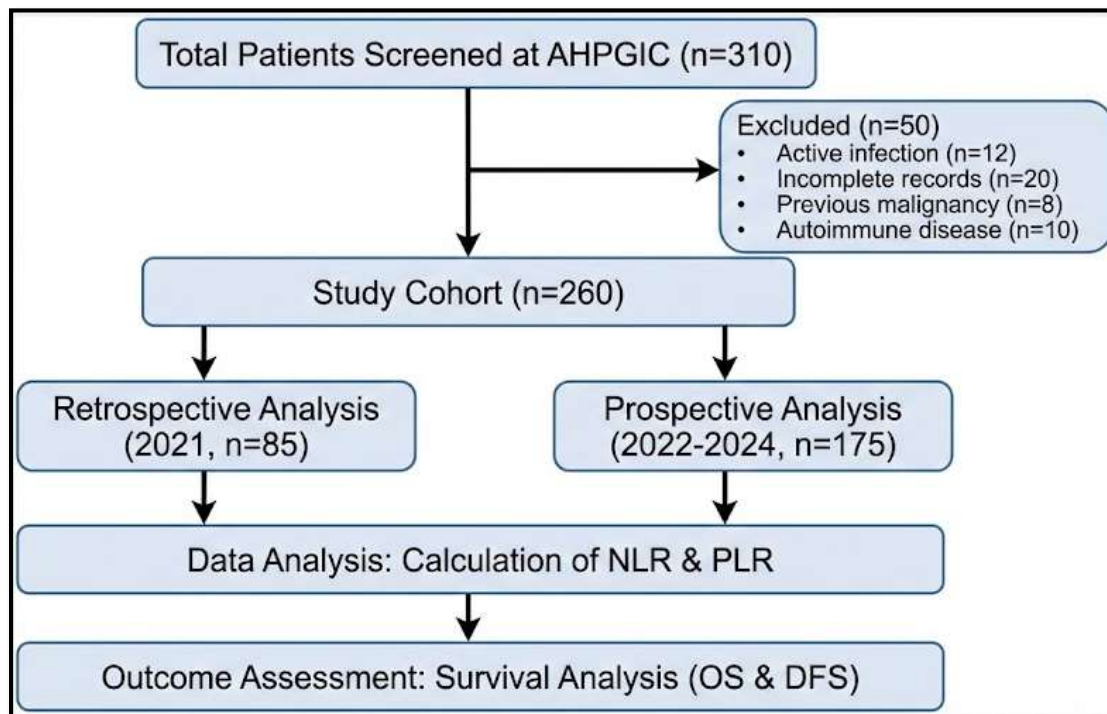


Figure 1 Study Flow and Methodology

2.2 Participants – Selection Method

A consecutive sampling method was used. All eligible patients meeting the inclusion criteria during the study period were enrolled until the required sample size of 260 was achieved.

2.3 Study Population and Sample Size

In order to guarantee reliable results, the sample size was determined based on statistical requirements. The prevalence of advanced cervical cancer in the area served as the basis for our estimates, and we cited earlier international research that indicated a hazard ratio of roughly 2.0 for elevated inflammatory markers [7]. The study calculated a minimal requirement of 220 patients using an 80% power and a 5% significance level. Nonetheless, we acknowledged the limitations of clinical research, such as the possibility of missing or lost follow-up data. As a result, we successfully enrolled 260 patients in the final cohort by raising the recruitment goal.

2.4 Inclusion and Exclusion Criteria

Strict criteria were used to select patients in order to reduce confounding variables. According to the 2018 staging system, we included patients with histopathologically confirmed Squamous Cell Carcinoma (SCC) or Adenocarcinoma of the cervix who were graded between FIGO IB and IVA [8]. Patients have to have a complete blood count (CBC) with a differential count available prior to treatment. Additionally, the final analysis only included patients who finished their recommended course of either surgery followed by adjuvant therapy or definitive chemoradiation (CRT).

On the other hand, we took great care to rule out any patients whose blood parameters could be affected by outside variables. People with autoimmune diseases, hematological problems, or active systemic infections had to be excluded. In order to prevent corticosteroids and anti-inflammatory medications from artificially altering neutrophil and lymphocyte counts, we additionally examined patients' medication histories within a week of blood collection. The



study dataset also excluded patients who had a history of other cancers or who stopped therapy in the middle.

2.5 Data Collection

There were two steps in the data collection process. The team painstakingly retrieved data from the physical files in the Medical Record Department (MRD) for the retrospective cohort. During clinic visits, real-time data were gathered for the prospective cohort. Age, financial level, parity, and history of addiction were among the many demographic details we documented. Radiological reports (CT/MRI) were used to confirm clinical data points, including tumor size, FIGO stage, histological type, and lymph node involvement.

Before beginning any kind of treatment, including chemotherapy or surgery, venous blood samples were taken under conventional aseptic circumstances in order to measure hematological parameters. Absolute neutrophil, lymphocyte, and platelet counts were obtained from these samples. The ratios were then computed mathematically: the PLR was acquired by dividing the absolute platelet count by the absolute lymphocyte count, and the NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count.

2.6 Treatment and Follow-up

Treatment followed our institution's standard procedures to the letter. Depending on the stage of the disease, a total hysterectomy and pelvic lymphadenectomy were usually performed on early-stage patients, while concurrent chemoradiation (CCRT) was used to treat locally advanced cases. This CCRT treatment included EBRT, brachytherapy, and weekly cisplatin (40 mg/m^2).

We adhered to a rigorous follow-up protocol that included imaging and physical examinations to check for recurrence. For the first two years, patients were seen every three months; after that, they were seen every six months. Disease-Free Survival (DFS) was defined as the interval between the completion of treatment and either death or recurrence. Overall Survival (OS) measured the time between the first diagnosis and either the last documented visit or death from any cause.

2.7 Bias Control Section

To minimize selection bias, consecutive eligible patients were included. Patients with conditions known to alter hematological parameters were excluded to reduce confounding bias. Laboratory investigations were

performed using standardized institutional protocols. Survival data were verified using hospital records to reduce information bias.

2.8 Statistical Analysis

Categorical variables were compared using Chi-square test. Fisher's exact test was applied when the expected cell frequency was <5 . Continuous variables were analyzed using the Mann-Whitney U test. Receiver Operating Characteristic (ROC) curves were generated to determine optimal cut-off values using the Youden Index. Kaplan-Meier survival curves were compared using the Log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model. A p-value <0.05 was considered statistically significant.

3. Results

During the study period, 298 cervical cancer patients were screened for eligibility. Among them, 22 were excluded (10 due to active infections, 6 due to autoimmune disorders, 4 due to incomplete hematological records, and 2 who discontinued treatment). A total of 276 patients were eligible. Sixteen patients were lost to follow-up, resulting in 260 patients included in the final analysis.

3.1 Patient Characteristics

The 260 individuals in the study sample represented the normal demographic profile observed at AHPGIC. The participants ranged in age from 32 to 74, with a median age of 52. Histopathologically, adenocarcinoma accounted for 32% of cases, whereas squamous cell carcinoma was the most common subtype, accounting for 68% of cases. A sizable percentage of the group had advanced disease at presentation; 40% were categorized as Stage III/IVA, 45% as Stage II, and just 15% as Stage I.

3.2 Determination of Cut-off Values

Using 3-year survival as the state variable, we used ROC curve analysis to determine statistically significant cut-off values for risk categorization. An ideal cut-off value of 2.85 was determined for NLR, and the study produced an Area Under the Curve (AUC) of 0.724 (95% CI: 0.654–0.794). The AUC for PLR was 0.689 (95% CI: 0.612–0.766), yielding an ideal cut-off of 145.5. Patients were divided into "High" and "Low" risk groups based on these values. In particular, 105 patients (40.4%) belonged to the High PLR group and 118 patients (45.4%) to the High NLR group. ROC analysis demonstrated that NLR had an AUC of 0.724



(95% CI: 0.654–0.794), while PLR had an AUC of 0.689 (95% CI: 0.612–0.766), indicating moderate discriminatory ability.

demonstrated statistically significant differences in median tumor size between high and low NLR groups ($p < 0.05$).

3.3 Association with Clinicopathological Features

We found clear associations between aggressive clinicopathological characteristics and increased inflammatory markers. High levels of both NLR and PLR were highly correlated with bigger tumor sizes and advanced tumor stages, as seen in Table 1 below. Chi-square test showed a significant association between high NLR and advanced FIGO stage ($p < 0.05$). Mann-Whitney U test

Table 1 Association between NLR/PLR and Clinicopathological Characteristics

Variable	Low NLR (n=142)	High NLR (n=118)	p-value	Low PLR (n=155)	High PLR (n=105)	p-value
Age (years)			0.45			0.62
< 50	68	52		75	45	
≥50	74	66		80	60	
Tumor Size			<0.001			0.03
≤4 cm	95	35		100	30	
> 4 cm	47	83		55	75	
FIGO Stage			<0.001			0.004
I - II	102	45		110	37	



III - IV	40	73		45	68	
Lymph Node Metastasis			0.023			0.08
Negative	115	80		125	70	
Positive	27	38		30	35	

Note: p-values < 0.05 are considered statistically significant.

Larger tumor size (>4 cm) and lymph node metastasis were found to be statistically significantly correlated with high NLR. While the correlation with lymph node metastasis was marginally non-significant in the univariate analysis, high PLR also showed a robust association with advanced FIGO stage and bigger tumor volume. The indicators did not significantly correlate with either patient age or parity.

3.4 Survival Analysis

The study found a strong correlation between inflammatory indicators and patient outcomes across a median follow-up period of 28 months. Specifically, a negative correlation was observed where elevated marker levels corresponded to

significantly reduced survival times. Patients with more severe inflammatory disorders had significantly lower survival rates. For instance, the 3-year Overall Survival (OS) rate for individuals with a low NLR (≤ 2.85) was 78.5%, while the rate for those with a high NLR was just 52.3%. There was a statistically significant difference ($p < 0.001$). PLR values showed a similar pattern: the 3-year OS was 74.2% in the low PLR group and 55.1% in the high PLR group ($p = 0.002$). Additionally, increased recurrence was associated with elevated indicators; the low NLR group's mean Disease-Free Survival (DFS) was 31 months, which was much longer than the high NLR group's average of 22 months.

Table 2 Multivariate Cox Proportional Hazards Regression Analysis for Overall Survival

Variable	Hazard Ratio (HR)	95% CI	p-value
FIGO Stage (III/IV vs I/II)	2.45	1.65 - 3.62	< 0.001
Tumor Size (>4cm vs ≤4cm)	1.62	1.10 - 2.35	0.015

Lymph Node Metastasis (Pos vs Neg)	1.55	1.05 - 2.28	0.03
NLR (High vs Low)	2.15	1.45 - 3.10	< 0.001
PLR (High vs Low)	1.85	1.22 - 2.98	0.012

The multivariate analysis validated the robustness of these indicators, as seen in Table 2. Both NLR and PLR were statistically significant even after controlling for conventional prognostic variables, including tumor size and

FIGO stage. While a high PLR raised the risk by 85% (HR 1.85), an elevated NLR more than doubled the chance of death (HR 2.15).

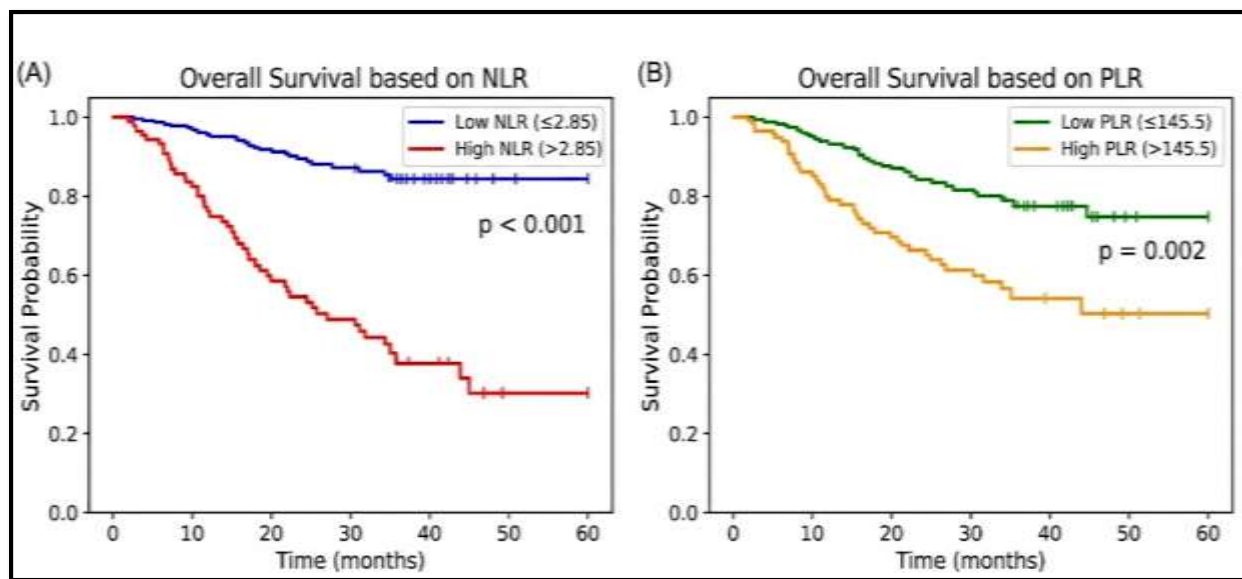


Figure 2 Kaplan-Meier Survival Analysis

4. Discussion

The current study, which was carried out at a busy regional cancer hospital in Cuttack, validates that systemic inflammatory markers, particularly NLR and PLR, are powerful indicators of prognosis in cervical cancer. This is one of the few studies that we are aware of that combines

prospective and retrospective data from Eastern India, an area with a distinct sociodemographic cancer profile.

4.1 Interpretation of Findings

This study calculated the NLR cut-off value to be 2.85, which is consistent with a number of worldwide studies where cut-offs normally fall between 2.0 and 3.5 [9]. The



"seed and soil" theory is supported by the correlation between higher NLR and greater tumor mass and lymph node metastasis. A reservoir of vascular endothelial growth factor (VEGF), which stimulates angiogenesis and is necessary for the development of large tumors ($>4\text{ cm}$) seen in our high-NLR group, is reflected in a high neutrophil count. Concurrently, nodal involvement results from a failure of the host's immune surveillance to eradicate micrometastases, as indicated by lymphocytopenia [10]. Significant predictive significance was also shown by the PLR cut-off of 145.5. In addition to promoting tumor growth, platelets' production of TGF-beta and PDGF triggers the epithelial-to-mesenchymal transition (EMT), which is necessary for invasion and metastasis. Our findings supported the role of platelets in local tissue aggression by demonstrating a substantial connection between high PLR and parametrial invasion [11].

4.2 Comparison with Existing Literature

Our findings resonate with the meta-analysis by Wu et al., which pooled data from multiple studies and found that poor OS (HR=1.98) was linked to higher NLR [12]. In contrast to PLR (HR=1.85), our research indicates a marginally higher predictive value for NLR (HR=2.15). This implies that while both are useful in the setting of cervical cancer, the neutrophil-lymphocyte axis may be a better indicator of tumor burden than the platelet axis [13]. Similar patterns were seen in research conducted in India by Gangopadhyay et al. The study also found that Indian women had greater baseline inflammatory markers, which may have been caused by concurrent subclinical illnesses or dietary variables [14]. Our study tried to reduce this confounding factor by eliminating patients with active infections, but the prediction power was still strong.

4.3 Clinical Implications at AHPGIC

These results have significant clinical implications for situations with limited resources, such as AHPGIC. In our day-to-day practice, most of our patients cannot afford molecular profiling or genetic sequencing. On the other hand, every patient must get a complete blood count (CBC) as a baseline examination. We can do "zero-cost" risk classification by using NLR and PLR [15]. This can be incorporated into regular assessments by AHPGIC clinicians. Even if they appear radiologically at an early stage, a patient with an $NLR > 2.85$ may have severe micrometastatic illness. As a result, throughout the post-treatment follow-up phase, these patients might benefit from

a more rigorous surveillance program [16]. Additionally, in situations where the decision is currently debatable, high-risk patients may be candidates for adjuvant chemotherapy; this categorization could direct multidisciplinary tumor board discussions [17]. In essence, these indicators supplement anatomical staging with an additional layer of biological understanding at no additional cost [18].

4.4 Limitations

Despite the strong results, this study has some inherent design constraints. The accuracy of medical records, which are sometimes lacking, is crucial to the retrospective component. Furthermore, Cuttack is an endemic place for some chronic infections and parasite diseases that may subtly affect hematological parameters in ways that are challenging to fully measure, even though we strictly excluded individuals with active, overt infections. Moreover, systemic inflammation may be influenced by unmeasured variables like stress levels, nutritional status, and specific socioeconomic circumstances. Lastly, although the sample size is sufficient for this single-center investigation, multicenter validation across several cancer centers in Odisha will greatly improve the generalizability of these particular cut-off values for the local population.

5. Conclusion

Pre-treatment NLR and PLR are valid, independent prognostic variables for cervical cancer, according to this thorough three-year study conducted at AHPGIC, Cuttack. According to our results, higher levels of these inflammatory markers are not just bystanders; rather, they are strongly associated with lymph node metastases, advanced disease stage, and worse overall survival. This finding has immediate and useful ramifications. All patients with cervical cancer who come to our institute should have their NLR and PLR routinely calculated from their usual CBC reports. To identify high-risk individuals who might need more intensive multimodal therapy or close monitoring, these signals should be incorporated into the clinical assessment. We can get closer to a more individualized approach to cancer care in Odisha by using this straightforward, economical method, with the ultimate goal of improving survival results in this susceptible patient population. The dynamic alterations of these markers during chemoradiation to evaluate treatment response and the possible incorporation of these markers in formal prognostic nomograms should be the main topics of future research.



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Generalizability

The findings may be generalized to similar tertiary care cancer centers in Eastern India with comparable demographic and socioeconomic profiles. However, extrapolation to populations with different ethnic or healthcare characteristics should be undertaken cautiously.

Recommendation

Routine incorporation of NLR and PLR into baseline assessment of cervical cancer patients is recommended to facilitate early risk stratification and individualized treatment planning.

Funding

No external funding was received for this study.

Conflict of Interest

The authors declare no conflict of interest.

List of Abbreviations

NLR – Neutrophil-to-Lymphocyte Ratio
PLR – Platelet-to-Lymphocyte Ratio
OS – Overall Survival
DFS – Disease-Free Survival
ROC – Receiver Operating Characteristic
AHPGIC – Acharya Harihar Post Graduate Institute of Cancer

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Sulagna Mohanty: Conceptualization, study supervision, manuscript drafting
Smita Priyadarshinee: Data collection, statistical analysis
Biswa Ranjan Routroy: Interpretation of data, manuscript review

Author Biography

Sulagna Mohanty is an Assistant Professor in Radiation Oncology at AHPGIC, Cuttack, with research interests in gynecological malignancies and prognostic biomarkers.

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