

**PREDICTIVE VALUE OF PRETREATMENT HAEMATOLOGICAL MARKERS IN
CERVICAL CANCER IN A THIRD LEVEL HEALTH INSTITUTION**

ABSTRACT

Background: Inflammatory biomarker measurement is a low-cost method of identifying patients with advance disease, and the risk of recurrence after treatment.

Objectives: To investigate if the pretreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used in predicting the stage of cervical cancer.

Material and Methods: A cross-sectional analysis of seventy-eight women newly diagnosed with cervical cancer managed at the University of Port Harcourt Teaching Hospital between January 1, 2019, and December 31, 2022. A data collection form was used to collect socio-demographic and clinical characteristics from the patients after informed consent was obtained. Blood samples were collected and used to determine the pretreatment levels of NLR and PLR. The Receiver Operating Characteristic (ROC) curve was used to assess the predictive accuracy of the different haematological parameters for late-stage cervical cancer.

Results: PLR was significantly higher in advanced-stage cancer ($p = 0.041$). There was no statistically significant strong positive correlation between NLR ($r = 0.195$) and PLR (0.078) with cervical cancer staging ($p > 0.05$). None of the haematological parameters could be used as predictive markers for advanced-stage cervical cancer.

Conclusion: Pretreatment NLR and PLR did not predict the stage of cervical cancer in this study.

Keywords: Cervical cancer, Neutrophil-to-Lymphocyte ratio, Platelet-to-Lymphocyte ratio, Predictive value, Port Harcourt

1. INTRODUCTION

Cervical cancer is an important public health issue especially in low-and middle-income countries, yet largely preventable [1,2]. It is the fourth most common cancer in women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020 [3]. Cervical cancer incidence and mortality rates vary widely by geographic region [4,5]. The highest incidence rates are found in sub-Saharan Africa, followed by Latin America and the Caribbean, and Southeast Asia. The lowest rates are found in North America, Western Europe, and Australia [6,7,8].

Many studies in recent years have shown that systemic inflammatory responses play a role in cancer patient prognosis [9]. Inflammation influences every stage of cancer development, from tumour formation to progression and metastasis [10].

Changes in the microenvironment are caused by the host's response to malignant tumours that cause systemic alterations. Several studies have shown that systemic inflammation plays a role in cancer progression at multiple stages, including initiation, promotion, invasion, and metastasis [10]. Systemic inflammation can be detected in a complete blood count (CBC) as neutrophilia, thrombocytopenia, and relative lymphocytopenia [10]. Routine laboratory tests for haematological biomarkers are easily accessible and inexpensive.

Many studies have shown that there is an association between several inflammatory markers in the peripheral blood, such as neutrophil count, lymphocyte count, thrombocyte, and C-reactive protein, and the prognosis of various cancers [11,12].

Cervical cancer haematological markers are important predictors because they may be helpful in early detection, monitoring, and prognosis. Individuals at risk of cervical cancer should have regular screening tests, including haematological markers, to detect the disease early and improve their chances of treatment success [13,14].

Neutrophils and platelets provide angiogenic, epithelial, and stromal growth factors, as well as matrix-remodeling enzymes, which are required for neoplastic progression [10,15]. Furthermore, an imbalance in the innate and adaptive immune systems, as evidenced by lymphocytopenia and an impaired T lymphocytic response, reduces the effectiveness of host-tumor immune responses [16]. Neutrophils, platelets, and lymphocytes may be involved in the progression of cancer. The progression of cancers to the advanced stage is characterized by neutrophilia, thrombocytosis, and lymphocytopenia. As a result, the combination of lymphocytes, neutrophils, and platelets has been studied as an independent prognostic factor in the progression of cancer [17].

Neutrophils and lymphocytes are the main elements of the tumour-related stroma that are linked to local inflammation and immune responses as well as reflect the balance between pro- and anti-tumour status [18,19]. Furthermore, IL-1, IL-2, and IL-6 are the main pro-inflammatory mediators that indirectly correlate with an elevated platelet count to indicate the severity of inflammation in cancer.

The most frequently studied parameters are neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Several studies have found that an increased peripheral neutrophil-to-lymphocyte ratio (NLR) is a poor prognostic indicator in various cancers [20]. PLR has also been linked to a poor outcome in various malignant tumours [20,21].

Pre-treatment NLR and PLR values have been shown to be predictive and prognostic in patients with cervical cancer [7,22-30]. Han et al. discovered that a high NLR was an independent predictor of poor overall survival in patients with cervical cancer [30]. Similarly, Long et al. observed that having a high PLR was associated with a lower progression free survival (PFS) and overall survival (OS) in cervical cancer patients [31]. However, the use of NLR and PLR as predictive markers in cervical cancer has not yielded a consistent conclusion. The findings from these studies are contradictory, and the prognostic significance of NLR and PLR in cervical cancer remains unknown [1,2,28]. As a result, the study sought to investigate NLR and PLR as haematological markers for predicting the stage of cervical cancer.

2. MATERIAL AND METHODS

2.1 Study Population

This cross-sectional study included 78 patients with newly diagnosed clinical stage IB to IVA cervical cancer who were managed at the University of Port Harcourt Teaching Hospital between January 1, 2019, and December 31, 2022, according to the 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system. Squamous cell carcinoma (SCC), adenocarcinoma, and adenosquamous carcinoma of the uterine cervix were histologically confirmed in all patients. After obtaining informed consent, the patients' information was collected using a data collection tool and data was entered in a sequential order. Patients' baseline characteristics, laboratory results, and pathology reports were all included in the data. Each participant was assigned a unique identity to ensure anonymity and ease of identification. The data collection tools were checked daily for accuracy and completeness. Patients with early cervical cancer with microscopic lesions (IA1 and IA2), as well as those with concurrent haematologic or infectious diseases, were excluded from this study.

2.2 Pretreatment Assessment and Analysis of Inflammatory Markers

At the time of admission, all patients underwent physical and gynaecological pelvic examinations. LN involvement and distant metastasis were assessed using pelvic MRI (Magnetic Resonance Imaging) and/or CT (Computed Tomography). The initial complete blood count was performed prior to the start of treatment at the time of admission. Absolute white blood cell (WBC) counts (AWC), absolute lymphocyte counts (ALC), absolute neutrophil counts (ANC), absolute monocyte counts (AMC), and absolute platelet counts (ACP) were among the haematological parameters measured. PLR was calculated by dividing the absolute platelet count (APC) by the absolute lymphocyte count (ALC). NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC). Thereafter, the patients all had examination under anaesthesia, staging, and biopsy to determine the clinical stage of the disease. The biopsy specimen was sent to the histopathologist to determine the histological type, depth of invasion and grading of the tumour.

2.3 Data Analysis

The data was summarized using mean and standard deviation as appropriate. Spearman Rank correlation was used to assess the correlation between stage of cervical cancer and NLR, PLR, BLR, and MLR. The discriminative role and cut-off values of NLR, PLR, BLR, and MLR were determined using Receiver Operating Curve (ROC) analysis with Area under the Curve (AUC). The cut-off values were used to determine the sensitivity and specificity of each haematological parameter. The p-value was set at 0.05 for statistical significance, and data analysis was done using SPSS version 25 at 95% confidence interval.

2.4 Ethical Consideration

The research and ethics committee of the University of Port Harcourt Teaching Hospital granted ethical approval for the study. Prior to their inclusion in the study, participants provided written informed consent. Personal identifying information was kept confidential.

3. RESULTS

The mean age of the patients was 57.21 ± 12.39 years. There was no significant difference found in age between the advanced stage group II (56.1 ± 12.7), III (57.3 ± 12.6), and IV (57.2 ± 12.34) using One-Way Anova. Haematological parameters such as PLR was significantly higher in the advanced-stage cancer groups compared to the early-stage group ($p = 0.041$) using the non-parametric Kruskal Wallis test. In contrast, NLR, BLR, and MLR were not different (Table 1). Partial correlation was used to analyze the correlation between blood parameters (NLR, PLR, BLR, and MLR) against the staging of cervical cancer by controlling age and parity. There was no statistically significant strong positive correlation between NLR ($r = 0.195$), PLR ($r = 0.078$), BLR ($r = 0.154$), MLR ($r = 0.188$), and with cervical cancer staging ($p > 0.05$). These findings illustrate that the increase in NLR, PLR, BLR, and MLR had only a mild positive correlation to the stage of cervical cancer. This is shown in Table 2.

Predictive models were performed through ROC curve analysis on NLR, PLR, BLR, and MLR parameters against advanced stage of cervical cancer as shown in figure 1. NLR has a sensitivity value of 81% and specificity of 82% with a cut-off value of 1.38. PLR has a sensitivity of 88% and specificity of 94% with a cutoff value of 3.91 (Table 3). However, none of the parameters was feasible to be used as a predictive model because they have an area under the curve (AUC) of less than < 0.7 . This means that there is less than a 70% chance of the model classifying patients correctly in this study.

Table 1: Patients Haematological Parameters

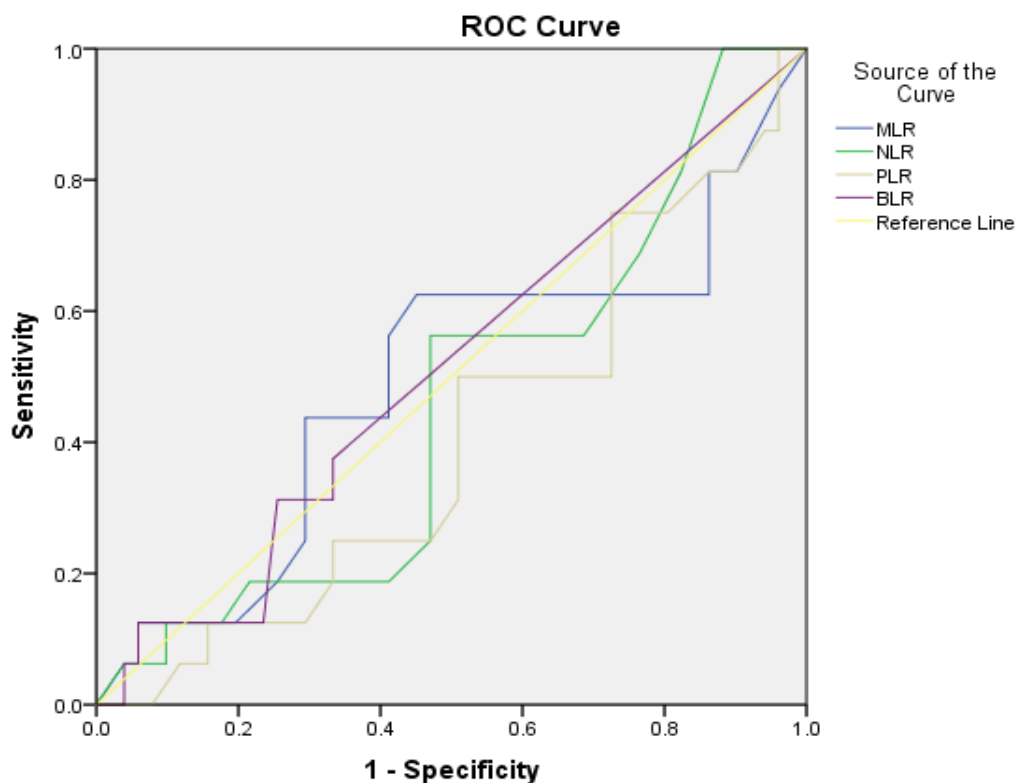
Variables	Mean \pm SD	p-value
Age	57.21 ± 12.39	0.264
NLR	2.56 ± 3.01	0.110
PLR	7.30 ± 1.70	0.041*
BLR	0.01 ± 0.00	0.615
MLR	0.22 ± 0.03	0.205

*Statistically significant ($p < 0.05$), NLR: Neutrophil-lymphocyte ratio, PLR: Platelets-lymphocyte ratio, BLR: Basophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio

Table 2: Correlation between Haematological Markers with stage of Cancer after Adjustment for Age and Parity

Haematological Parameters	FIGO stage r (correlation coefficient)	p-value
NLR	0.195	0.096
PLR	0.078	0.511
BLR	0.154	0.220
MLR	0.188	0.108

NLR, neutrophil-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.



Diagonal segments are produced by ties.

Figure 1: ROC Analysis of NLR, PLR, MLR, and BLR as Predictive Values in advanced Stage Cervical Cancer

Table 3: AUC, Cut-off Value, Sensitivity, Specificity for NLR, PLR, MLR, and BLR in Cervical Cancer Patients

Parameter	AUC	95% CI	Cut-off	Sensitivity	Specificity	p-value
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				%	%	
NLR	0.456	0.30-0.61	1.38	81	82	0.60
PLR	0.406	0.25-0.56	3.91	88	94	0.26
BLR	0.510	0.35-0.67	0.02	31	26	0.90
MLR	0.491	0.32-0.67	0.19	63	71	0.91

NLR, neutrophil-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; AUC, area under the curve; CI, confidence interval

4. DISCUSSION

The relationship between cancer and immunity has been one of the most widely discussed topics in recent times [9,10,32]. Many studies have shown that systemic inflammatory response plays a significant role in cancer development [32]. Many cancers are caused by environmental factors and develop in areas of chronic irritation and inflammation [10,26]. In general, neutrophilia, thrombocytosis, and relative lymphopenia are markers of systemic inflammation in peripheral blood [10]. These immune cells and inflammatory mediators play a significant role in the tumour microenvironment.

The mechanism by which increased neutrophil and decreased lymphocyte counts cause tumour progression is unknown. Neutrophils produce a variety of inflammatory cytokines, including vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9, causing DNA damage, inhibiting apoptosis, and promoting angiogenesis. Lymphocytes inhibit tumour cell proliferation by secreting interleukin-2, which stimulates the proliferation of cytotoxic lymphocytes while inhibiting tumour cell proliferation, thereby mediating antitumour immune responses [10,24,33].

The release of both angiogenic and anti-angiogenic factors by activated platelets results in stimulation of tumour angiogenesis because of platelet endothelial interaction [34]. Platelet activation causes release of angiogenic and anti-angiogenic factors, and the overall effect of platelet endothelial interaction is stimulation of tumour angiogenesis [34]. To predict the development of several cancers, various combinations of these inflammatory markers are currently being assessed as independent prognostic factors.

Clinicians are increasingly using haematologic parameters to determine prognosis and management of cervical cancer [35]. NLR has been proposed for estimating cervical cancer mortality and recurrences. A high NLR is associated with poor prognosis in patients with cervical carcinoma [22,35,36]. The NLR can provide a reliable prediction of the prognosis of a patient with stage IIB cancer and lymph node metastasis [13]. Furthermore, the NLR may be useful in determining the severity of cervical cancer. It is proposed that the NLR can be used as a predictor of cancer invasion [13].

The PLR is dependent on the systemic inflammatory response, which is significantly influenced by cancer and other inflammatory conditions [37]. These conditions can lead to misdiagnosis and ineffective, if not harmful, treatment. It is used to predict lymph node metastasis in cervical cancer and to improve the categorization of risk for predicting survival. In addition, the PLR provides a simple and easily accessible test for predicting the severity of cervical cancer [38].

According to the findings of the current study, pretreatment NLR and PLR could not be used as predictive haematological markers to stage cervical cancer, implying that the models would be unreliable in correctly classifying patients. The small patient population could explain the non-significant association. Similarly, some researchers also observed that neither NLR nor PLR had a significant predictive value for overall survival, disease-free survival, or recurrence-free survival in patients with early-stage cervical cancer [27]. As a result, they concluded that although preoperative NLR and PLR are not clinically useful in predicting prognosis in early-stage cervical cancer, they may be useful in determining the risk for adjuvant therapy.

However, the study by Ergen et al., found that cervical cancer patients with high pretreatment NLR values had a more advanced stage, larger tumour size (> 4cm), and poorer treatment response. The cancer stages of patients with high PLR values were also more advanced [1]. Increased NLR has been described as a sign of poor prognosis in many earlier studies. According to Lee et al., NLR could be used to calculate the mortality and recurrence rates in cervical cancer patients [22]. They opined that in patients with locally advanced cervical cancer treated with radical chemoradiotherapy, post-treatment haematological parameters rather than pre-treatment haematological parameters may be used as a prognostic indicator [29]. These conflicting outcomes could be the result of various patient characteristics, study designs, and sample size. The small sample size may have been the reason we could not determine the predictive values of NLR and PLR.

Furthermore, there is no validated threshold value for NLR or PLR. In each study, a different value (median value or ROC cut-off value) is used. In general, the NLR and PLR values used in these studies range from two to five and from 150 to 300 [11,12,39,40]. These are general inflammatory markers. At the same time, because these are systemic inflammation parameters, they may be difficult to interpret in the presence of concurrent chronic illness.

Also, there is not yet a validated threshold value for NLR and PLR. Different values (median value or cut-of value determined by ROC) are used in each study. In general, the NLR and PLR values used in these studies ranged from two to five and 150 to 300, respectively [11,12,39,40]. These are general inflammatory markers. At the same time, because they are systemic inflammation parameters, they may be difficult to interpret in the presence of concurrent chronic illness.

The fact that this study is prospective, that it is the first to assess the predictive value of haematological markers in cervical cancer patients at the centre, and that our cohort was exclusively made up of patients with a histologic diagnosis of the disease are some of its strengths. Complete blood counts are routinely performed at low cost before and during, as well

as during follow up visits; as a result, they are regarded as a practical and reproducible laboratory parameter.

The clinical significance of pretreatment NLR and PLR can therefore be a helpful predictive indicator for cancer stage if it is well defined. The study does, however, have some drawbacks, such as a small sample size and the fact that it was conducted in a single centre, so the results cannot be generalized. Larger multicentre clinical studies should be carried out to confirm the predictive values and cutoff values of NLR and PLR.

5. CONCLUSION

Finally, we were unable to establish the predictive value of pre-treatment NLR and PLR in this study. However, pretreatment NLR and PLR can be used as a simple and cost-effective biomarker in the future, particularly in developing countries where cervical cancer remains a major public health concern. In addition to clinical stage, it may be useful for stratifying patients at high risk of recurrence and death from cervical cancer.

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