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Pretreatment Systemic Inflammatory Markers, Neutrophil Lymphocyte Ratio, and Platelet Lymphocyte Ratio as a Prognostic Factor in Cervical Cancer: A Retrospective Study

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Abstract

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Inflammation has been recognized as a promoter of the neoplastic process initiation and progression. Neutrophilia, lymphocytopenia, and thrombocytosis are hallmarks of inflammatory reaction. The aim of this study is to find the correlation and prognostic value of pretreatment neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), with the recurrence in carcinoma cervix.

Data of 208 biopsy-proven cases of squamous cell carcinoma cervix treated with definitive chemoradiotherapy were retrospectively analyzed. Neutrophil, lymphocyte, and platelet count at diagnosis were recorded and NLR and PLR were calculated. The cutoff value of NLR and PLR were calculated using receiver operator characteristics curve analysis. Correlation between locoregional recurrence (LRR) and NLR and PLR is evaluated. Median age of diagnosis is at 50 years. International Federation of Gynecology Obstetrics stage IIB was the most prevalent stage in this study. The NLR and PLR were statistically significantly affecting the LRR. The cutoff value of NLR was 2.45 with a sensitivity of 82.6% and specificity of 77.7%. The cutoff value for PLR was 140.6 with a sensitivity of 85.5% and specificity of 80.6%. On univariate regression analysis stage ($p = 0.045$), tumor grade ($p = 0.001$), addiction ($p = 0.024$), NLR ($p < 0.001$), and PLR ($p < 0.001$) were associated with LRR. Multivariate regression analysis showed that NLR ($p = 0.005$) risk group and PLR ($p < 0.001$) risk group are independent risk factors associated with LRR.

Conclusion High value of NLR and PLR correlate with poor prognosis in squamous cell carcinoma cervix. Hence, these biomarkers may be used as surrogates for tumor prognosis.

Keywords

- cervical cancer
- prognosis of cancer cervix
- neutrophil to lymphocyte
- platelet to lymphocyte
- ratio

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Introduction

Carcinoma cervix is the most prevalent disease among member countries of the developing world. The worldwide incidence of carcinoma cervix as per GLOBOCON 2020 data was 604,100 in 2020 and deaths due to cervical cancer was 341,831 in 2020 alone.[1] This calls for a need for better prognostication of the patients with cervical cancer. The complete blood count (CBC) is a cost-effective method to study the intensity of the inflammatory process in a known case of malignancy. Hanahan and Weinberg described the hallmarks of cancer as sustaining of proliferative signaling, evasion of growth suppressors, resistance against cell death, enabling of replicative immortality through means of angiogenesis, and activation of invasion and metastasis.[2] Inflammation provides for all these through multiple pathways.

Inflammation mediates the neoplastic process in both its early as well as late stages of development. In the early stages of the neoplastic process, inflammatory cells act as tumor promoters. In the late stages of neoplastic process, tumor cells vitiate immune processes to favor tumor development. Distant metastasis is made possible by coating of tumor cells by certain inflammatory molecules like selectins and chemokines, hence enabling receptor recognition which helps in spreading cells via lymphatics and capillaries and evading host defense mechanisms.[3] Neutrophils, eosinophils, and monocytes are recruited as macrophages in the inflammatory process and lymphocytes along with various cytokines and chemokines participate in this inflammation-mediated tumor proliferation activity.[3,4] A high neutrophil count is therefore a surrogate marker for tumors with greater proliferative capacity and provides insight into cancer with a higher chance of posing risk of recurrence and metastasis.[5]

The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been linked to poor prognosis in several solid malignancies like head and neck cancer, esophageal cancer, colon cancer, and gynecological malignancies.[6–11]

Materials and Methods

This retrospective study included 208 patients treated with definitive chemoradiotherapy at the Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata, West Bengal, India, from June 2017 to December 2019. Staging was done with the 2018 International Federation of Gynecology Obstetrics (FIGO) staging system.[12] The diagnosis was confirmed by histopathological examination of tissue biopsy from cervical growth. The staging workup included clinical examination, review of the histopathological report, contrast-enhanced computed tomography scan (CT scan) of abdomen and pelvis, contrast-enhanced magnetic resonance imaging pelvis, cystoscopy, rectosigmoidoscopy, CT scan thorax, or chest X-ray. The routine blood examinations included CBC, liver function test, and renal function test, done in all patients.

The inclusion criteria were as follows: (1) age more than 18 years, (2) without any history of prior chemotherapy or radiotherapy, and (3) histologically confirmed case of squamous cell carcinoma cervix. Patients were excluded from the study if having cervical carcinoma other than squamous cell carcinoma, distant metastases at presentation, with any chronic diseases, and with any hematological disorder or autoimmune disease or on corticosteroid therapy. Clinical data of all patients were recorded along with CBC test reports, at the time of diagnosis. NLR and PLR were calculated as the ratio of absolute neutrophil or platelet counts, respectively, to the absolute lymphocyte count. All patients received external beam radiotherapy (EBRT) with telecobalt unit (Bhabhatron II, Panacea Medical Technologies, Bengaluru, Karnataka, India). ONCENTRA (Nucletron, Elekta AB, Stockholm, Sweden) EBRT treatment planning system was used for three-dimensional conformal radiotherapy planning. All patients received 50 Gray (Gy) in 25 fractions, 2 Gy per fraction, 5 fractions a week concurrently using weekly injection cisplatin 40 mg/m^2. After completion of EBRT all patients received intracavitary radiotherapy using the MicroSelectron Brachytherapy Afterloading (Elekta AB) platform equipped with Ir^{192} high dose rate brachytherapy. A gap of 5 to 7 days was allowed after the completion of EBRT. The dose prescription of brachytherapy was 7 Gy each fraction once weekly for total of 3 to 4 fractions depending upon the stage of the disease and clinical findings at the end of EBRT. Cervical cancers with stage I the EQD2 (equivalent dose in 2 Gy per fraction) doses of 80 Gy was considered and EQD2 dose of $>$ 80 Gy was considered for stage IIA or more. Follow-up data including clinical findings and imaging every three monthly after treatment completion were also recorded. Local recurrence of the disease was confirmed by biopsy and defined as locoregional recurrence (LRR). Time interval from initiation of treatment to progression of the cervical cancer is used to calculate the progression free survival (PFS).

Statistical Analysis

The Statistical Package for the Social Sciences (IBM SPSS for Windows, version 25.0) was used for statistical analysis. Descriptive statistics were used to describe the population. The partial correlation of local recurrence to NLR and PLR was determined by point-biserial correlation. The receiver operating characteristics (ROC) curve analysis was used to determine the predictive cutoff values of NLR and PLR by utilizing the area under the curve (AUC). Univariate and multivariate regression analyses were done to determine the factors associated with LRR. The Kaplan–Meier estimate and survival curve were used to calculate the PFS. A p-value of < 0.05 was considered statistically significant in all performed analyses.

Results

Patient and Tumor Characteristics

In this study 208 patients meeting the inclusion criteria with cervical cancer were analyzed. The median age of the patients was 50 years. Tobacco addiction was seen in 3.8% of patients. FIGO staging distribution of the patients showed stage IB3, IIA1, IIA2, IIB, IIIA, IIIB, and IIIC1 as 2.9, 11.5, 5.8, 32.2, 12, 28.8, and 6.7%, respectively. Most of the patients had

Table 1 Demographic characteristics

		Count	Table, *N* %
Family history of cancer	No	205	98.6
	Yes	3	1.4
Addiction history	No	200	96.2
	Tobacco	8	3.8
FIGO stage	IB3	6	2.9
	IIA1	24	11.5
	IIA2	12	5.8
	IIB	67	32.2
	IIIA	25	12
	IIIB	60	28.8
	IIIC1	14	6.7
ECOG PS	ECOG 0	6	2.9
	ECOG 1	190	91.3
	ECOG 2	12	5.8
Grade	Grade 1	15	7.2
	Grade 2	166	79.8
	Grade 3	27	13.0
Duration of completion of treatment	$\leq$ 8 weeks	27	13.0
	> 8 weeks	181	87.0
NLR risk group	Low risk	120	57.7
	High risk	88	42.3
PLR risk group	Low risk	122	58.65
	High risk	86	41.35
Local recurrence	Yes	69	33.2
	No	139	66.8
Distant metastases	Yes	26	12.5
	No	182	87.5

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; FIGO, International Federation of Gynecology Obstetrics; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 (91.3%). The epidemiological, clinical, and pathological data are depicted in ►Table 1. The mean absolute count of neutrophils, lymphocytes, and platelets were 4,490 (thousand/mm^3), 2,036 (thousand/mm^3), and 2.37 ($\times 10^5$/cmm), respectively. The NLR mean value was 2.68 (range 0.95–11.42). PLR had a mean value of 135.14 (range 50–455.50), depicted in ►Table 2. The median duration of completion of treatment (EBRT and brachytherapy) was 9.2 weeks (standard deviation $\pm$0.744). Only 13% of patients completed their treatment within 8 weeks. Note that 33.2, 44.7, and 9.1% patients completed their treatment in > 8 to 9, > 9 to 10, and > 10 weeks, respectively. The median EQD2 dose was 89.67 Gy. The distribution of EQD2 dose according to the FIGO stage is depicted in ►Table 3. Follow-up data till April 2022 revealed 32.2% of patients had LRR and 12.5% had distant metastasis. Among the 26 (12.5%) patients with distant metastasis, 12 patients also had LRR.

Correlation of NLR and PLR with Local Recurrence of Cervical Cancer

Using partial correlation analysis, the correlation between NLR as well as PLR with LRR was calculated by controlling for age, family history, addiction, and ECOG PS. Statistically significant strong positive correlation was seen between PLR and LRR (the correlation coefficient, $r = 0.583$; $p < 0.001$), while moderate positive correlation was seen between NLR and LRR (the correlation coefficient, $r = 0.437$; $p < 0.001$). This finding suggests that an increase in NLR and PLR will lead to an increased risk of LRR.

Optimal Cutoff for NLR, PLR, and ROC Curve

The optimal cutoff points of NLR and PLR were analyzed for LRR of the patients using ROC curve. The results showed that 2.45 was the optimal cutoff value for NLR (AUC = 83.9%; 95% confidence interval [CI] 0.782–0.896; $p < 0.001$), at which there was significant difference in LRR. The sensitivity and specificity were 82.6 and 77.7%, respectively, at NLR cutoff of 2.45. Patients were divided between high and low NLR risk group on the basis of NLR cutoff value, patients with NLR $\geq$ 2.45 were included in the high-risk and NLR < 2.45 were included in the low-risk group. The frequency of distribution of NLR risk group, that is, low-risk NLR and high-risk NLR groups were 57.7 and 42.3%, respectively. The high-risk NLR group was significantly associated with LRR (p-value < 0.001). Similarly, the optimal predictive cutoff value of PLR was 140.6 (AUC = 89.2%; 95% CI 0.847–0.936; $p < 0.001$), at which there was significant difference in LRR. The sensitivity and specificity were 85.5 and 80.6%, respectively, at PLR cutoff of 140.6. Patients were divided between high and low PLR risk group on the basis of PLR cutoff value, patients with PLR $\geq$ 140.6 were included in the high-risk and PLR < 140.6 were included in the low-risk group (►Fig. 1). The distribution of low-risk and high-risk PLR groups were 58.65 and 41.35%, respectively. The high-risk PLR group was significantly associated with LRR (p-value < 0.001) (►Table 4).

Regression Analysis of Factors Influencing Locoregional Recurrence

On univariate regression analyses, addiction of tobacco ($p = 0.024$), FIGO stage ($p = 0.045$), grade of tumor ($p = 0.001$), NLR risk group ($p < 0.001$), and PLR risk group ($p < 0.001$) are significantly associated with LRR. On multivariate regression analyses, only the NLR risk group ($p = 0.005$) and PLR risk group ($p < 0.001$) are found to be independent factors affecting LRR (►Table 5).

Survival Analysis

Note that 33.2% patients had progression of the disease or LRR at the time of analysis. The median PFS was not reached. The mean PFS was 40.133 months (95% CI 38.290–41.977). Three-year PFS was 100, 71, and 33% in stage I, stage II, and stage III, respectively (►Fig. 2).

Table 2 The distribution of clinical and hematological parameters

	N	Minimum	Maximum	Mean	Median	Standard deviation
Age (y)	208	28	60	49.48	50	7.37
Duration of symptoms (mo)	208	1	36	5.77	5	4.94
Hemoglobin	208	5.4	14.2	10.16	10.15	1.55
Absolute neutrophil count (thousand/mm^3)	208	2,000	10,920	4,490	4,050	1659.78
Absolute lymphocyte count (thousand/mm^3)	208	630	4,400	2,036	1,980	871.23
Absolute eosinophil count (thousand/mm^3)	208	0	1,600	306	225	244.55
Absolute monocyte count (thousand/mm^3)	208	0	1,805	226	170	201.80
Absolute basophil count (thousand/mm^3)	208	0	47	0.23	0	3.25
NLR	208	0.95	11.42	2.68	2.16	1.78
Platelet ($\times 10^5$/cmm)	208	1.00	5.10	2.37	2.16	0.87
PLR	208	50.00	455.50	135.15	120.12	67.65

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 3 EQD2 dose distribution and stage

		≤ 80 Gy		> 80–85 Gy		> 85 Gy	
		Count	*N* %	Count	*N* %	Count	*N* %
FIGO stage	IB3	6	2.88	0		0	
	IIA1	24	11.53	0		0	
	IIA2	12	5.76	0		0	
	IIB	25	12.01	3	1.44	39	18.75
	IIIA	0		5	2.40	20	9.61
	IIIB	0		12	5.76	48	23.07
	IIIC1	0		2	0.96	12	5.76

Abbreviations: EQD2, equivalent dose in 2 Gy per fraction; FIGO, International Federation of Gynecology Obstetrics.

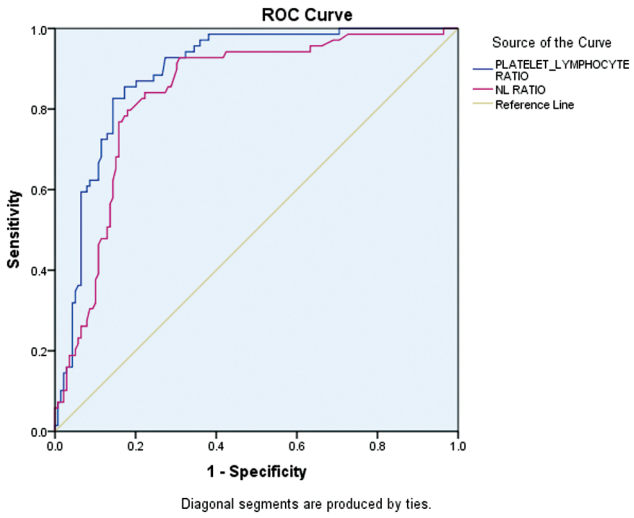

Fig. 1 Redline—The receiver operator characteristics curve of the cutoff point for NLR; area under ROC curve = 83.9%; sensitivity = 82.6%; specificity = 77.7%. Blue line—The ROC curve of the cutoff point for PLR; area under ROC curve = 89.2%; sensitivity = 85.5%; specificity = 80.6%. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ROC curve, receiver operating characteristics curve.

Discussion

Inflammation plays major decisive role at tumor development including initiation, promotion, malignant transformation, invasion, and metastasis. It also acts as immune surveillance and response to therapy. Elevated inflammatory mediators are related to poor prognosis in patients with cancer.[3] Several studies demonstrated raised NLR and PLR as a well-known poor prognostic factor of cervical cancer.[13–19] Tavares-Murta BM et al were one of the first groups to study hematological markers and their prognostic value in cervical cancer and peculiarly included cases of cervical intraepithelial neoplasia (CIN) as well as all stages of cervical cancer. Their conclusions were rather paving a way for extensive research in this direction. They found out how neutrophilia, leukocytosis, and lymphopenia were more frequently seen in advanced stage cervical cancer and that neutrophilia was more common in early-stage cervical cancer cases when compared with cases of CIN. Also, an NLR value of more than 5 was more common in late-stage cervical cancer.[13]

Median age of the study population was 50 years. This correlated well with other studies.[14,17] Stage IIB was the

Table 4 Association of NLR, PLR, and locoregional recurrence

Variable	Risk group	Locoregional recurrence				*p*-Value
		Yes		No		
		Count	*N* %	Count	*N* %	
NLR group	High risk	57	27.4	31	14.9	< 0.001
	Low risk	12	5.8	108	51.9	
PLR group	High risk	59	28.4	27	13	< 0.001
	Low risk	10	4.8	112	53.8	

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table 5 Univariate and multivariate logistic regression analysis of factors associated with local recurrence

Characteristics	Univariate logistic regression			Multivariate logistic regression		
	Odds ratio [(Exp (B)]	*p*-Value	95% Confidence interval	Odds ratio [(Exp (B)]	*p*-Value	95% Confidence interval
Family history of cancer	0.993	0.995	0.088–11.141			
Addiction	0.153	0.024	0.030–0.781	4.407	0.191	0.477–40.703
ECOG PS	0.537	0.155	0.228–1.267			
Hb level group	0.584	0.071	0.326–1.046			
FIGO stage	0.858	0.045	0.739–0.996	1.106	0.335	0.901–1.359
Grade of tumor	0.275	0.001	0.133–0.569	2.426	0.052	0.994–5.922
Duration of treatment	0.415	0.091	0.150–1.150			
NLR risk group	16.548	< 0.001	7.899–34.670	4.085	0.005	1.544–10.807
PLR risk group	24.474	< 0.001	11.095–53.985	9.173	< 0.001	3.426–24.562

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; FIGO, International Federation of Gynecology Obstetrics; Hb, hemoglobin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

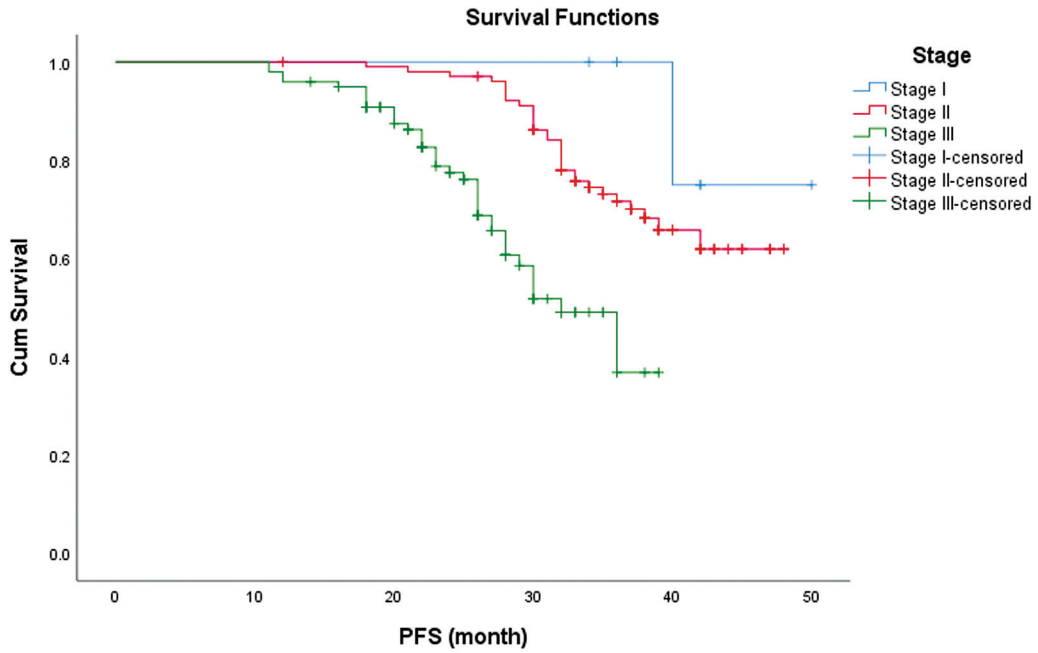

Fig. 2 Kaplan–Meier survival curve, estimated PFS with statistically significant difference in PFS according to stage of cervical cancer with log-rank $p < 0.001$. PFS, progression-free survival.

most prevalent stage consisting of 32.2% of the study population followed by stage IIIB (28.8%). A similar finding was seen in a study by Haraga et al where stage IIB (42.1%) was followed by stage IIIB (27.3%). In the same study they found NLR $\geq$ 2.78 (AUC = 0.635, sensitivity: 63.9%, specificity: 49.2%) and PLR $\geq$ 172.50 (AUC = 0.597, sensitivity: 58.3%, specificity: 55.9%) as the most accurate cutoff values for predicting PFS.[20] This NLR value differ little from our study but a striking similarity in mean value of NLR was found with the study by Prabawa et al where NLR was 2.68 in early-stage group scenarios.[21] In some studies PLR correlated with survival outcomes[19,22] while some found NLR to have correlation with survival outcomes,[15,20,23] whereas some found both NLR and PLR to correlate with poorer survival outcomes.[16,24,25]

In this study, ROC curve analysis of local recurrence yielded the NLR cutoff value as 2.45 (AUC = 0.839) with a sensitivity of 82.6% and specificity of 77.7% and the PLR cutoff value 140.6 (AUC = 0.892) with a sensitivity of 85.5% and specificity of 80.6%. This matched with another study, the sensitivity value for NLR was 82% and specificity 71% with a cutoff of 3.38 using ROC analyses and 72 and 70% with cutoff of 172.05 for PLR, respectively, for predicting stage with NLR and PLR.[21]

On univariate regression analysis, addiction, FIGO stage, tumor grade, NLR risk group, and PLR risk group were significantly associated with LRR. NLR and PLR were the statistically significantly associated prognostic factor for recurrence on multivariate analysis. NLR also was found to have the most significant hazard ratio with disease recurrence in a study by Lee et al where for every increase of 0.1 in NLR, the risk of progression and death increased by 13 and 19%, respectively.[14] Santos Thuler et al performed a study with 1,266 patients in 2021, to find predictors of worse overall survival (OS) in the form of NLR ($>$ 2.57), PLR ($\geq$ 146.70), derived NLR ($\geq$ 1.778), and PLR + NLR in combination but only in locally advanced disease.[25] Another study tried to correlate these hematological parameters with stage of cervical cancer and found that patients with higher NLR and PLR have a tendency for higher stage disease and additionally, on ROC curve analyses, only NLR and PLR were feasible to be used as predictive models.[21] In 2016, Zheng et al found PLR and serum albumin as prognostic factors in early-stage cervical cancer patients; the cutoff value for PLR was 128.3, high PLR risk groups demonstrated shorter OS and disease-free survival with significant *p*-values.[22]

Zhu et al tried to predict parametrial involvement with help of NLR and PLR. Furthermore, they discovered PLR as an independent prognostic factor for PFS and OS on univariate analyses while no such relation was found between NLR and survival outcomes.[19] A PLR of more than 322 predicted poorer prognosis for recurrence of cervical cancer in patients who underwent chemoradiotherapy,[26] and Mizunuma et al found low NLR to predict complete response to treatment and NLR was the only prognostic factor for PFS and OS.[23]

NLR and PLR also related to prognostication of patients with early-stage disease. A Chinese study analyzing 460 cervical cancer patients undergoing radical surgery found that NLR was significantly associated with depth of stromal infiltration, both NLR and PLR were significantly associated with lymph node metastasis. A study done by Chen et al found that only PLR was significantly associated with lymph node metastases on early-stage patients having definite surgery. He also showed significant association of both NLR and PLR with reduced recurrence-free survival and OS.[16]

Conclusion

Inflammation has been established as a mediator of cellular proliferation in neoplastic tissue. High NLR and PLR are markers of inflammation and correlate with disease recurrence in carcinoma cervix as evident in this study. Hence, NLR and PLR can be strongly used as biomarker for prognostication and outcome of patients with carcinoma cervix. However, a well-designed larger study with longer follow-up is warranted.

Ethical Approval

The Local Ethics Committee of the Institute of Post Graduate Medical Education and Research, Kolkata waived ethical approval in view of the retrospective nature of the study and all the procedures being performed were part of the standard management.

Authors' Contributions

S.S., B.M., S.M.D., D.S., and S.D. participated in the acquisition of data and drafting the manuscript. All authors read and approved the final manuscript.

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None.

Conflict of Interest

The authors declare that they have no competing interests.

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