

Preoperative Neutrophil to Lymphocyte Ratio (NLR) Can Predicts High Risk Surgicopathological Features in Patients of Early Stage Cervical Cancer (stage IB to IIA) Treated by Radical Hysterectomy with Pelvic Lymphadenectomy

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Abstract

Introduction: Globally cervical cancer is the 4th most common cancer in females after breast, colorectal, and lung cancer. In patients with early-stage cervical cancer (stage IB-IIA) who have undergone radical hysterectomy, postoperative histopathologic features along with clinical staging predict prognosis and are used for planning further treatment. Neutrophil-lymphocyte ratio (NLR) is a nonspecific marker to predict prognosis. This study aimed to evaluate the predictive values of preoperative values of NLR for high-risk surgical-pathological features identification in patients with early-stage cervical cancer undergoing primary radical hysterectomy with pelvic lymphadenectomy. **Methods:** This cross-sectional study was carried out in the Department of Gynaecological Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU) between July 2019 and June 2020 to evaluate the relationship of preoperative NLR with surgical-pathological features of cervical cancer stage IB-IIA who underwent primary radical hysterectomy and pelvic lymph node dissection. A total of fifty cervical cancer patients were enrolled in this study. Their clinical and histopathological findings and complete blood count reports were collected and analyzed. **Result:** The ROC curve revealed NLR was 2.670 (sensitivity 63%; specificity 91.3%; Areas under the curves 0.801). Surgical pathological analysis showed that NLR was linked to lymphovascular space invasion. Sixty-three percent of patients having NLR >2.670 were 17.85 times more likely to have LVSI. **Conclusion:** The study findings conclude that high pretreatment NLR was linked to lymphovascular space invasion. Thus NLR can be used preoperatively to predict the prognosis of cancer cervix and triage the patients into monovalent treatment- either surgery or chemoradiation.

Keywords: Cervical cancer, Neutrophil-lymphocyte ratio (NLR), high-risk surgical-pathological features, prognosis.

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INTRODUCTION

Noncommunicable diseases especially cancer are expected to rank as the leading cause of global death. Globally cervical cancer is the 4th most common cancer in females after breast, colorectal, and lung

cancer. In 2018, it was estimated that there were approximately 570,000 new cases and 3,11,000 deaths due to cervical cancer [1]. The burden of cervical cancer is disproportionately high in the developing world. In the Southeast Asian region, about half a million people die every year from cancer [2].

Bangladesh, like other developing countries, faces a large cancer burden. Cervical cancer constitutes 20-29% of female cancers and 70% of all gynecological malignancies in Bangladesh [3]. Every year 11956 women are diagnosed with cervical cancer and 6,582 die from the disease [4].

Clinical staging as defined by the International Federation of Gynecology and Obstetrics (FIGO) is used to recommend specific treatments for cervical cancer [5]. Stages IB to IIA can be treated using Piver-Rutledge class III radical hysterectomy and bilateral pelvic lymphadenectomy with or without postoperative adjuvant radiotherapy [5]. But despite complete treatment, one-third of the patients with cervical cancer die due to disease recurrence or progression [6]. Presently, many tumor-specific parameters are identified as prognostic factors for cervical cancer, and most of these factors are based on post-operative histopathological findings such as tumor size, lymph node status, depth of invasion, histological grade, and parametrial involvement [6]. Although clinical staging is a strong preoperative predictor of outcome, the clinical stage was frequently inaccurate, especially in cases of more advanced disease [7, 8]. As a result, in early-stage cervical cancer, in patients who are candidates for radical surgery, several pathological findings after surgery, are used as predictors for recurrence and for planning further treatment [9]. Furthermore, we cannot apply these pathological risk factors for the prediction of prognosis in advanced disease because the treatment of choice in such cases is concurrent chemoradiation (CCRT) [9, 10].

Studies have shown that both inflammatory reaction and immune status are prognostic factors for tumor formation [11, 12]. Tumor-associated inflammatory responses consist of inflammatory cells and a series of inflammatory mediators, resulting in a tumor-related inflammatory microenvironment that plays vital roles in the pathogenesis and progression of tumors [13]. On the other hand, tumor-induced inflammatory responses can lead to changes in hematological components such as neutrophils, lymphocytes, monocytes, and platelets [13]. Neutrophil/lymphocyte ratio (NLR) is a useful inflammation-based non-specific prognostic indicator. Since hematological markers of inflammation are readily measured, it has been frequently reported that a combined index using neutrophil and lymphocyte counts in the form of NLR have been used as cost-effective and simple parameters of systemic inflammation [14, 15]. These markers can reflect relative changes in different components of the blood and have been proven as potential prognostic markers in various cancers such as hepatobiliary, esophageal, non-small cell lung, gastric and renal cancers [16-21].

Many researchers have focused on the application of preoperative NLR in cervical cancer [22-24]. In patients of cervical cancer increased NLR has been reported to be associated with lymph node metastasis and depth of stromal invasion [22-24]. They have found that it is useful for stratifying patients at high risk of recurrence and death in addition to clinical stage [23].

NLR has been reported to act as a valuable tool in predicting therapeutic response to radiation therapy (RT) and concurrent chemoradiation therapy (CCRT) also [25, 26]. However, little is known about the prognostic values of preoperative NLR in cervical cancer patients treated with primary radical surgery. Therefore, the present study aimed to investigate the predictive values of NLR in patients with early-stage cervical cancer. For the treatment of early-stage cervical cancer, the main principle is to choose monotherapy. If the correlation between NLR and a high-risk group can be effectively established before surgery, the mode of treatment can be changed in favor of radiotherapy or concurrent chemoradiotherapy. Thus we can be able to avoid the complications of dual modalities of treatment. The present study was undertaken to determine whether preoperative NLR can predict prognostic features in early-stage cervical cancer treated by radical hysterectomy with bilateral pelvic lymphadenectomy.

OBJECTIVE

- To evaluate the predictive values of preoperative values of NLR for high-risk surgical-pathological features identification in patients with early-stage cervical cancer undergoing primary radical hysterectomy with pelvic lymphadenectomy.

METHODS & MATERIALS

This cross-sectional study was carried out from July 2019 to June 2020, on patients of the early operable stage (IB - IIA) of cervical cancer who were admitted to the Department of Gynecological Oncology BSMMU, Dhaka for radical hysterectomy with bilateral pelvic lymphadenectomy. The institutional Review Board (IRB) of BSMMU approved the protocol of the study. A total of 50 admitted patients were included in the study. Purposive sampling was done. Informed written consent was taken from each patient. Detailed history and findings of relevant investigations were recorded. Blood was collected for CBC with proper aseptic measures. Then NLR was calculated. The NLR is simply the number of neutrophils divided by the number of lymphocytes which is easily calculated from the differential cell count, using either absolute cell counts or percentages, as shown here: $NLR = \frac{\text{absolute count of neutrophil}}{\text{absolute count of lymphocyte}} = \frac{\text{relative \% of neutrophil}}{\text{relative \% of lymphocyte}}$ The optimal cut off value will vary depending on the

specific patient population and disease state and calculated using Receiver Operating Characteristics (ROC) curve. Interpretation of NLR depends on the clinical context. The mean of preoperative NLR was calculated from CBCs. The cut-off value of NLR was calculated using the ROC curve. All the selected patients for radical hysterectomy, were at first underwent Examination under Anesthesia to ascertain clinical staging finally who were selected for surgery underwent radical hysterectomy and bilateral pelvic lymphadenectomy. After the operation, the specimen was sent for histopathological examination to determine tumor-related features. Histopathological reports were recorded in a performed structured questionnaire. Then correlation of NLR was done with each of tumor-related features like tumor size, FIGO stage, histopathological type of the tumor, histopathological grade, lymphovascular space invasion (LVSI), lymph node status, and depth of stromal infiltration to determine the prognostic value. The relationships between NLR and the clinico-surgico-pathological variables were analyzed by the X2 test. The descriptive statistics of the study were presented in tables or suitable graphs. Statistical Package for Social Science (SPSS) 25.0 software was used for the statistical analysis. The p-value <0.05 was considered statistically significant.

Inclusion Criteria

- Patients who were histopathologically diagnosed with early-stage cervical cancer (stage IB-IIA).
- Patients with a histopathological type of squamous cell carcinoma and adenocarcinoma of the cervix.
- Patients who underwent radical hysterectomy and pelvic lymphadenectomy.
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Known case of acute or chronic infection.
- Patients undergoing fertility-saving surgery.
- Patients who received neoadjuvant chemotherapy or preoperative radiotherapy.
- Patients taking preoperative corticosteroid
- Patients with hematologic, autoimmune, or infectious diseases.
- Patients with multiple primary site cancer or advanced stage cervical cancer or with histological types other than squamous cell or adenocarcinoma.
- Patients who did not give consent to participate in the study.

RESULTS

Table 1: General Characteristics of the patients (N=50)

Characteristics	N	%
Age (years)		
32-42	15	30.0
43-52	20	40.0
>52	15	30.0
Parity		
Multipara	46	92.0
Primipara	04	8.0
Literacy		
Literate	29	58.0
Illiterate	21	42.0
Socioeconomic status		
Low income	10	20.0
Low to middle income	37	74.0
High income	03	6.0

A total of 50 patients were enrolled in this study who underwent radical hysterectomy and pelvic lymphadenectomy. The minimum age was 32 years and the maximum age was 70 years. About 70% of the patients' age was below 50 yrs. Most (92%) of the patients were multipara. About half of the respondents were literate (58%) and 74% of the patients were in the low to middle-income group [Table 1].

Table 2: Distribution of the patients by tumor-related parameters (N=50)

Tumour Related Parameters	N	%
FIGO Stage		
Stage IB	37	74.0
Stage IIA	13	26.0
Histological Grade		
Grade 1	6	12.0
Grade 2	37	74.0
Grade 3	7	14.0
Histologic type		
Squamous cell carcinoma	40	80.0
Adenocarcinoma	10	20.0
Tumor Size (in cm)		
< 4	33	66.0
≥ 4	17	34.0
Depth of stromal infiltration		
<½ thickness	24	48.0
>½ thickness	26	52.0
Lymph node metastasis		
Present	14	28.0
Not present	36	72.0
Lymphovascular space invasion		
Present	27	54.0
Not present	23	46.0

74% were stage 1B and 26% were stage IIA. According to histological grading, more than half (74%) were Grade II cervical cancer. Most patients had

Squamous cell carcinoma (80%), and the rest had adenocarcinoma (20%). Regarding tumor size, 66% of patients had <4 cm and 36% had >4 cm tumors. Among all the tumors with stromal infiltration, 48% had <1/2

thickness and 52% had >1/2 thickness of cervical stroma. Lymph node metastasis was found in 28% of patients and Lymphovascular space invasion (LVSI) was found in 54% of patients [Table 2].

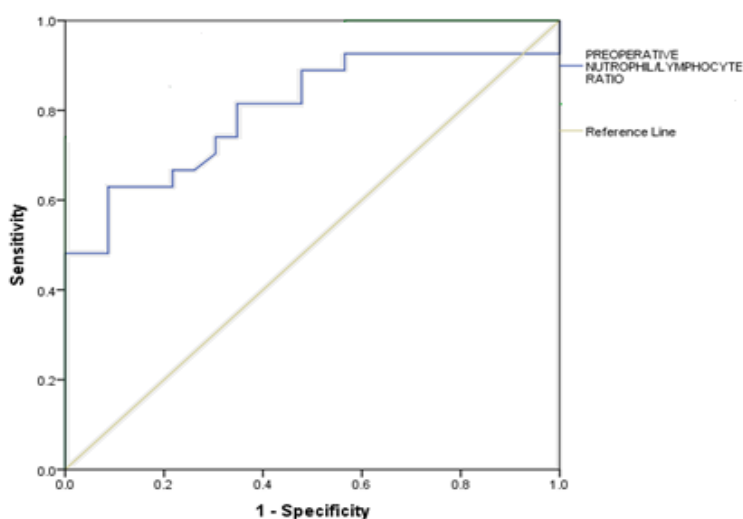


Figure 1: ROC curve of preoperative NLR for lymphovascular space invasion (N=50)

ROC Curve analysis was used to determine the predictive significance of preoperative values of NLR for Lymphovascular Space Invasion (LVSI) as shown in figure 1. Areas under the curves (AUC) for NLR were 0.801 (p=0.000). It was revealed that the predictive efficacy of NLR was highly significant for lymphovascular space invasion. The cutoff value was 2.670 for NLR (sensitivity 63.0%; specificity 91.3%) [Figure 1].

Table 3: Distribution of the patients by NLR status (N=50)

NLR	N	%	Mean ± SD
< 2.6	31	62.0	2.91 ± 2.03
≥ 2.6	19	38.0	

The mean NLR of the patients was 2.9 ± 2.03. The cutoff value of NLR was 2.670 which was calculated by the ROC curve. 62% of patients had NLR<2.6 and 38% had ≥ 2.6 NLR [Table 3].

Table 4: Association between NLR and tumor-related parameters (N=50)

Variables	N	NLR, N (%)		Test statistics
		≥ 2.670	<2.670	
Histologic Type				
Adenocarcinoma	10	2 (20.0)	8 (80.0)	p=0.197
Squamous Cell carcinoma	40	17 (42.5)	23 (57.5)	
Clinical Stage				
IB	37	13 (35.1)	24 (64.9)	p=0.481
IIA	13	6 (46.2)	7 (53.8)	
Histologic Grade				
G1/G2	43	17 (39.5)	26 (60.5)	p=0.695
G3	7	2 (28.6)	5 (71.4)	
Tumor size (in cm)				
<4	33	14 (42.4)	19 (57.6)	p=0.369
≥ 4	17	5 (29.4)	12 (70.6)	
Depth of stromal infiltration				
<1/2 thickness	24	9 (37.5)	15 (62.5)	p=0.197
>1/2 thickness	26	10 (38.5)	16 (61.5)	
Lymph node metastasis				
Present	14	8 (57.1)	6 (42.9)	p=0.082
Not present	36	11 (30.6)	25 (69.4)	
Lymphovascular space invasion (LVSI)				
Present	27	17 (63.0)	10 (37.0)	p=0.000 OR=17.850
Not present	23	2 (8.7)	21 (91.3)	

Sixty-three percent of the patient having lymphovascular space invasion had $\text{NLR} \geq 2.67$ and with $\text{NLR} \geq 2.67$ had 17.85 times more likely to have LVSI ($p=0.000$, $\text{OR}=17.850$) and it was statistically significant. In contrast, no statistically significant relationship was seen between NLR and histologic type, FIGO clinical stage, histologic grade, tumor size, depth of stromal invasion, and lymph node metastasis [Table 4].

DISCUSSION

The present cross-sectional study was carried out to evaluate the relationship of preoperative Neutrophil-to-Lymphocyte Ratio with high-risk surgicopathological features of early-stage cervical cancer (stage IB to all) patients treated by radical hysterectomy with bilateral pelvic lymphadenectomy. This study demonstrated that preoperative NLR can predict lymphovascular space invasion (LVSI) significantly, which is a marker of the advanced stage of the disease. This result indicates that the development of cervical cancer and its progression is related to inflammation-induced changes in neutrophils and lymphocytes. This result also suggests that NLR could act as a preoperative index in predicting high-risk features associated with unfavorable clinical outcomes.

Several previous studies revealed the prognostic value of LVSI in patients with early-stage cervical cancer where LVSI was positively associated with the depth of stromal invasion and lymph node metastasis [27] which indicates the advanced stage of cervical cancer with unfavorable clinical outcome.

In this study sixty-three percent of patients having lymphovascular space invasion had $\text{NLR} \geq 2.67$ and with $\text{NLR} \geq 2.67$ had 17.85 times more likely to have LVSI ($p=0.000$, $\text{OR}=17.850$) and it is statistically significant. Our results were similar to some of the previous studies where elevated NLR can predict high-risk features in early-stage cervical cancer which was associated with poor prognosis. Zhang Y *et al.*, conducted a study where 460 cervical cancer patients were enrolled from February 2005 to June 2008, at the Department of Gynecology, the Third Affiliated Hospital of Harbin Medical University, China [24]. The median NLR was 2.213. The clinicopathologic analysis showed that NLR was highly associated with depth of stromal infiltration ($P = 0.007$) and lymph node metastasis ($P = 0.003$). They concluded that preoperative NLR was found to be correlated to unfavorable histopathologic features of cervical cancer and the preoperative NLR may be used as a potential and easy biomarker for survival prognosis in patients with cervical cancer receiving initial radical hysterectomy with pelvic lymphadenectomy.

In a study [22] conducted by Meilin Zhu *et al.*, 616 patients who underwent initial radical hysterectomy with pelvic lymphadenectomy for cervical cancer

between July 2012 and December 2014 in China were retrospectively investigated. The ROC curve revealed NLR had a significant ability to predict parametrial involvement, and the cutoff value for NLR was 2.5 which is near to us. ROC curve analysis: Areas under the Curves (AUC) for NLR were 0.600 ($P=0.000$). Clinicopathologic analysis showed that NLR was linked to age, parametrial involvement, tumor-invasion depth, and histologic grade that is NLR was associated with the high-risk clinico-surgicopathological characteristics of cervical cancer.

Lee Y. Y *et al.*, [23] designed a study to investigate the prognostic value of the neutrophil: lymphocyte ratio (NLR) in 1061 cervical cancer (IB to IVA) patients at Samsung Medical Center, Seoul, Korea, from 1996 to 2007 retrospectively. The median NLR was 1.9, with a range of 0.3-27.0. In multivariable analysis, higher pretreatment NLR was identified as being an independent poor prognostic factor for survival. They concluded that pretreatment NLR may be a cost-effective biomarker to stratify the risk of recurrence and death in patients with cervical cancer.

This study fails to establish any significant relationship between NLR and with FIGO clinical stage. It may be due to the small sample size. Zhang *et al.*, 's [24] also showed in their study that there was no significant relation between the FIGO stage with NLR. The reasons for the discrepant findings between NLR and FIGO stages may be explained by the fact as follows. First, the clinical FIGO stage was frequently inaccurate, especially in cases of more advanced disease [7, 8]. Thus, it may lead to inconclusive results. Second, the differences might be due to the discrepant genetic composition between these ethnic populations, environmental factors, and lifestyle backgrounds [22].

Although the mechanisms by which elevated NLR can predict poor survival in patients with various types of cancers as well as cervical cancer is not elucidated, the following points can help in the explanation. Pretreatment neutrophil and lymphocyte count indicate the level of systemic inflammation or stress, and neutrophils and lymphocytes play different roles in the tumor. On one hand, neutrophilia may establish an adequate environment for the development and progression of tumor cells, and also circulating neutrophils have been proven to contain and secrete vascular endothelial growth factor, IL-18, and matrix metalloproteinases [28] which contribute to tumor-related angiogenesis, tumor growth, and metastasis. Thus, the high-density circulating neutrophils may adversely affect the tumor-bearing host, resulting in a negative association between neutrophil density and patient survival [29]. On the other hand, circulating lymphocyte has been shown to secrete cytokines, which prevent the proliferation and metastasis of tumor cells and have an important function in cytotoxicity [30]. It was confirmed that more CD4+ T lymphocytes at tumor

margins resulted in a less patient risk for recurrence and a better prognosis in colorectal cancer [31]. Meanwhile, subsets of lymphocytes, such as CD4+, CD8+, CD3-, and CD56+ T cells, were reduced in patients with advanced disease, despite the increased white blood cells in advanced stages [31]. Thus, a decreased number of lymphocytes may result in a weaker lymphocyte-mediated antitumor cellular immune response. Moreover, the antitumor immune responses of activated T cells and natural killer cells may be restrained by the increased number of neutrophils [30]. When considered together, NLR can reflect the balance between the host's inflammatory response and immune response. An increase in NLR indicates that the balance is upset for protumor inflammatory response and leads to a negative association with oncologic outcome.

Lymph node metastasis is considered to be a crucial factor in the management of cervical cancer. Therefore, preoperative indices in predicting lymph node metastasis may bring great gospel for patients with cervical cancer to select which treatment, especially in early-stage cervical cancer patients. And in advanced cervical cancer patients, it could help in identifying the appropriate range of radiation. Our results suggested that NLR and PLR act as preoperatively predictive markers for LVSI and lymph node metastasis in cervical cancer patients. It is of paramount importance to help decrease the multimodality treatment of early-stage cervical cancer. Thus, the identification of patients who are at low risk for lymph node metastasis might allow a surgical approach. On the contrary, primary chemoradiation could be directed at patients with a high risk of lymph node metastasis and could be spared the morbidity of a multimodal treatment.

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

The study findings concluded that high pretreatment NLR was linked to lymphovascular space invasion. Thus NLR can be used preoperatively to predict the prognosis of cancer cervix and triage the patients into monovalent treatment- either surgery or chemoradiation. The limitations of this study are it is a single institutional study with a relatively small sample size. As the sample size is small, the relationship between preoperative NLR with the high-risk surgical-pathological features in early-stage cervical cancer may not be statistically observable.

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Conflict of Interest: None declared.

Ethical Approval: The study was approved by the Institutional Ethics Committee.

RECOMMENDATION

Our recommendations are a well-designed prospective study with a larger number of patients in multiple different regions with cervical cancer who will undergo radical surgery is needed and these results should be confirmed. Finally, the postoperative NLR and the change of NLR should also be investigated, which may reflect the dynamic change of balance between the host inflammatory response and immune response.

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