

# Evaluation of the Risk Factors for Pelvic Lymph Node Metastasis in Early Stage Cervical Cancer

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## Abstract

**Objective:** This study evaluated the risk factors for pelvic lymph node metastasis in patients with early stage cervical cancer. **Material and Methods:** A cross sectional study was carried out in the Division of Gynaecologic Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU) between July 2014 and July 2015 to evaluate demographic factors and histopathological findings of women with cervical cancer stage IB-IIA who underwent primary radical hysterectomy and bilateral pelvic lymph node dissection. **Results:** Fifty women aged 30 years or above were included in the study. Lymph node metastases were identified in 20% of patients. By univariate analysis, preoperative anemia, a history of smoking, tumor size greater than 4 cm and lack of cervical inflammatory reaction by histopathology were significant variables associated with lymph node metastasis. Multivariate analysis showed that the lack of inflammatory reaction in the uterine cervix was the most important predictor for pelvic lymph node metastasis when adjusting for other variables. Moderate to severe inflammatory reaction in the uterine cervix was 18 times less likely to have pelvic lymph node metastasis than those who had mild inflammation. **Conclusion:** An association was found between the presence of pelvic lymph node metastasis in cervical cancer and certain variables: the lack of contraceptive use, smoking, preoperative anemia, bulky tumors, invasion of deep two-third of the uterine cervix, mild inflammatory reaction in the cervix, and keratinizing carcinoma. After adjusting for other factors, presence or absence of inflammatory reaction in the cervix was found to be the most important predictor for pelvic lymph node metastasis.

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## Keywords

Cervical Cancer, Lymph Node Metastases, Inflammation

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### 1. Introduction

Cervical cancer is a disease of significant morbidity and mortality worldwide. More than 85% of the global burden occurs in developing countries where it accounts for 13% of all female cancers [1]. There were about 530,000 new cases and 275,000 deaths due to cervical cancer worldwide in 2008 [1]. The burden of cervical cancer is disproportionately high in the developing world and its contribution to cancer burden is significant across all cultures and economies [2]. In the South East Asian region, about half a million people die every year from cancer [3]. 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 [4]. According to the cancer registry report of National Institute of Cancer Research and Hospital in 2005-2007, cervical cancer is the second most common cancer (21.5%) after breast cancer (25.6%) in women treated at that hospital [5]. Clinical staging as defined by the International Federation of Gynecology and Obstetrics (FIGO) is used to recommend specific treatments for cervical cancer [6]. Stages IB and IIA can be treated by means of Piver-Rutledge class III radical hysterectomy and bilateral pelvic lymphadenectomy with or without postoperative adjuvant radiotherapy [7]. About 20% of patients with Stage Ib and Iia carcinoma of the uterine cervix develop disease recurrence despite appropriate treatment by radical surgery and postoperative adjuvant radiotherapy or concurrent chemo radiotherapy [8]. Ninety percent of recurrences occur within two years [9]. Persistent microscopic locoregional disease and/or pre-existing distant spread lead to these recurrences [10].

The literature describes a variety of risk factors for recurrence of early stage carcinoma cervix. Pelvic lymph node metastasis is one of the most important factors influencing prognosis and drives further therapy in patients with cervical cancer [11]. In one cases series of patients with stage IB1 cervical carcinoma, the five-year disease-free interval for patients without lymph node metastasis was 91%, while it was 40% in those with lymph node metastasis [11]. There are also differences in survivability between unilateral and bilateral pelvic lymph node involvement [11]. Well-established risk factors for lymph node metastasis in cervical cancer include the depth of tumor invasion in the cervical stroma, invasion of the lateral cervical ligaments, blood and or lymphatic capillary embolization, histological type, tumor size, and the clinical stage [12] [13].

Cervical cancer is a major public health problem in Bangladesh [14]. In early stage disease, risk of pelvic lymph node metastasis is 15% - 20% for stage I and is 33% for stage II cervical cancer [15]. To date in Bangladesh, there have been no

prior studies examining the risk factors for pelvic lymph node metastasis in early stage cervical cancer. The objective of this study was to determine the risk factors for lymph node metastasis in operable cases of cervical cancer in Bangladesh. This information will help to predict the recurrence rates for women with early stage disease and potentially help identify at-risk women who will need neoadjuvant and adjuvant therapy.

#### **Objective of the study:**

The general objective of this study was to determine the risk factors for pelvic lymph node metastasis in patients with invasive cervical cancer at stages IB1, IB2, IIA1, IIA2. Specific objectives included identifying the association of the following factors with metastases to pelvic lymph nodes: 1) Socio-demographic characteristics like age, education, monthly income, parity, contraceptive user and smoking; 2) The clinical findings of body mass index, hemoglobin level, tumor size, type of growth and stage of the disease; and 3) The histo-pathological findings like histological type, histological grade, deep stromal invasion, invasion of the lateral cervical ligaments, lympho-vascular space involvement and intensity of inflammatory reaction in the uterine cervix.

## **2. Materials and Methods**

From July 2014 through July 2015, a prospective cross-sectional analytical study was performed at the Gynaecological Oncology Division of the Department of Obstetrics and Gynaecology at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, Bangladesh. The Institutional Review Boards (IRB) of BSMMU approved the protocol of the study. The aims and objectives of the study along with the surgical procedure, alternative diagnostic methods, risks and benefits of this study were explained to the patient's in easily understandable local language and then an informed written consent was taken from each of them. Patients were assured that all information and records would be kept confidential. The study benefits included identifying important clinical information to help make rational treatment decisions in the future. Data was collected in a pre-designed structured data collection sheet.

On admission, the particulars of the patients including socio-demographic status, detailed history, presenting complaints and findings of relevant investigations were recorded. The findings of general, abdominal, vaginal and rectal examination and clinical staging were recorded. Operative findings and final histopathology reports were recorded. The sample size was based on the inclusion and exclusion criteria (see below) for the one-year period July 2014 through July 2015.

Fifty patients who were admitted to the Gynaecologic Oncology Division of the Dept of Obstetrics & Gynaecology of Bangabandhu Sheikh Mujib Medical University (BSMMU) with the diagnosis of invasive cervical cancer at FIGO (Federation International Gynecology and Obstetrics) stages IB1, IB2, IIA1, IIA2 fulfilled the inclusion criteria and underwent a radical hysterectomy with bilateral pelvic lymphadenectomy.

Inclusion Criteria for the study included the following: A histologically confirmed invasive cervical cancer. IB1, IB2, IIA1, IIA2 clinical stages based on the criteria established by the International Federation of Gynecology and Obstetrics (FIGO) and confirmed by examination under anesthesia together with CT scan imaging and no other treatment prior to surgery, except for diagnostic conization or LEEP.

Patients were excluded if they had received pre-operative chemotherapy and/or radiotherapy, had clinical stage IA1, IA2, IIB, IIIA, IIIB, IVA, and IVB disease, invasive cervical cancer with pregnancy, co-morbidities such as diabetes mellitus, tuberculosis or a history of taking any immunosuppressive drugs.

Operational definitions were established as the following:

**Education:** Initially the patients were grouped into four groups on the basis of educational background—primary, secondary, higher secondary and graduate and above. For the purpose of fulfilling the statistical assumption of Chi-square test, the four groups were regrouped and categorized into illiterate (those who have no institutional education and could not sign a consent form) and literate (those who have institutional education and could sign a consent form).

**Contraceptive use:** Use of estrogen-progestin contraceptives (usually oral contraceptives, (OCs)) is classified by the International Agency for Research on Cancer (IARC) as a risk factor for the development of cervical cancer. In the present study, only a history of taking oral contraceptive pills was identified.

**BMI (Body Mass Index):** BMI was calculated on the day prior to the surgical procedure.

**Hemoglobin level:** The recorded hemoglobin level was the first laboratory value after diagnosis of cervical cancer prior to interventions with blood transfusions or hematinics.

**Histological grade:** A number of histological grading systems have been proposed that depend upon the type and degree of differentiation of the predominant malignant cells. This study used a modification of the Broder's grading system and divided invasive cancers into the following:

- Large cell keratinizing tumors or well differentiated type—Grade I;
- Large cell non-keratinizing tumors or moderately differentiated tumors—Grade II;
- Small cell non-keratinizing tumors or poorly differentiated tumors—Grade III.

**Keratinizing:** The tumors contain keratin pearls composed of circular whorls of squamous cells with central nests of keratin. Intercellular bridges, keratohyalin granules and cytoplasmic keratinization are usually observed. Cells usually have bizarre shapes and mitotic figures are not frequent.

**Non-keratinizing:** The tumors are composed of generally recognizable polygonal squamous cells that may have individual cell keratinization and intercellular bridges, but keratin pearls are absent. Cellular and nuclear pleomorphism is more obvious, mitotic figures are numerous.

**Histopathological examination:** Slides of the histopathological samples were evaluated and scored by a single histopathologist (author SA) through observation via a Olympus – B × 51 optical microscope.

**Inflammatory reaction in the uterine cervix:** Lack of standardization of the criteria utilized for defining the intensity of the inflammatory reaction is responsible for bias by variation between observers. Hence, a single histopathologist viewed all the slides. Inflammatory reactions in the uterine cervix were categorized into mild, moderate and severe by the presence of chronic inflammatory cells like lymphocytes in and around the cervical stroma.

**Data analysis procedure:**

Data were analyzed using SPSS version 20 (SPSS Incorporation, Chicago, IL, USA). The outcome variable was the presence of pelvic lymph node metastasis.

Independent variables included: age, education, monthly income, parity, contraceptive use, smoking, BMI, pre-operative hemoglobin level, tumor size, type of growth, stage of the disease, histological type, histological grade, deep stromal invasion, invasion of the parametrium, lympho-vascular space involvement, and intensity of inflammatory reaction in the uterine cervix.

The results were expressed as the mean ± Standard Deviation (SD) for the continuous variables and the categorical variables were expressed as frequency and percentage. Pearson Chi-Square test or Fisher's exact test were chosen to initially analyze the association between lymph node status and socio-demographic, clinical and histopathological variables. Odd ratios (OR) obtained from the multiple logistic regressions were used to estimate the risk of developing pelvic lymph node metastasis.

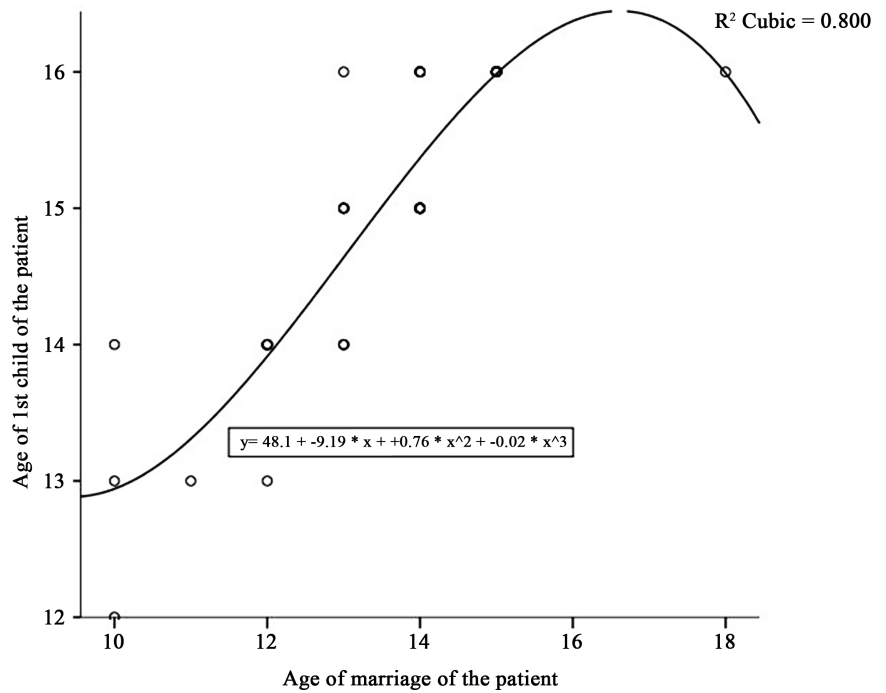
### 3. Results

Fifty women aged 30 years or above were included in the study. **Table 1** and **Table 2** summarizes the clinical characteristics of these women. **Table 1** shows that more than half of the patients were older than 50 years with little or no education, were multiparous, and of a lower income status. About fifty-five percent of patients used contraception and thirty percent of patients were smokers.

The mean age of the patients (**Table 2**) was 47.22 years with SD ± 8.9 (range: 32 - 70 years). The mean age of menarche of the patients was 12.42 years (SD = 0.67 years, range: 11 - 15 years). The mean age of marriage of the patients was 13.58 years (SD ± 1.53 years, range: 10 - 18 years) and the mean age of the first delivery was 15.02 years (SD ± 1.02, range: 12 - 16 years). **Figure 1** shows the distribution of age of marriage and age of first delivery for the patients. Early marriage is common among women from Bangladesh especially those who are impoverished.

The mean body mass index (BMI) of the patients was 22.64 kg/m<sup>2</sup> with SD 3.79, with the range: 15.63 - 33.16 kg/m<sup>2</sup>. The mean hemoglobin (Hb) level of the patients was 10.17 gm/dl with SD 1.37, with the range: 6.50 - 12.20 gm/dl.

**Table 3** and **Table 4** summarize the size and histopathological features of cervical cancers in these 50 patients. **Table 3** shows that in the majority of cases, the



**Figure 1.** The distribution of the age of marriage and maternal age of first pregnancy for fifty women with stage ib and iia cervical cancer.

**Table 1.** Socio-demographic characteristics of fifty patients with early stage cervical cancer.

	No (%)
<b>Age</b>	
<50 years	24 (48)
≥50 years	26 (52)
<b>Education</b>	
Illiterate	28 (56)
Literate	22 (44)
<b>Monthly income*</b>	
≤10,000 Taka (118 USD)	26 (52)
>10,000	24 (48)
<b>Parity</b>	
Multipara	34 (68)
Grand multipara	16 (32)
<b>Contraceptive Use</b>	
Yes	27 (54)
No	23 (46)
<b>Smoking</b>	
No	35 (70)
Yes	15 (30)

\*1 Bangladeshi Taka = 0.012 USD.

**Table 2.** Age of fifty patients with early stage cervical cancer and their age of menarche, marriage and first pregnancy. Descriptive statistics of the continuous variables in the study.

	Minimum	Maximum	Mean	Standard Deviation
Age of the patient	32	70	47.22	8.95
Age of menarche	11	15	12.42	0.67
Age of marriage	10	18	13.58	1.53
Age of first Pregnancy	12	16	15.02	1.02

**Table 3.** Clinical finding of the cervical tumor growth for fifty patients with early stage cervical cancer.

<i>Growth size</i>	No (%)
≤4	32 (64)
>4	18 (36)
<i>Type of growth</i>	
Cauliflower	18 (36)
Ulcerative	5 (10)
Infiltrative	12 (24)
Polypoidal	15 (30)
<i>Stage of tumor</i>	
IB1	26 (52)
IB2	5 (10)
IIA1	6 (12)
IIA2	13 (26)

size of the growth was  $\leq 4$  cm (which include patients with Stages Ib1 and IIA1). Maximum growth was cauliflower-like and the majority of patients (52%) had stage IB1 cancers. **Table 4** shows that morphological categorization was squamous cell carcinoma in most of the cases. The majority of the patients presented with moderately differentiated or grade II lesions. In 28% of cases, the depth of stromal invasion was equal to or greater than two-thirds of cervical stroma. Lymphovascular space invasion was found in majority of the patients, parametrial invasion was histologically identified in 4% of patients and in only 10% of patients was there severe inflammatory reaction of the uterine cervix.

The histopathological study identified lymph node metastases in ten patients (20%). In these patients, the number of involved lymph nodes ranged from 1 to 20. By univariate analysis of clinical and sociodemographic variables, a history of smoking, non-contraceptive user, the preoperative hemoglobin level less than 10.0 gm/dl, tumor size more than 4 cm and mild inflammatory reaction in the uterine cervix were the significant variables associated to pelvic lymph node metastasis ( $p < 0.05$ ). **Table 5** shows that lymph node metastasis was higher in

**Table 4.** Histopathological findings of the radical hysterectomy specimen for fifty patients with early stage cervical cancer.

<i>Histological Type</i>	No	(%)
Squamous Cell Carcinoma	43	(86)
Adenocarcinoma	7	(14)
<b><i>Histological Grade</i></b>		
Grade I	9	(18)
Grade II	32	(64)
Grade III	9	(18)
<b><i>Depth of Invasion</i></b>		
<1/3 Stroma	30	(60)
1/3 - 2/3 Stroma	6	(12)
≥2/3 Stroma	14	(28)
<b><i>Lymphovascular Invasion</i></b>		
No	12	(24)
Yes	38	(76)
<b><i>Invasion of Parametrium</i></b>		
No	48	(96)
Yes	2	(4)
<b><i>Inflammatory Reaction of Uterine Cervix</i></b>		
Mild	18	(36)
Moderate	27	(54)
Severe	5	(10)

**Table 5.** Sociodemographic characteristics and metastasis to the pelvic lymph nodes for fifty patients with early stage cervical cancer.

	Metastasis to pelvic lymph nodes		Chi-Square	P value	Crude OR with 95% CI
	No	Yes			
	N (%)	N (%)			
<b><i>Age</i></b>					
<50 years	17 (71)	7 (29)	1.45	0.23	0.32 (0.07, 1.41)
≥50 years	23 (89)	3 (11)			
<b><i>Education</i></b>					
Illiterate	23 (82)	5 (18)	0.005	0.94	1.35 (0.34, 5.43)
Literate	17 (77)	5 (23)			
<b><i>Monthly income</i></b>					
≤10,000	20 (77)	6 (23)	0.045	0.83	0.67 (0.16, 2.73)
>10,000	20 (83)	4 (17)			
<b><i>Parity</i></b>					
Multipara	27 (79)	7 (21)	0.000	1.00	0.89 (0.20, 4.01)
Grand multipara	13 (81)	3 (19)			
<b><i>Contraceptive Use</i></b>					
Yes	25 (93)	2 (7)	4.23	0.048	6.67 (1.25, 35.65)
No	15 (65)	8 (35)			
<b><i>Smoking</i></b>					
No	32 (91)	3 (9)	7.29	0.007	9.33 (1.96, 44.36)
Yes	8 (53)	7 (47)			



young, multiparous patients having less income but the findings were not statistically significant ( $p > 0.05$ ). It was observed that less use of contraception was associated with a higher incidence of lymph node metastasis and this was statistically significant ( $p = 0.048$ ). Similarly, lymph node metastasis was significantly more likely among the smoker than the non-smoking patient ( $p = 0.007$ ).

**Table 6** shows that there is a greater incidence of lymph node metastases for stage IB2 and IIA2 tumors though this was not statistically significant ( $p = 0.26$ ). It was observed that lower hemoglobin levels were associated with the lymph node metastasis and this was statistically significant ( $p = 0.03$ ). Similarly there was association between size of the growth and the lymph node metastasis. The greater the size of the tumor, the increased likelihood of lymph node metastasis and it was statistically significant ( $p = 0.04$ ).

**Table 6.** Clinical findings and metastasis of pelvic lymph-nodes for fifty patients with early stage cervical cancer.

	Metastasis of Pelvic Lymph Nodes		Chi-Square	P value	Crude OR with 95% CI
	No	Yes			
	N (%)	N (%)			
<b>Body Mass Index</b>					
<18.5 kg/m <sup>2</sup>	5 (83)	1 (17)	0.30	0.91	
18.5 - 23.49 kg/m <sup>2</sup>	18 (82)	4 (18)			
≥23.5 kg/m <sup>2</sup>	17 (77)	5 (23)			
<b>Hemoglobin</b>					
<10 gm/dl	13 (65)	7 (35)	4.69	0.03	0.21 (0.05, 0.93)
≥10 gm/dl	27 (90)	3 (10)			(1 ÷ 0.21 = 4.7)
<b>Cervical Tumor Size</b>					
≤4	29 (90)	3 (10)	4.72	0.04	1.7 (1.15, 2.08)
>4	10 (56)	8 (44)			
<b>Type of Tumor</b>					
Cauliflower	15 (83)	3 (17)	1.98	0.58	
Ulcerative	5 (100)	0 (0)			
Infiltrative	9 (75)	3 (25)			
Polypoidal	11 (73)	4 (27)			
<b>Stage of Tumor</b>					
IB1	23 (88)	3 (12)	3.977	0.266	
IB2	4 (80)	1 (20)			
IIA1	5 (83)	1 (17)			
IIA2	8 (62)	5 (38)			

Among the histopathological variables, squamous-cell keratinizing carcinoma or grade I lesion versus others ( $p = 0.49$ ), depth of tumor invasion more than two-third of cervical stroma ( $p = 0.46$ ), presence of lympho-vascular invasion and invasion of parametrium ( $p = 0.36$ ) were associated with lymph node metastasis but this was not statistically significant.

**Table 7** summarizes the histopathologic features of cell type, grade, depth of invasion, lymphovascular space involvement, and inflammatory infiltrate for the fifty radical hysterectomy specimens and correlation with nodal involvement. Lymph node metastases were higher for adenocarcinomas but it was not statistically significant ( $p = 0.13$ ). Similarly, there was a higher frequency of lymph node metastases in well-differentiated keratinizing carcinoma but statistically it was not significant ( $p = 0.49$ ). It was also observed that lymph node metastases

**Table 7.** Histopathological findings and metastases of pelvic lymph nodes for fifty patients with early stage cervical cancer.

	Metastasis of Pelvic Lymph Nodes		Chi-Square	P value	Crude OR with 95% CI
	No	Yes			
	N (%)	N (%)			
<b><i>Histological Type</i></b>					
<b>Squamous Cell Carcinoma</b>	36 (84)	7 (16)	2.66	0.13	3.86 (0.70, 21.15)
<b>Adenocarcinoma</b>	4 (57)	3 (43)			
<b><i>Histological Grade</i></b>					
<b>Grade I</b>	6 (67)	3 (33)	1.41	0.49	
<b>Grade II</b>	27 (84)	5 (16)			
<b>Grade III</b>	7 (78)	2 (22)			
<b><i>Depth of Invasion</i></b>					
<b>&lt;1/3</b>	24 (80)	6 (20)	2.14	0.46	
<b>1/3 - 2/3 Stroma</b>	6 (100)	0 (0)			
<b>≥2/3 Stroma</b>	10 (71)	4 (29)			
<b><i>Lymphovascular Invasion</i></b>					
<b>No</b>	10 (83)	2 (17)	0.000	1.000	1 (0.17, 5.77)
<b>Yes</b>	30 (79)	8 (21)			
<b><i>Invasion of Parametrium</i></b>					
<b>No</b>	39 (81)	9 (19)	1.17	0.36	4.33 (0.25, 76.05)
<b>Yes</b>	1 (50)	1 (50)			
<b><i>Inflammatory Reaction of Uterine Cervix</i></b>					
<b>Mild</b>	9 (50)	9 (50)	14.04	0.000	0.038 (0.004, 0.347) (1 ÷ 0.038 = 26)
<b>Moderate</b>	26 (96)	1 (4)			
<b>Severe</b>	5 (100)	0 (0)			

were more frequent when stromal invasion was more than two-thirds of the cervical stroma, though it was not statistically significant ( $p = 0.46$ ). The association was found between inflammatory reaction in the uterine cervix and the lymph node involvement, with the less the inflammatory reaction, the higher frequency of lymph node metastases ( $p = 0.000$ ).

By univariate analysis, the history of non-contraceptive use, smoking, pre-operative anemia, tumor size > 4 cm and mild inflammatory reaction in the uterine cervix was found to be statistically significantly associated with pelvic lymph node metastases among cervical cancer patients (Table 8).

These variables were also selected for multivariate analysis by constructing a binary logistic model to find out the important predictors for pelvic lymph node metastases while adjusting for other factors. The Hosmer-Lemeshow test for goodness-of-fit showed the model Chi-Square was not significant. The factors in the model explained 66% of the variability of the outcome variable [Nagelkerke R square 65.6]. The model also classifies the cases 90% correctly. The model showed samples with moderate to severe inflammatory reaction in the cervix were eighteen times less likely to have pelvic lymph node metastases than those who had mild inflammation in the cervix ( $\chi^2 = 5.07$ ,  $p = 0.024$ , Adjusted Odds ratio with 95% CI [0.054, (0.004, 0.68)]).

#### 4. Discussion

This is a cross-sectional study that included patients with stage IB1, IB2, IIA1 to IIA2 invasive cervical cancer who were admitted to the division of gynaecologic oncology of BSMMU, fulfilled the inclusion criteria of our study and underwent radical hysterectomy with bilateral pelvic lymphadenectomy. To improve the quality of the data, the histopathologic examination was undertaken by a single pathologist, which helped to reduce any bias associated to inter-observer variability.

The lymph node metastases were identified in 20% of the patients. The frequency of lymph node metastases reported in this study agrees with rates reported by other authors for Stages IB and IIA (15.0% to 25.0%) [12]. In this study lymph node metastasis was observed in higher frequency in young,

**Table 8.** Predictor for pelvic lymph node metastasis for fifty patients with early stage cervical cancer: logistic regression.

	Wald	Sig.	Exp(B) (Odds Ratio)	95% C.I. for EXP(B)	
				Lower	Upper
H/o Contraceptive	3.059	0.080	7.611	0.783	74.009
H/o Smoking	0.759	0.384	2.631	0.298	23.201
Hb < 10 mg/dl	0.041	0.839	0.794	0.086	7.361
Growth size	0.000	0.999	0.000	-	-
<b>Moderate to severe inflammation</b>	<b>5.072</b>	<b>0.024</b>	<b>0.054</b> (1 + 0.054 = 18)	<b>0.004</b>	<b>0.685</b>

multiparous patients having less income but the findings were not statistically significant ( $p > 0.05$ ). It was observed that, the less the use of contraception, the more the lymph node metastasis and this was statistically significant ( $p = 0.048$ ). Similarly, lymph node metastasis was significantly more common among the smoker than the non-smoker ( $p = 0.007$ ). These variables are not cited in the previous literature as a predictor of regional lymph node metastasis in cervical cancer. To see the association between lymph node metastasis and the use of contraception, studies with a larger sample size are needed.

Another important observation was the association of a lower the hemoglobin level with an increased frequency of lymph node metastasis and this was statistically significant ( $p = 0.03$ ). Size of tumor was associated with increased lymph node metastasis ( $p = 0.04$ ). Preoperative anemia (hemoglobin less than 10.0 gm/dl) has been frequently cited in the literature as a predictor of regional lymph node metastasis in cervical cancer. There are several studies that have demonstrated the prognostic importance of anemia in patients with cervical cancer who are treated with radiotherapy [16] [17]. Anemia leads to low tumor oxygenation and consequently may induce angiogenesis through an increase of endothelial growth factor expression, such as VEGF (vascular endothelial growth factor) [18]. The increase in the tumor microvascular density would facilitate the tumor dissemination through the blood. Neoplastic cells can also reach the lymph nodes via hematogenous pathway through the anastomoses of blood and lymphatic systems [19] [20]. While one study found that the expression of the main pro-lymphangiogenic factor (VEGF-C) is not induced by tumor hypoxia [21], lymphangiogenesis may be stimulated by anemia, as both angiogenesis and lymphangiogenesis are events that frequently co-exist [19].

The reason for a greater frequency of lymph node metastases in cervical cancer with deep cervical stromal invasion is related to the mechanisms of tumor progression and dissemination. A degradation of the extracellular matrix produced by proteolytic enzymes synthesized by the neoplastic cells is a requisite for the neoplastic invasion of the cervical stroma [19] [22]. The enzymatic digestion of the extracellular matrix releases some fragments with pro-angiogenic and pro-lymphangiogenic activity, thus forming new blood and lymph capillaries. The increase in the lymph microvascular density is responsible of the dissemination of neoplastic cells to regional lymph nodes [20] [21] [23] [24].

In our study, regional lymph node metastases were more frequent in well-differentiated keratinizing carcinoma than in the other histological types. Typically, the keratinizing carcinoma is considered a well-differentiated type of cancer, which is not thought to have greater metastatic potential than more poorly differentiated cancers [25]. Stratified non-keratinized epithelium lining covers the uterine cervix. Therefore, keratin production is not a normal state for the epithelium cells of the uterine cervix; however, keratin may be produced during neoplastic transformation. The synthesis of keratin would indicate a modification in the genetic profile of the cervical epithelium cells. It is reasonable to expect that such a modification not only involve the genes associated to keratin

expression, but also others [26]. It is likely that some of the genes associated with the mechanisms of tumor progression and dissemination also suffer modifications in their expression. The presence of keratin in carcinoma of the uterine cervix would represent an indirect histopathological signal of changes in the genetic cell profile, which would be the carriers of a greater potential for metastasis. This is just a speculative hypothesis that should be confirmed in future studies. Published studies on keratinization of uterine cervix carcinoma have not analyzed this variable as a potential predictor of regional lymph node metastasis, but have assessed its prognostic value [27] [28].

We found a strong inverse relationship between inflammatory reaction in the uterine cervix and lymph node metastasis ( $P = 0.000$ ). The inflammatory reaction in the uterine cervix was weak (absent or mild) as a host response, which determined a greater risk of lymph node metastasis. This finding should be interpreted keeping in mind that the immune system has an important role in the suppressing control of neoplasms. Failures in the immune surveillance system, particularly in the cell-mediated immunity, may be involved not only in the carcinogenesis but also in the progression and dissemination of neoplastic cells [29] [30] [31].

It is well known that tumor cells manage to escape from the mechanisms of immune surveillance and to promote a depression in cell immunity. Several mediators involved in the immune depression which are produced by the neoplastic cells include: TGF- $\beta$  (transforming growth factor- $\beta$ ) interleukin IL-4, interleukin IL-6, interleukin IL-10, MCP-1 (macrophage chemotactic protein-1), MDF (macrophage deactivating factor), SER (suppressive E-receptor), IAP (immunosuppressive acidic protein), prostaglandin PGE<sub>2</sub>, protein p15E, metallo-proteinases, among others [32] [33]. Therefore, it is not surprising that the absence of an effective inflammatory response to uterine cervix carcinoma is associated to a greater frequency of pelvic lymph node metastasis. The results presented here agree with those reported by Bethwaite *et al.*, where a significant association between the T-lymphocytes low-density in the tumor and the presence of lymph node metastasis was found among 73 patients with uterine cervix carcinoma (stage IB) [34]. Another study including 59 women with uterine cervix carcinoma reported lower rates of lymph node metastases in patients with cervixes which were densely infiltrated by CD8<sup>+</sup> lymphocytes [35]. Our data supports this finding.

## 5. Conclusions

This study has found that the presence of pelvic lymph node metastasis in cervical carcinoma, stages IB1, IB2, IIA1, IIA2 was associated to smoking, non user of contraception, preoperative anemia (hemoglobin rate less than 10.0 g/dl), bulky tumors, and absent or slight inflammatory reaction in the uterine cervix. Among these factors, the lack of inflammatory reaction in the uterine cervix was found to be the most important predictor for pelvic lymph node metastasis when adjusting for other risk factors.

Patients with moderate to severe inflammatory reaction in the cervix of the radical hysterectomy specimen were eighteen times less likely to have pelvic lymph node metastases than those who had mild inflammation in the cervix.

### Limitation of the Study

In this study, the sample size is small, so other important risk factors for pelvic lymph node metastases in early stage cervical cancer may not be statistically observable. Additionally, the patients who were chosen were highly selected to undergo primary surgery without prior chemotherapy or radiation. In Bangladesh with the high burden of cervical cancer and limited cancer care facilities; the majority of women with cervical cancer receive neoadjuvant chemotherapy while waiting to undergo a surgical approach [36]. Our selected population may not be representative of cervical cancer patients in Bangladesh as a whole.

### Conflicts of Interest

The authors have no conflicts of interest.

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