Original Article

Association between Preoperative Neutrophil to Lymphocyte Ratio and Pelvic Lymph Node Metastasis in Early Stage Cervical Cancer

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Objective: To assess the association of pre-operative neutrophil to lymphocyte ratio [NLR] with pelvic lymph node [LN] metastasis and other clinical features including, stage, progression-free survival [PFS], and overall survival [OS] in early stage cervical cancer.

Materials and Methods: Clinical and pathological data of early stage cervical cancer patients (stage IA2 to IIA2) undergoing radical hysterectomy with pelvic lymphadenectomy between January 1, 2008 and December 31, 2015 were collected and analyzed.

Results: Mean age of 121 patients included in the study was 45±10.32 years. After a median follow-up of 38 months (range, 6 months to 114 months), 8 had recurrences (6.6%) and 3 were dead (2.5%). The 5-year PFS and 5-year OS were 91.8% and 93.8% respectively. High NLR (≥2.03) was significantly associated with higher FIGO stage (stage II) and pelvic lymph node metastases. Only FIGO stage and adjuvant treatment, but not high NLR, were significantly associated with survivals.

Conclusion: High NLR was significantly associated with LN metastasis bot not survival in cervical cancer patients initially treated with radical surgery.

Keywords: Early stage cervical cancer, Neutrophil to lymphocyte ratio, Pelvic node metastasis

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Cervical cancer is the second most common cancer in South-Eastern Asia with the age-standardized incidence rate (ASR) of 16.3 in 100,000 persons per year. In Thailand, there are over 8,000 new cases of cervical cancer each year[1].

Treatment modalities for cervical cancer include surgery, radiation, chemotherapy, or concurrent chemoradiation. The type of treatment depends mainly on stage of diseases which is traditionally categorized by clinical data according to the International Federation of Gynecology and Obstetrics [FIGO][2]. Early stage disease is generally treated by surgery while more advanced stages are treated with concurrent chemoradiation, radiation or chemotherapy alone. Surgical procedures for stage I-IIA cancer are radical hysterectomy and pelvic lymph node dissection, with or without para-aortic lymphadenectomy.

Several clinical and surgico-pathological prognostic factors are recognized in early stage cervical cancer, such as, tumor size, lymphovascular invasion [LVSI], depth of stromal invasion, parametrial involvement, surgical margin status, and lymph node metastasis[3-5]. Among these, lymph node metastasis which is one of the most important features has major impact on treatment. Presence of nodal metastasis evidenced from pre-operative imaging in early stage disease may avert the main treatment from surgery to concurrent chemoradiation[6]. On the other hand, nodal metastasis discovered from the surgico-pathological results mandate adjuvant treatment to reduce

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recurrences[7].

Pre-operative imaging, e.g. CT scan, MRI, or PET scan provide more clinical information of tumor than mere physical examination and also give a clue regarding the status of pelvic and para-aortic lymph nodes. Although encouraged by FIGO, the imaging procedure is not mandatory because it is not possible in all patients especially in low-resource settings. Thus, other means to predict the status of these lymph nodes would be useful.

Many studies showed that the neutrophil to lymphocyte ratio [NLR] was associated with prognosis of various cancers, such as, colon, liver, breast[8-11] and many gynecologic cancers including of endometrium, vulva, and ovary[12-15]. However, only few studies evaluated a prognostic role of preoperative NLR in cervical cancer[16-18]. Furthermore, the results of these studies were inconsistent especially in patients with early stage disease treated by surgery. Recently, there were two systematic review and meta-analysis evaluating the prognostic role of NLR in cervical cancer patient, and concluded that the elevated pre-treatment NLR was associated with poorer overall survival and shorter progression free survival. However, most of the studies included in the meta-analysis reports were retrospective and had small sample[19,20].

The present study aimed to determine the association of pre-operative NLR and lymph node metastasis in early stage cervical cancer patients treated with radical hysterectomy and pelvic node dissection. The association of NLR with other prognostic factors and survivals were also evaluated.

Materials and Methods

Study sample

The study obtained an approval from the Ethics Committee for Research involving Human Subjects of the institution. The patients with early stage cervical cancer (FIGO stage IA to IIB) treated with radical hysterectomy with pelvic node dissection at the Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital between January 1, 2008 and December 31, 2015 were identified. Exclusion criteria were the patients who had: surgery elsewhere and referred to our hospital for adjuvant treatment, radiation or chemotherapy prior to surgery, history of other cancer(s), hematologic or autoimmune diseases, received the immune suppressive drugs, incomplete medical records including the preoperative laboratory data, operative note, and pathological reports. The patients who had signs of infection within one week before operation were excluded from the study. Infection was defined when there was any of the following: body temperature >38°C or <36°C, pulse rate >90 bpm, systolic blood pressure <90 mmHg, respiratory rate >20 bpm, $PaCO_2$ <32 mmHg, lactic acidosis diagnosed from blood sampling, or specific site of infection identified[21].

Outcome assessment

Data collected were: age, pre-operative complete blood count, stage of disease according to the FIGO 2009 criteria, histopathology, tumor grade, date of surgery, histopathology, tumor size, depth of invasion, presence of parametrial involvement, presence of lymphovascular invasion, number of lymph node retrieved, status of lymph node, date of last follow-up, status of disease at last follow-up, and living status. Pre-operative complete blood count must be within a month prior to the date of surgery. Disease-free survival [DFS] was calculated from date of surgery until date of recurrence, or last evaluation in the patients who were lost to follow-up. Overall survival [OS] was obtained from date of surgery to date of death or last evaluation in patients who were alive at the end of study.

Statistical methods

Data were analyzed using SPSS statistical software, version 22.0 (IBM corporation, Armonk, NY, USA). Descriptive statistics were used to analyze demographic data and were summarized as numbers with percentage or median with range. The optimal value of NLR significantly associated with nodal metastasis was determined by the receiver operating characteristic curve (ROC curve). Its association with other clinicopathological factors of cervical cancer was also studied by χ^2 test or fisher exact test as appropriate. Survivals were analyzed by the Kaplan-Meier method and were compared between groups with log rank test. Multivariable analysis was performed by Cox regression analysis. The *p*-values of <0.05 were considered significant.

Results

We found 151 patients had early stage of cervical cancer (FIGO stage IA-IIA) during the study period. Thirty patients who had received and NACT before surgery or incomplete data were excluded. A total of 121 patients were included in the study: 106 patients (87.6%) were in stage I and 15 patients (12.4%) in stage II. The mean age was 45 years (SD 10.32). Mean tumor size was 2.29 cm (SD 1.52). Squamous cell

carcinoma [SCC] was the most common cell type that found in 82 patients (67.8%) whereas other cell types was found in only 39 patients (32.2%). We found 31 patients (25.6%) had deep stromal invasion, 11 patients (29.1%) had tumor at margin, 16 patients (13.2%) had parametrial involvement, 27 patients (22.3%) had LVSI, and 15 patients (12.4%) had positive pelvic lymph node metastasis.

Adjuvant treatment was given to 47 patients (38.8%) according to the risk factors identified: RT in 32 patients (26.4%), and CCRT in 15 patients (12.4%). Of the 121 patients, eight patients had recurrences (6.6%), most occurred in the first year after surgery and 3 patients (2.5%) were dead. The 5-year PFS and 5-year OS were 91.8% and 93.8% respectively. The clinic-pathologic data are shown in Table 1.

The median of NLR of our patients was 2.03 (range, 0.74 to 30). NLR at different levels were studied to determine the most optimal cut-off point to predict lymph node metastasis and stage of disease. We found NLR of 2.03 could best predict lymph node metastasis with the sensitivity of 73.3% and the specificity of 47.2%. The high NLR (≥2.03) was significantly associated with pelvic lymph node metastasis ($p = 0.049$) and higher FIGO stage ($p = 0.049$). We did not find any association between high NLR and other clinic-pathological factors including age, cell type, tumor size, LVSI, stromal invasion, margin status, parametrial involvement, the use of adjuvant treatment, recurrence, and living status.

We also determined the association of NLR as well as other clinic-pathological factors and PFS and OS by univariate analyses. FIGO stage and adjuvant treatment were the only significant prognostic factors for PFS and OS but not NLR nor other prognostic factors. FIGO stage, adjuvant treatment, NLR, and LN metastasis were included for multivariate analyses. Only adjuvant treatment [RT] was significantly associated with survivals. Hazard ratios [HRs] of more advanced stage (stage II) were 0.394 (95% confidence interval [CI], 0.088 to1.776; $p = 0.226$) for PFS and 0.367 (95% CI, 0.078 to 1.726; $p = 0.204$) for OS. The corresponding HRs of adjuvant treatment [RT] were 0.079 (95% CI, 0.008 to 0.809; $p = 0.033$) for PFS and 0.068 (95% CI, 0.006 to 0.707; $p = 0.024$) for OS. On the other hand, HRs of adjuvant treatment [CCRT] were 0.418 (95% CI, 0.093 to 1.884; $p = 0.256$) for PFS and 0.447 (95% CI, 0.090 to 2.534; $p = 0.385$) for OS.

The NLR was not a significant prognostic factor for both PFS and OS, with HR of 0.349 (95% CI, 0.088 to 2.359; $p = 0.349$) and 0.477 (95% CI, 0.090 to 2.534; $p = 0.385$) respectively.

Discussion

Many clinicopathological factors including of FIGO stage, tumor size, marginal status, parametrial involvement, deep stromal invasion, and LVSI were associated with progression of disease, recurrences, and survivals in cervical cancer patient. Among these, lymph node status is one of the most important factors because the presence of LN metastasis was found to be associated with higher rate of recurrences, lower PFS and OS comparing to those without nodal metastasis. Hence, prediction of LN metastasis before operation would be useful for the physician to tailor the modality of treatment for each patient.

Many pre-operative imaging studies can be used to predict LN status, the sensitivity, specificity, and accuracy for detecting LN metastasis were 64.3%, 69.1%, and 67.5% for MRI, and 28.6%, 83.6%, and 65.1% for PET/CT, respectively. MRI was more sensitive than PET/CT for detecting metastatic LN in patients with cervical cancer[22]. Aside from the limited sensitivity to detect nodal metastasis, some techniques are not available in low-resource settings or limited access due to the cost or reimbursement policy. Therefore, other alternative means to detect nodal metastasis would be useful.

Current knowledge has shown a positive relationship between inflammatory process and cancer pathogenesis. Pre-clinical studies showed inflammatory cytokines and antigen-specific T and B cells can stimulate cancer growth, promote cancer cell implantation and metastasis, and prolong cancer cells survival[23]. The increase of neutrophil and relative decrease of lymphocyte in the inflammatory response, hence, has been investigated as a poor prognostic factor in many cancers.

The NLR is a ratio of neutrophils count over lymphocytes. The value can easily be obtained mathematically from the complete blood count which is a basic laboratory test routinely assessed in every patient pre-operatively. The role of NLR as a prognostic factor for survivals in cervical cancer was reported. However, data about the association between NLR and LN metastasis in cervical cancer patients especially in the early stage initially treated with surgery was still limited[16-18].

The present study aimed to demonstrate the association between the preoperative NLR and pelvic node metastasis in early stage cervical cancer patient who was initially treated with radical hysterectomy and

Table 1. Association between NLR and clinicopathological factors of cervical cancer

Variables	No. of patients (n = 121)	NLR		*p*-value*
		<2.03	≥2.03	
Age (years)				0.081
<45	67 (55.4)	33 (49.3)	34 (50.7)	
≥45	54 (44.6)	28 (51.9)	26 (48.1)	
Cell type				0.602
SCC	82 (67.8)	40 (48.8)	42 (51.2)	
Non SCC	39 (32.2)	21 (53.8)	18 (46.2)	
FIGO stage				0.049
Stage I	106 (87.6)	57 (53.8)	49 (46.2)	
Stage II	15 (12.4)	4 (26.7)	11 (73.3)	
Tumor size (cm)				0.489
≤4	112 (92.6)	57 (50.9)	55 (49.1)	
>4	9 (7.4)	4 (44.4)	5 (55.6)	
LVSI				0.254
No	94 (77.7)	50 (53.2)	44 (46.8)	
Yes	27 (22.3)	11 (40.7)	16 (59.3)	
Stromal invasion				0.498
No	90 (74.4)	47 (52.2)	43 (47.8)	
Yes	31 (25.6)	14 (45.2)	17 (54.8)	
Margin				0.73
Negative	110 (90.9)	56 (50.9)	54 (49.1)	
Positive	11 (9.1)	5 (45.5)	6 (54.5)	
Lymph node metastasis				0.049
No	106 (87.6)	57 (53.8)	49 (46.2)	
Yes	15 (12.4)	4 (26.7)	11 (73.3)	
Parametrium involvement				0.084
No	105 (86.8)	56 (53.3)	49 (46.7)	
Yes	16 (13.2)	5 (31.30	11 (68.7)	
Adjuvant treatment				0.668
No	74 (61.2)	39 (52.7)	35 (47.3)	
RT	32 (26.4)	16 (50.0)	16 (50.0)	
CCRT	15 (12.4)	6 (40.0)	9 (60.0)	
Recurrence				0.163
No	113 (93.4)	59 (52.2)	54 (47.8)	
Yes	8 (6.6)	2 (25.0)	6 (75.0)	
Living status				0.119
Alive	118 (97.5)	61 (51.7)	57 (48.3)	
Dead	3 (2.5)	0 (0)	3 (100)	

Data are presented as number (%)
* *p*-value obtained by Chi-square
CCRT = concurrent chemoradiation, FIGO = the International Federation of Gynecology and Obstetrics, LVSI = lymphovascular space invasion, NLR = neutrophil to lymphocyte ratio, RT = radiation therapy, SCC = squamous cell carcinoma

pelvic node dissection. We found that NLR of ≥2.03 (high NLR) was associated with pelvic LN metastasis and higher stage (FIGO stage II). However, we could not demonstrate the association of NLR and other unfavorable prognostic factors as well as survivals. Only higher stage and receiving adjuvant therapy were significant poor prognostic factors for survivals by univariate analyses in present study.

The results of the present study were compared with findings from two previous studies

Table 2. Univariate analysis of progression-free survival and overall survival of cervical cancer patients

Variables	Number (n = 121)	PFS		OS	
		Percent	*p*-value*	Percent	*p*-value*
Age (years)			0.709		0.791
<45	67	94		97	
≥45	54	92.6		98.1	
NLR			0.13		0.068
<2.03	61	96.7		100	
≥2.03	60	90		95	
Cell type			0.739		0.982
SCC	82	93.9		97.6	
Non SCC	39	92.3		97.4	
FIGO stage			0.001		<0.001
Stage I	106	96.2		99.1	
Stage II	15	73.3		86.7	
Tumor size (cm)			0.429		0.659
≤4	112	92.9		97.3	
>4	9	100		100	
LVSI			0.142		0.433
No	94	91.5		96.8	
Yes	27	100		100	
Stromal invasion			0.559		0.941
No	90	94.4		97.8	
Yes	31	90.3		96.8	
Margin			0.085		0.633
Negative	110	94.5		97.3	
Positive	11	81.8		100	
Lymph node metastasis			0.216		0.088
No	106	94.3		98.1	
Yes	15	86.7		93.3	
Parametrium involvement			0.97		0.204
No	105	93.3		98.1	
Yes	16	93.8		93.8	
Adjuvant treatment			0.001		0.003
No	74	98.6		98.6	
RT	32	90.6		100	
CCRT	15	73.3		86.7	

* *p*-value obtained by log rank test.
CCRT = concurrent chemoradiation, FIGO = the International Federation of Gynecology and Obstetrics, LVSI = lymphovascular space invasion, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PFS = progression free survival, RT = radiation therapy, SCC = squamous cell carcinoma

which evaluated the prognostic role of NLR[17,18]. The study of Wang et al. did not show significant association between NLR and LN metastasis while the result from our study showed marginal significant association ($p = 0.049$). Of note, the patients in their study had neoadjuvant chemotherapy prior to surgery. The pre-operative treatment may have altered the status of LN, resulting in their negative finding[17].

The study by Zhang et al which included a large number of cervical cancer patients initially treat with radical surgery (465 patients) was the only study which could find NLR as a poor prognostic factor. The NLR was significantly associated with LN metastasis and deep stromal invasion as well as poor survival[18]. In contrast, both the present study and Wang's study could not demonstrate the prognostic role of NLR to

Table 3. Multivariate survival analysis of OS and PFS

Variables	PFS		OS	
	HR (95% Cl)	*p*-value*	HR (95% Cl)	*p*-value*
FIGO stage	0.394 (0.088 to 1.776)	0.226	0.367 (0.078 to 1.726)	0.204
Adjuvant RT	0.079 (0.008 to 0.809)	0.033	0.068 (0.006 to 0.707)	0.024
Adjuvant CCRT	0.418 (0.093 to 1.884)	0.256	0.359 (0.079 to 1.639)	0.186
NLR	0.349 (0.088 to 2.359)	0.349	0.477 (0.090 to 2.534)	0.385

* *p*-value obtained by Cox regression analysis
CI = confidence interval, CCRT = concurrent chemoradiation, FIGO = the International Federation of Gynecology and Obstetrics, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PFS = progression free survival, RT = radiation therapy

predict survivals. The smaller number of patients in our study and the use of neoadjuvant chemotherapy in the study of Wang et al as mentioned above may hinder the influence of NLR on prognosis.

Further studies with larger number of patients with similar characteristic features are needed to confirm the role of NLR as a prognostic factor in early stage cervical cancer. Aside from a small number of patients, other limitations in our study were aware of. Being a retrospective study, selective bias could hardly be avoided. Some patients had to be excluded due to incomplete data or were suspicious of infection.

Conclusion

The present study confirmed that the high NLR was associated with LN metastasis in cervical cancer patients initially treated with radical surgery. The high NLR failed to predict both PFS and OS in this group of patients. Only FIGO stage and adjuvant treatment were the only significant prognostic factors for survival.

What is already known on this topic?

High NLR has been proved as a poor prognostic marker for various cancers including cervix. The meta-analysis showed the correlation of lymph node metastasis and high NLR and shorter survival in cervical cancer patient. Unfortunately, data about the association between NLR and lymph node metastasis in the early stage initially treated with surgery was limited.

What this study adds?

The present study confirmed the association between NLR and lymph node metastasis in early stage cervical cancer patients initially treated with surgery. However, this study could not demonstrate significant association of NLR and survival.

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Potential conficts of interest

The authors declare no conflict of interest.

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