Pretreatment Neutrophil:Lymphocyte Ratio as a Prognostic Factor in Cervical Carcinoma

YOO-YOUNG LEE, CHEL HUN CHOI, HA-JEONG KIM, TAE-JOONG KIM, JEONG-WON LEE, JE-HO LEE, DUK-SOO BAE and BYOUNG-GIE KIM

Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Abstract. *Aim: This study was designed to investigate the prognostic value of the neutrophil:lymphocyte ratio (NLR) in cervical cancer. Patients and Methods: Patients with clinically staged cervical carcinoma (IB to IVA) at Samsung Medical Center, Seoul, Korea, from 1996 to 2007 were retrospectively enrolled. Results: We enrolled 1061 patients with cervical cancer. The median NLR was 1.9, with a range of 0.3-27.0. When the cohort was divided according to the median NLR, poorer survival outcomes were observed in the group with higher NLR (≥1.9) than in the lower NLR group (<1.9). Patients of the higher NLR group (≥1.9) were younger in age and had more advanced staged disease when compared with those of the lower NLR group (<1.9). In multivariable analysis, higher pretreatment NLR was identified as being an independent poor prognostic factor for survival. Conclusion: Pretreatment NLR may be a cost-effective biomarker to stratify risk of recurrence and death in patients with cervical cancer.*

Even though the incidence and mortality of invasive cervical cancer have steadily decreased (1), cervical cancer is still the second most common type of cancer in females worldwide and the leading cause of cancer death in women in developing countries (2). Nearly one-third of patients with cervical cancer die due to disease recurrence or progression (3).

Clinical staging has been adopted worldwide and determines the prognosis in patients with cervical cancer. However, clinical staging has been shown to be frequently inaccurate, especially in cases of more advanced disease (4, 5). As a result, in early-stage cervical cancer, in patients who are candidates for radical surgery, several pathological findings after surgery, including lymph node (LN) status, tumor size, depth of invasion, *etc*., are used as predictors for recurrence and for planning further treatment (6). Nevertheless, the role of other prognostic criteria beside LN status is still unclear. Furthermore, we cannot apply these pathological risk factors for prediction of prognosis in cases of advanced disease because the treatment of choice is not surgery but concurrent chemoradiation (CCRT) (7, 8).

In many types of cancer, it has been reported that tumors have been linked with systemic inflammation (9, 10). For example, elevated neutrophil counts (11-13) or decreased lymphocytes counts (14) before pretreatment may be prognostic indicators of poor survival. More recently, it has been reported that a combined index using neutrophil and lymphocyte counts in the form of a neutrophil:lymphocyte ratio (NLR), which has been used as a cost-effective and simple parameter of systemic inflammation or stress in critically ill patients without cancer (15), may also be related to prognosis in many types of cancer including gastrointestinal tract malignancies (16), hepatocelluar carcinoma (17), pancreatic cancer (18), and non-small cell lung cancer (19). However, the prognostic significance of NLR in cervical cancer is still unclear.

The purpose of this study was to determine the factors associated with elevated pretreatment NLR and also the prognostic value of the NLR in patients with cervical cancer.

Patients and Methods

Patients. Patients with clinically staged cervical carcinoma (IB to IVA) who were treated at Samsung Medical Center, Seoul, Korea, from 1996 to 2007 were retrospectively enrolled in our study. The data, including patients' basal characteristics, laboratory results and pathology reports, were collected from electronic medical records with Institutional Review Board approval. In this study, we excluded patients as follows: early cervical cancer with microscopic lesions (IA1 and IA2); histological types except squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma; patients who

Correspondence to: Professor Byoung-Gie Kim, MD, Ph.D., Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul, 135-710, Korea. Tel: +82 234103513, Fax: +82 234100630, e-mail: bgkim@skku.edu

Key Words: Neutrophils, lymphocytes, uterine cervical neoplasms, prognostic, biological markers, survival.

underwent fertility saving surgery; patients with concurrent hematologic, or infectious diseases; patients without data for complete blood cell counts with differential cell count within two weeks before starting initial treatment.

Treatment. There were two treatment streams for cervical cancer including surgery with or without adjuvant therapy and primary radiation therapy with or without concurrent chemotherapy. Surgery was usually performed for early cervical cancer (IB1 to IIA) and primary radiation therapy was considered for locally advanced cervical cancer (IIB to IVA).

Standard surgery consisted of type III radical hysterectomy with bilateral pelvic LN dissection. Bilateral salpingo-oophorectomy and para-arotic LN dissection were not routine procedures. In cases of bulky tumors, cisplatin-based neoadvjuvant chemotherapy for three cycles before surgery was admitted based on the physician's preference. Adjuvant therapy after surgery was considered based on pathological risk factors. Patients who had more than one of the three high-risk factors (positive pelvic LN, microscopic parametrial invasion, and positive resection margins with tumor) received adjuvant radiotherapy (RT) or concurrent chemoradiation (CCRT). Cisplatin-based chemotherapy was administered in all cases. Patients with two or more risk factors of the three intermediate risk factors (stromal invasion of more than half of the cervix or stromal invasion more than 1 cm, lymphovascular space invasion (LVSI), and the largest diameter of 4 cm or greater) received adjuvant RT alone.

Radiation protocols were as previously described (20). In brief, each patient received external beam radiation therapy using 10-15 MV photons to the whole pelvis for a total dose of 50.4 Gy. The daily fraction size was 1.8 Gy, administered five times per week. Patients were irradiated with a four-field box technique (anterior, posterior, and bilaterals) to spare some of the small bowel anterior to the iliac nodes. High-dose rate intracavitary brachytherapy was begun four to five weeks after the initiation of external beam radiotherapy. The dose was prescribed to point A according to the recommendations of the International Commission on Radiation Units and Measurements. The median dose of high-dose-rate brachytherapy was 24 Gy at point A, with 4 Gy per fraction twice a week for three weeks. All concurrent chemotherapy were cisplatin based.

Policies using concurrent chemotherapy with adjuvant RT for patients with high-risk factors after surgery and on primary RT for patients with locally advanced disease varied according to time and attending physician.

Patients had follow-up examinations approximately every three months for the first two years, every six months for the next three years, and every year thereafter. During the routine follow-up, imaging studies including computed tomography (CT) or magnetic resonance imaging (MRI) and chest X-ray were performed annually and when tumor recurrence was suspected based on clinical findings or imaging studies, biopsy of that lesion was performed on a case by case basis. We defined the progression-free survival as the time from the initial treatment to relapse noted on images, or the last follow-up visit, and the overall survival as the time from the initial treatment to death due to cervical carcinoma, or the last follow-up visit.

Statistical analysis. The Wilcoxon rank sum test or two-sample t-test was used to compare the median and mean values, respectively, after confirming whether the data had non-normal or normal distributions with the Shapiro-Wilks test. Frequency distributions between categorical variables among the groups were compared using the χ^2 test. The Fisher's exact test was used if the expected frequency was <5. Receiver operating characteristic plots were constructed for the patients who were not censored for 5 years to determine the maximum sensitivity and specificity of a threshold value to stratify patients at high risk of recurrence. The overall and disease-free survival curves were calculated according to the Kaplan-Meier method with the log-rank test. The Cox proportional-hazards model was used for the multivariable analyses. Statistical analyses were performed by SPSS software (version 12.0; SPSS, Chicago, IL, USA). A *p*-value of ≤0.05 was considered statistically significant and all *p*-values were two-sided.

Table I. *Patients' characteristics*.

	Total
No. of patients	1061
Median age, years (range)	50 (21-85)
Median white cell count, n/μl (range)	6230 (2000-33350)
Median neutrophil count, n/μl (range)	3690 (640-31116)
Median lymphocyte count, n/μl (range)	1881 (169-5167)
Median NLR (range)	1.9 (0.3-27.0)
FIGO stage (%)	
IB1	631 (59.4)
IB2	77 (7.3)
IIA	164 (15.5)
IIB	119 (11.2)
IIIA	4 (0.4)
IIIB	50 (4.7)
IVA	16 (1.5)
Cell type (%)	
SCC	840 (79.2)
AC	166 (15.6)
ASC	55 (5.2)
Treatment, n (%)	
RH alone	416 (39.2)
RH + RT*	201 (18.9)
RH + CCRT*	156 (14.7)
NAC + RH	21 (2.0)
NAC + RH + RT*	20 (1.9)
NAC + RH + CCRT*	15 (1.4)
RT alone†	78 (7.4)
CCRT†	154 (14.5)

NLR, Neutrophil/lymphocyte ratio; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; RH, type III radical hysterectomy; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; NAC, neoadjuvant chemotherapy; *adjuvant setting; †primary setting.

Results

We enrolled 1061 patients with cervical cancer who had macroscopic lesions at initial diagnosis (IB to IVA). The basal characteristics of participants are presented in Table I. The median age of the cohort was 50 years with a range of 21-85 years. The median follow-up was 52.9 months, with a range of 1-181 months, and the five-year survival rate was 86.0%. More than half of the patients had early-stage disease

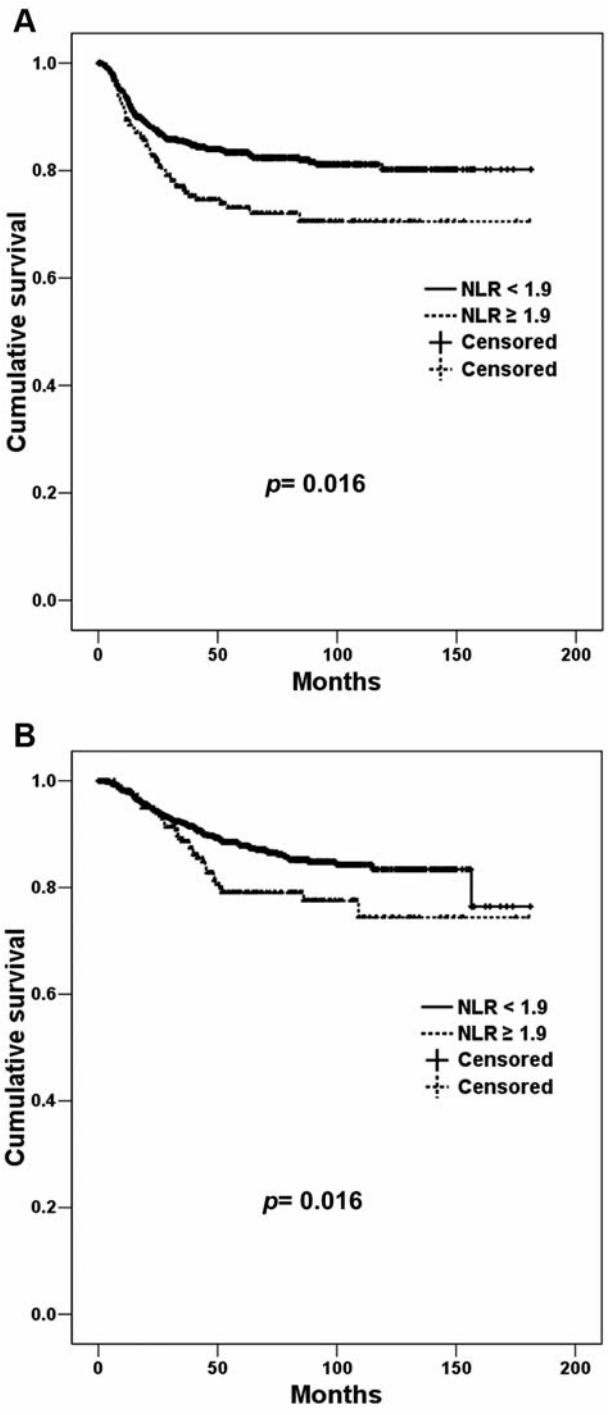

Figure 1. *A: Progression free survival B: Overall survival. (in all cervical cancer patients).*

(IB to IIA=872/1061, 82.2%) and were treated with management consisting of radical surgery (829/1061, 78.1%). There were 189 cases of cervical cancer recurrence and 135 cases of cancer-specific death.

Table II. *Patients' characteristics according to neutrophil:lymphocyte ratio (NLR) cutoff of 1.9.*

	NLR		
	<1.9 (n=486)	≥1.9 (n=575)	*p*-Value
Median age, years (range)	52.5 (23-83)	48.0 (21-85)	<0.001
FIGO stage, n (%)			<0.001
IB1	314 (64.6)	317 (55.2)	
IB2	30 (6.2)	47 (8.2)	
IIA	82 (16.9)	82 (14.3)	
IIB	43 (8.8)	76 (13.2)	
IIIA	2 (0.4)	2 (0.3)	
IIIB	13 (2.7)	37 (6.4)	
IVA	2 (0.4)	14 (2.4)	
Cell type, n (%)			0.938
SCC	385 (79.2)	455 (79.1)	
AC	77 (15.8)	89 (15.5)	
ASC	24 (4.9)	31 (5.4)	
Treatment, n (%)			<0.001
RH alone	218 (44.8)	198 (34.5)	
RH + RT*	99 (20.4)	102 (17.7)	
RH + CCRT*	65 (13.4)	91 (15.8)	
NAC + RH	11 (2.3)	10 (1.7)	
NAC + RH + RT*	4 (0.8)	16 (2.8)	
NAC + RH + CCRT*	7 (1.4)	8 (1.4)	
RT alone†	33 (6.8)	45 (7.8)	
CCRT†	49 (10.1)	105 (18.3)	

NLR, Neutrophil/lymphocyte ratio; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; RH, type III radical hysterectomy; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; NAC, neoadjuvant chemotherapy; *adjuvant setting; †primary setting.

NLR was shown to have the most significant hazard ratio (HR=1.16; 95% confidence interval (CI)=1.12-1.20) for recurrence (for the neutrophil count, HR=1.00, CI=1.00-1.00; and for the lymphocyte count, HR=0.99, CI=0.99-1.00). The median NLR was 1.9 (0.3-27.0). When the cohort was divided according to the median value of 1.9, patients with higher NLRs (≥1.9) demonstrated poorer prognoses than participants with lower NLRs (Figure 1). In comparative analysis of two groups based on the median level of NLR, the higher NLR group (≥1.9) was younger in age and had more advanced stage disease, which resulted in high incidence of primary CCRT, standard treatment of advanced disease, when compared with those of the lower NLR group (Table II).

In univariable analysis, all clinical parameters including age, NLR, stage, cell type, and type of treatment had prognostic significance for survival (Table III). After adjusting for other factors in the Cox proportional hazards model, the prognostic significance of NLR remained and when the NLR increased 0.1, the risk of progression and death increased by 13% (HR= 1.13; CI= 1.08-1.18) and 19% (HR= 1.19; CI= 1.13-1.25), respectively (Table IV).

Table III. *Univariable analysis for progression-free survival (PFS) and overall survival (OS).*

	PFS		OS	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	1.02 (1.01-1.03)	0.009	1.04 (1.02-1.05)	<0.001
NLR	1.16 (1.12-1.20)	<0.001	1.19 (1.15-1.24)	<0.001
FIGO stage				
IB1	1		1	
IB2	4.67 (2.89-7.57)	<0.001	0.08 (0.04-0.21)	<0.001
IIA	2.94 (1.90-4.55)	<0.001	0.40 (0.15-1.05)	0.062
IIB	6.80 (4.55-10.45)	<0.001	0.43 (0.18-1.02)	0.056
IIIA	4.66 (0.64-33.74)	0.128	0.75 (0.32-1.79)	0.516
IIIB	11.12 (6.90-17.91)	<0.001	2.00 (0.40-9.94)	0.397
IVA	7.78 (3.52-17.19)	<0.001	1.61 (0.66-3.95)	0.295
Cell type				
SCC	1		1	
AC	1.53 (1.07-2.18)	0.008	1.48 (0.97-2.25)	0.048
ASC	2.02 (1.20-3.39)	0.019	1.88 (1.01-3.51)	0.070
Treatment				
RH alone	1		1	
RH + RT*	2.43 (1.30-4.56)	0.006	3.90 (1.66-9.21)	0.002
RH + CCRT*	7.11 (4.12-12.29)	<0.001	9.09 (4.13-20.01)	<0.001
NAC + RH	3.30 (0.97-11.19)	0.056	0‡	0.951
NAC + RH + RT*	7.88 (3.13-19.85)	<0.001	10.12 (3.05-33.60)	<0.001
NAC + RH + CCRT*	9.47 (3.51-25.52)	<0.001	20.59 (6.73-63.00)	<0.001
RT alone†	15.04 (8.51-26.58)	<0.001	27.64 (12.76-59.87)	<0.001
CCRT†	11.31 (6.64-19.27)	<0.001	20.06 (9.41-42.76)	<0.001

HR, Hazard ratio; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; RH, type III radical hysterectomy; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; NAC, neoadjuvant chemotherapy; *adjuvant setting; †primary setting; ‡there was no event of death.

For the patients who were not censored for 5 years (n=618), an NLR value of 1.95 corresponded to the maximum sensitivity (66.1%) and specificity (60.1%) on the receiver operating characteristic plot (Figure 2), which was similar to the median value of NLR.

Discussion

In this study, we observed that elevated pretreatment NLR was associated with advanced stage and remains an independent survival factor in patients with cervical cancer, even after adjustment for known prognostic factors including age and stage.

Our findings that high NLR is associated with poor prognosis for survival correspond well with the results of previous studies. In colorectal cancer, pretreatment NLR is an independent risk factor for prognosis related to cancer following surgery (16, 21, 22), and chemotherapy (23). These findings were also confirmed in advanced gastric cancer (24), hepatocellular carcinoma (25) and lymphoma (26). In gynecological malignancies, Cho *et al*. reported that pretreatment NLR, in combination with CA125, may be a useful marker to identify ovarian carcinomas, and an elevated

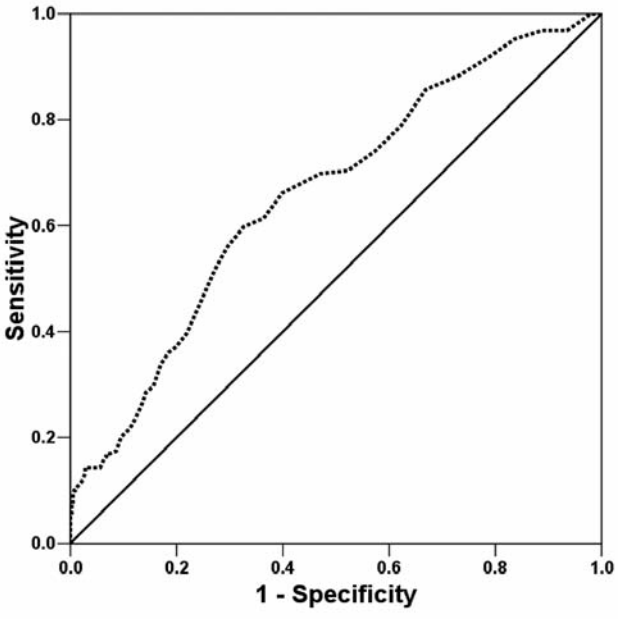

Figure 2. *Recurrence of cervical cancer in 618 patients during 5-year follow-up without being censored. NLR, Neutrophil:lymphocyte ratio; ROC, receiver operating characteristic.*

Table IV. *Multivariable analysis for progression-free survival (PFS) and overall survival (OS).*

	PFS		OS	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	1.00 (0.99-1.02)	0.953	1.02 (1.00-1.04)	0.014
NLR	1.13 (1.08-1.18)	<0.001	1.19 (1.13-1.25)	<0.001
FIGO stage				
IB1	1		1	
IB2	2.98 (1.73-5.10)	<0.001	3.08 (1.50-6.34)	0.002
IIA	1.81 (1.13-2.90)	0.014	2.86 (1.62-5.05)	<0.001
IIB	2.66 (1.48-4.78)	0.001	2.58 (1.27-5.21)	0.009
IIIA	0.57 (0.07-5.07)	0.616	0.88 (0.14-5.54)	0.891
IIIB	4.12 (2.12-8.00)	<0.001	4.78 (2.24-10.20)	<0.001
IVA	2.93 (1.18-7.28)	0.021	3.13 (1.12-8.76)	0.030
Cell type				
SCC	1		1	
AC	2.95 (2.03-4.28)	<0.001	2.86 (1.83-4.48)	<0.001
ASC	3.31 (1.91-5.73)	<0.001	3.71 (1.91-7.24)	<0.001
Treatment				
RH alone	1		1	
RH + RT*	2.26 (1.19-4.31)	0.013	3.12 (1.30-7.46)	0.011
RH + CCRT*	5.20 (2.90-9.33)	<0.001	5.63 (2.45-12.93)	<0.001
NAC + RH	2.63 (0.73-9.43)	0.138	0‡	0.954
NAC + RH + RT*	4.97 (1.81-13.63)	0.002	5.69 (1.56-20.68)	0.008
NAC + RH + CCRT*	4.61 (1.57-13.47)	0.005	11.60 (3.48-38.70)	<0.001
RT alone†	8.38 (3.93-17.89)	<0.001	10.68 (4.08-27.97)	<0.001
CCRT†	5.74 (2.78-11.86)	<0.001	8.02 (3.12-20.63)	<0.001

HR, Hazard ratio; CI, confidence interval; NLR, neutrophil/lymphocyte ratio; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; RH, type III radical hysterectomy; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; NAC, neoadjuvant chemotherapy; *adjuvant setting; †primary setting; ‡there was no event of death.

NLR may predict adverse outcome in ovarian cancer (27). There were some reports that high circulating neutrophil counts (28) or low levels of lymphocytes (29) may have negative impacts on survival in advanced cervical cancer, however, the prognostic role of NLR was unclear. We found a negative impact on survival of high NLR in all stages of cervical cancer from the results of our study.

Interestingly, gender may have an effect on the circulating immune system mediators following surgical treatment (30). In the study of Gwak *et al*., NLR was higher in female patients than in male patients after gastrectomy due to stomach cancer; therefore, females may be more vulnerable to changes in immune response following surgical stress or serious illness. Although this previous study did not present gender differences in survival outcomes due to short-term follow-up, prognostic markers related to immune response may be more useful in malignancy in females, including gynecological cancer.

The mechanism underlying our results has not been elucidated yet. However, there are some possible explanations for our observation. Firstly, inflammatory diseases can increase the risk of developing many types of cancer, including bladder, cervical and gastrointestinal cancer (10). Oncogenic changes induce an inflammatory microenvironment that promotes the development of tumors, and inflammation can promote angiogenesis and metastasis (9, 10). Various factors originating in the tumor microenvironment may contribute to the systemic inflammatory changes associated with cancer (9). Clinically, these findings have been repeated for many types of cancer (31). Secondly, we may explain these observations as a kind of paraneoplastic hematological syndrome with granulocytosis (32). Thirdly, recently, granulocyte colony-stimulating factor (G-CSF)-producing malignant tumor has been reported in cervical cancer, which has an aggressive nature with marked leukocytosis (33, 34). As well as in cases of G-CSF-producing cervical cancer, a subclinical increased level of G-CSF may have a role in poor prognosis.

Variation in immune response has been observed in different types of cancer. For example, patients with pancreatic ductal adenocarcinoma have more marked lymphocytopenia preoperatively and postoperatively when compared with patietns with gastric or colorectal carcinoma (35). However, NLR is not associated with cancer prognosis in esophageal cancer (36), or pancreatic cancer (14). Furthermore, age may also be a confounder in immune response (37, 38). Therefore, multifactorial immune response,

which could be affected by gender, age, and tumor type, as well as other immunological factors (9, 10), may not be uniformly interpreted to predict survival in diverse patients with various types of cancer. Another problem could be that the NLR cut-off values that served as independent prognostic factors were different among studies, which indicate the NLR cut-off values can also be cancer-specific. Finally, the postoperative immune response should also be considered because surgical stress can inhibit cellular immune responses that are relevant to cancer prognosis, including natural killer (NK)-cell toxicity and T-cell responses (39). Further study of the immunological role in cancer patients is warranted.

In conclusion, an elevated pretreatment NLR was an independent predictor of survival in patients with cervical cancer. Pretreatment NLR may be a potential and cost-effective biomarker, which is especially important issue in developing country where the cervical cancer is still a heavy burden on public health resources (40), useful for stratifying patients at high risk of recurrence and death in cervical cancer in addition to clinical stage.

Conflict of Interest

The Authors have no conflicts of interest to declare.

Acknowledgements

This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry for Health & Welfare Affairs, Republic of Korea (A092255). This study was supported by a grant from the National R&D Program for Cancer Control, Ministry for Health, Welfare and Family affairs, Republic of Korea (0920010).

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Received February 17, 2012
Revised March 17, 2012
Accepted March 19, 2012