

Prognostic nutritional index as a predictor of survival in patients with recurrent cervical cancer

NAOYUKI IDA, KEIICHIRO NAKAMURA, MASAYUKI SAIJO,
TOMOYUKI KUSUMOTO and HISASHI MASUYAMA

Department of Obstetrics and Gynecology, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Okayama 700-8558, Japan

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Abstract. Systemic inflammatory responses (SIRs) can help predict survival in various cancers. The present study investigated the accuracy of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and prognostic nutritional index (PNI) in predicting survival for patients with recurrent cervical cancer. A retrospective review of prognoses examined the associations among NLR, PLR, and PNI, and clinical characteristics and survival in 79 patients with recurrent cervical cancer after undergoing concurrent chemoradiation therapy (CCRT) or radical hysterectomies with or without CCRT. The Mann-Whitney U-test was used for statistical analyses. In addition, 12-month, 24-month and overall survival were analyzed by the Kaplan-Meier method. Cox's proportional hazard regression was used for univariate and multivariate analyses. Median survival was 15.0 months over follow-up periods of 2-93 months. At the last follow-up point, 54 had succumbed to disease and 25 were alive with disease. In univariate analysis, NLR, PLR and PNI were significantly associated with 12-month, 24 month and overall survival (12 months: $P=0.021$, $P=0.001$ and $P<0.001$; 24 months: $P=0.020$, $P=0.008$ and $P<0.001$; overall; $P=0.032$, $P=0.032$ and $P<0.001$, respectively). In multivariate analyses, PNI was an independent prognostic factor for 12-month, 24-month and overall survival ($P=0.001$, $P=0.001$ and $P<0.001$, respectively). PNI is a useful predictor of survival of recurrent cervical cancer.

Introduction

Recurrence rates for cervical cancer are 11-22% in FIGO stage IB-IIA and 28-64% in FIGO stage IIB-IVA (1). Treatment

for patients who suffer recurrent cervical cancer is designed to offer the patient and her family medical, emotional, and spiritual care near the end of life. Predicting these patients' life expectancy is thus important for clinicians and patients. Realistic survival estimates help clinicians decide on appropriate medical interventions, discharge planning and timing of referral to palliative care services.

Systemic inflammatory responses (SIRs), such as relative differences in neutrophil, platelet, lymphocyte counts, and albumin, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have been shown to promote various cancer characteristics (2,3) and to affect survival (4-7). PLR has been shown to predict prognosis in patients with recurrent cervical cancer after undergoing CCRT (8). Although some data on survival outcomes for patients whose cervical cancers recur after undergoing CCRT has been published (8), patients treated only with surgery or surgery plus adjuvant treatment have not been sufficiently investigated. In this study, we investigated the correlation between inflammatory markers (NLR, PLR and PNI) of patients with recurrent cervical cancers.

Patients and methods

Patients. The study population consisted of 79 patients whose cervical cancer recurred after undergoing concurrent chemoradiation therapy (CCRT), or radical hysterectomy with or without CCRT in the Department of Obstetrics and Gynecology of our hospital between April 2004 and December 2015. A total of 79 women underwent positron emission tomography/computed tomography (PET/CT) or CT within the 2 weeks prior to any oncologic treatment. The images were evaluated by 2 diagnostic radiology physicians informed about the clinical data of the patient at the time of the scan.

The study protocol was approved by our hospital's institutional review board [Systemic inflammatory responses were examined prognostic predictor of survival in patients with recurrent cervical cancer (Number: 1605-514)]. Informed consent was obtained from all patients.

Laboratory analysis. Differential white blood cell (WBC) counts and albumin levels were measured within 1 week before their treatments; WBC, neutrophil, lymphocyte, and

Correspondence to: Dr Keiichiro Nakamura, Department of Obstetrics and Gynecology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama, Okayama 700-8558, Japan
E-mail: k-nakamu@cc.okayama-u.ac.jp

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platelet counts were measured in automated blood cell counters (Bayer HealthCare, Diagnostics Division, Tarrytown, NY, USA). Levels of serum albumin were measured by latex nephelometry (LT Auto Wako, Osaka, Japan). NLR was defined as the absolute neutrophil count (μl) divided by the absolute lymphocyte count (μl); PLR was defined as the absolute platelet count (μl) divided by the lymphocyte count (μl). PNI was calculated as described previously (9); briefly, $\text{PNI} = [10 \times \text{albumin (g/dl)}] + [0.005 \times \text{total lymphocyte count (\mu l)}]$.

Treatment. Patients with recurrent cervical cancer had several possible treatments. In general, radiotherapy is the main option for patients with pelvic recurrence, or with solitary localized recurrence outside the radiation field, after previous radiotherapy. Chemotherapy is the main option for patients with recurrence within the radiation field, or metastases to multiple organs, following previous radiotherapy. Conventional TC was also administered as second-line chemotherapy to patients that developed evidence of clinical or radiographic relapse within the 6 months subsequent to completing adjuvant and/or neo-adjuvant chemotherapy. Chemotherapy for the treatment of recurrent disease was continued until complete response (CR) or progressive disease (PD) was identified. Patients with PD received regimens of chemotherapy that were different from the adjuvant and second-line combinations. We used second-line chemotherapy, as weekly TC-paclitaxel; 80 mg/m² and carboplatin (area under the plasma-concentration curve [AUC]: 2). Third-line chemotherapy consisted of single-agent irinotecan (CPT-11; 70 mg/m² weekly for 3 weeks followed by 1 week off); fourth-line chemotherapy was single-agent gemcitabine (GEM; 700 mg/m² weekly for 3 weeks followed by 1 week off). Surgery was considered for solitary distant metastases or local recurrences. Palliative treatment was considered in some cases after comprehensive assessment of the effectiveness of radiotherapy and/or chemotherapy, patients' performance status, and degree of cancer spread. We evaluated 13 patients treated with surgery, 14 with radiation, 48 with chemotherapy, and 4 with palliative care. Patients had follow-up examinations approximately every 1-2 months.

Statistical analysis. Statistical analyses used the Mann-Whitney U-test for comparisons with controls (10). Receiver operating characteristic (ROC) curves were generated for pre-treatment NLR, PLR, and PNI to determine cut-off values that predicted 12-month, 24-months and overall survival that yielded optimal sensitivity and specificity; patients were then grouped by these cut-off values. 12-months, 24-months and overall survival of the groups were analyzed using the Kaplan-Meier method (11). We performed univariate and multivariate analyses using Cox's proportional hazards model to determine which factors predicted 12-months, 24-months and OS after adjusting for effects of known prognostic factors (12,13). Analyses were performed using SPSS Software, version 20.0 (SPSS Inc., Chicago, IL, USA). P<0.05 was considered significant.

Results

Patients' ages, histology, treatment-free interval, number of metastases, distant metastasis and treatment are listed in Table I. Their median SIR values were NLR: 3.52 (range:

Table I. Patient and tumor characteristics.

Baseline characteristics	Numbers	All patients Mean, 52.4; range, 25-78 (%)
Age at diagnosis, years		
Histology		
SCC	50	63.3
AD	18	22.7
ADSQ	7	8.9
Others	4	5.1
Treatment free interval		
≤6 months	33	41.8
7-12 months	24	30.4
13-24 months	11	13.9
>25 months	11	13.9
Number of metastasis		
Simple	44	55.7
Multiple	35	44.3
Distant metastasis		
Hematogenous metastasis	29	36.7
Lymphogenous metastasis	34	43
Treatment		
Operation	13	16.4
Radiation	14	17.7
Chemotherapy	48	60.8
Palliative care	4	5.1

SCC, squamous cell carcinoma; AD, adenocarcinoma; ADSQ, adenosquamous carcinoma.

1.28-14.30); PLR: 271.52 (range: 114.30-885.99); and PNI: 45.30 (range: 26.26-56.55; Table II). NLR (P=0.003) and PLR (P<0.001) were significantly associated with treatment type. PNI was significantly associated with number of metastasis (P=0.022), hematogenous metastasis (P=0.027) and treatment type (P<0.001; Mann-Whitney U-test).

Patients with recurrent cervical cancer had median OS of 15.0 months over follow-up periods of 2-93 months. At the last follow-up point, 54 had died of their disease, and 25 were alive with disease. The time between diagnosis and mortality was ≤6 months in 9 patients (16.7%), 7-12 months in 12 patients (22.2%), 13-18 months in 16 patients (29.7%), 19-24 months in 7 patients (13.0%), 19-24 months in 5 patients (9.2%), and ≥31 months in 5 patients (9.2%; Fig. 1A).

We used receiver operating characteristic (ROC) curve analyses to determine optimal cut-off values of NLR, PLR, and PNI to predict 12-month, 24-month and overall survival. The analyses identified NLR ≥3.92 (AUC: 0.809, 81.0% sensitive, 56.1% specific), PLR ≥300.00 (AUC: 0.775, 76.2% sensitive, 70.7% specific), and PNI ≤40.64 (AUC: 0.845, 84.5% sensitive, 66.7% specific), as the most accurate cut-off values for predicting 12-month survival; NLR ≥2.90 (AUC: 0.736, 72.7% sensitive, 57.1% specific), PLR ≥265.00 (AUC: 0.669, 65.9% sensitive, 60.0% specific), and PNI ≤46.70 (AUC: 0.791, 80.0% sensitive, 75.0% specific), as the most

Table II. Associations of NLR, PLR, and PNI with clinical factors in recurrent cervical cancer.

Variable	Numbers	NLR	P-value	PLR	P-value	PNI	P-value
Histology			0.564		0.408		0.076
SCC	50	3.86±2.76		283.05±124.66		44.85±6.29	
Non-SCC	29	3.45±3.46		247.45±209.18		47.27±4.7.53	
Treatment free interval			0.541		0.422		0.124
≤6 months	34	3.88±3.29		293.28±154.56		44.98±6.95	
>7 months	45	3.46±2.79		263.97±164.01		47.35±6.53	
Number of metastasis			0.472		0.706		0.022 ^a
Simple	44	3.46±1.98		267.39±130.4		47.13±6.34	
Multiple	35	3.97±3.77		281.45±186.92		43.61±7.11	
Hematogenous metastasis			0.564		0.915		0.027 ^a
Absent	50	3.49±2.97		273.37±147.79		46.98±6.70	
Present	29	3.90±3.14		277.37±181.31		43.43±6.93	
Lymphogenous metastasis			0.282		0.634		0.34
Absent	45	3.90±2.87		287.451±169.91		46.76±6.86	
Present	34	3.15±3.28		270.01±147.18		45.28±6.69	
Treatment			0.003 ^a		<0.001 ^a		<0.001 ^a
Operation or radiation	27	2.53±1.90		196.34±114.55		48.61±4.98	
Chemotherapy or palliative cares	52	4.28±3.20		319.25±167.62		42.45±6.98	

^aP<0.05. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index.

accurate cutoff values for predicting 24-month survival; and NLR ≥2.80 (AUC: 0.693, 70.4% sensitive, 52.0% specific), PLR ≥260.00 (AUC: 0.616, 61.1% sensitive, 56.0% specific), and PNI ≤46.90 (AUC: 0.730, 72.0% sensitive, 68.5% specific), as the most accurate cutoff values for predicting overall survival (Fig. 1B).

When patients were classified into those above and below each cut-off value for 12 months, 24 months and overall survival, Kaplan-Meier curves of survival show patients with high NLR and PLR were significantly shorter than rates of patients with low NLR and PLR (12 months survival; P<0.001 and P<0.001, 24 months survival; P=0.015 and P=0.005, overall survival; P=0.027 and P=0.027, respectively). The Kaplan-Meier curves showed that patients with low PNI were shorter than for patients with high PNI (12 months survival; P<0.001, 24 months survival; P<0.001, overall survival; P<0.001, respectively) (Fig. 2).

Correlations between clinical factors and 12-month, 24-month and overall survival were assessed in univariate and multivariate analyses (Table III). Treatment-free interval (P=0.036), treatment type (P=0.015), NLR (P=0.001), PLR (P=0.001) and PNI (P<0.001) were significantly associated with 12-month survival in univariate analyses; treatment-free interval (P=0.012) and PNI (P=0.001) were independent predictors of 12-month survival in multivariate analyses.

Treatment-free interval (P=0.001), multiple metastases (P=0.007), treatment type (P<0.001), NLR (P=0.020), PLR (P=0.008) and PNI (P<0.001) were significantly associated with 24-month survival in univariate analyses; treatment-free interval (P=0.005), treatment type (P=0.008) and PNI

(P=0.001) were independent predictors of 24-month survival in multivariate analyses.

Treatment-free interval (P=0.001), multiple metastases (P=0.001), treatment type (P<0.001), NLR (P=0.032), PLR (P=0.032) and PNI (P<0.001) were significantly associated with overall survival in univariate analyses; treatment-free interval (P=0.004), treatment type (P<0.001) and PNI (P<0.001) were independent predictors of overall survival in multivariate analyses.

Discussion

Among patients with recurrent cancer, prognosis is based on different criteria for those with advanced disease than for those with earlier-stage disease, in whom prognosis depends mainly on the primary site and histology. However, the prognostic values of SIRs are still unknown for recurrence of cervical cancer. This is the first study to evaluate whether NLR, PLR and PNI are predictors of survival for patients whose cervical cancer has recurred after undergoing treatment.

SIRs have been examined as possible predictors of prognosis in various types of cancer. Neutrophils release inflammatory cytokines, leukocyte chemotactic factors and other phagocytic mediators that can damage cellular DNA, inhibit apoptosis and promote angiogenesis (14-17). Platelets can release potent mitogens or adhesive glycoprotein, such as platelet-derived growth factor, transforming growth factor-β, and vascular endothelial growth factor (18-20). Albumin levels decrease with increased levels of pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor,

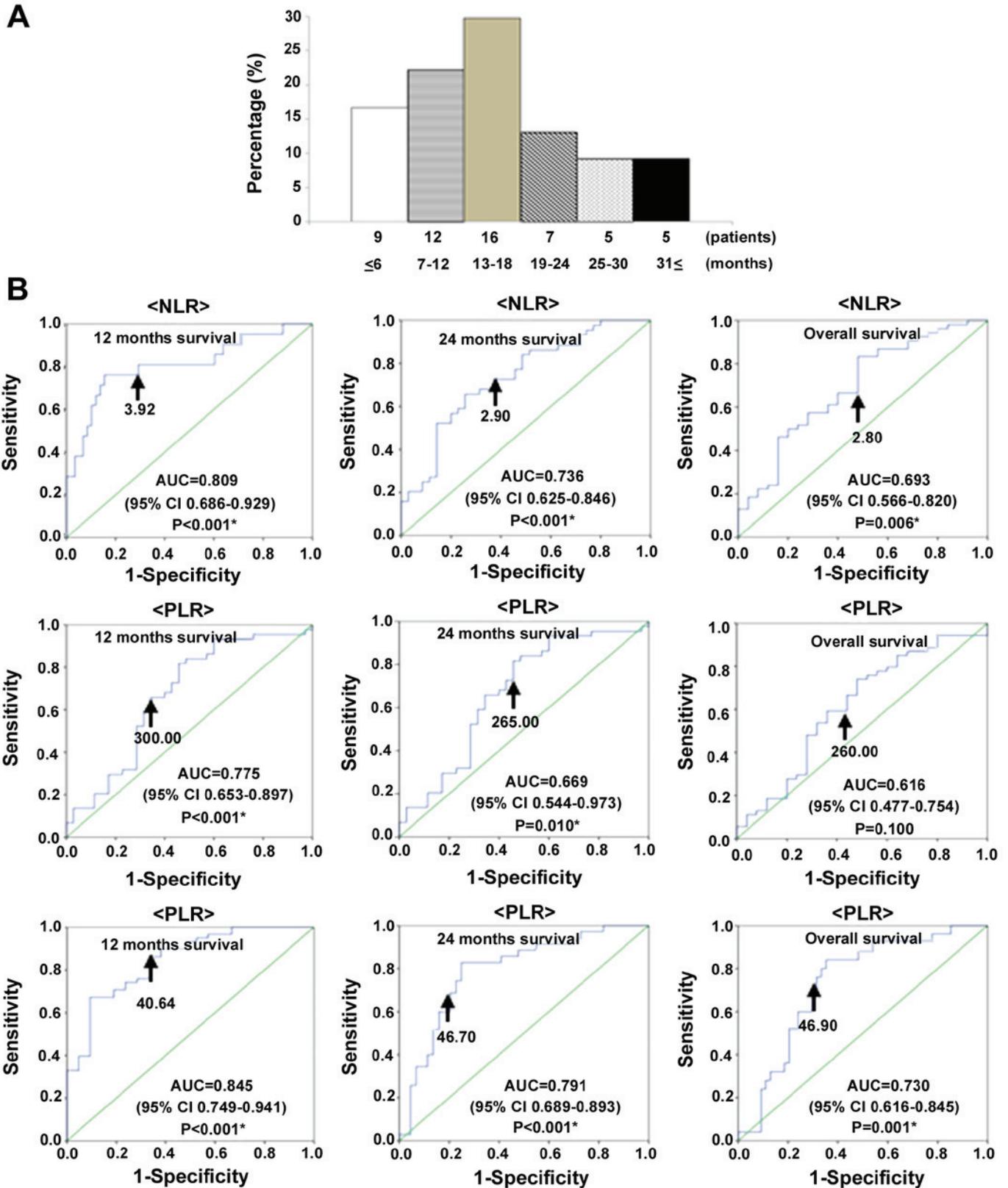


Figure 1. (A) Time between diagnosis and mortality in patients with recurrent cervical cancer. (B) Receiver operating characteristic curve analyses to determine optimal cut-off values for NLR, PLR, and PNI to predict 12-month and overall survival with recurrent cervical cancers in 79 patients. Optimal cutoff values to predict 12-month survival were NLR: 3.92 (AUC=0.809; 95% CI: 0.636-0.929; P<0.001); PLR: 300.00 (AUC=0.775; 95% CI: 0.653-0.891; P<0.001); and PNI: 40.64 (AUC=0.845; 95% CI: 0.749-0.941; P<0.001). Optimal cutoff values to predict 24-month survival were NLR: 2.90 (AUC=0.736; 95% CI: 0.625-0.846; P<0.001); PLR: 265.00 (AUC=0.669; 95% CI: 0.544-0.973; P=0.010); and PNI: 46.70 (AUC=0.791; 95% CI: 0.689-0.893; P<0.001). Optimal cutoff values to predict overall survival were NLR: 2.80 (AUC=0.693; 95% CI: 0.566-0.820; P=0.006); PLR: 260.00 (AUC=0.616; 95% CI: 0.477-0.754; P=0.100); and PNI: 46.90 (AUC=0.730; 95% CI: 0.616-0.845; P=0.001).

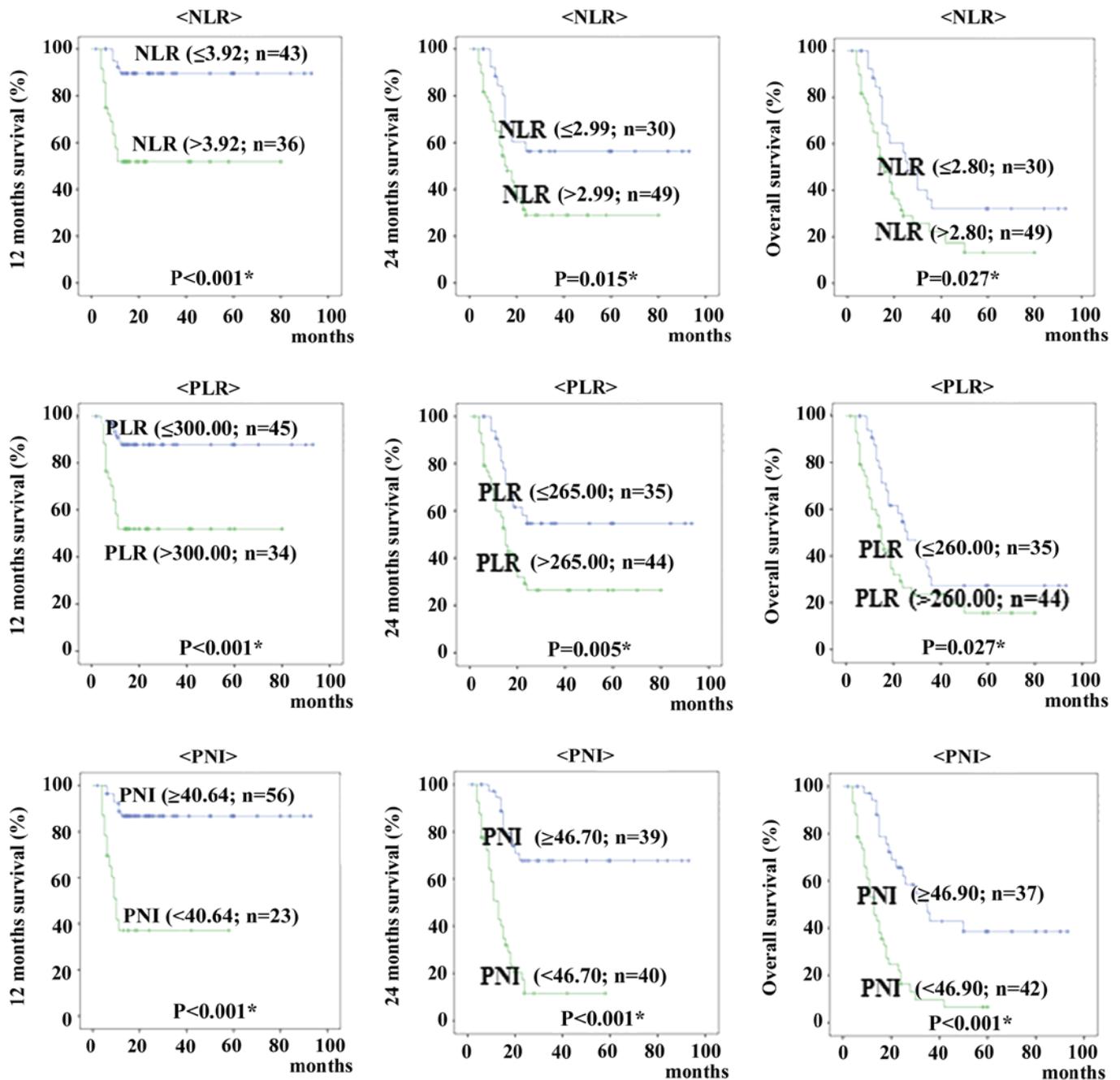


Figure 2. Kaplan-Meier plots for 12 months, 24 months and overall survival in 79 patients with recurrence cervical cancer, according to neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI).

which modulate albumin production (21). Lymphocytes can affect growth and metastasis such as CD3⁺ T cells and NK cells (22). Recent evidence has shown that relative differences in neutrophil, platelet, albumin and lymphocyte counts, NLR, PLR, and PNI are systemic indicators of prognosis. The PNI is based on albumin and absolute lymphocyte count, which are measured routinely in clinical practice. It was originally derived to assess immunologic and nutritional condition of patients undergoing surgical treatment for disease of the digestive tract. Mizunuma *et al* reported that NLR was a significant prognostic factor for PFS and OS in patients with cervical cancer who had been treated with CCRT or RT (23). Reportedly, PLR is an important predictor of prognosis in patients whose cervical cancers recur after

undergoing CCRT (8). The current investigation of correlations among clinicopathological parameters and NLR, PLR and PNI found NLR and PLR were significant associated with treatment type; and PNI was significantly associated with multiple metastases, hematogenous metastasis and treatment type.

This study mainly evaluated correlations between the SIR parameters, such as NLR, PLR and PNI, and survival (12 months, 24 months and overall survival) of patients whose cervical cancer recurred after undergoing CCRT or radical hysterectomy (with or without CCRT). We found that 12-month, 24-month and overall survival for patients with higher NLR and PLR were significantly shorter than for patients with lower NLR and PLR. We also found that

Table III. Prognostic factors for 12, 24 months survival and overall survival with recurrent cervical cancer selected by Cox's univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
12 months survival						
Histology	0.808	0.326-2.002	0.645			
Treatment free interval	2.568	1.064-6.201	0.036 ^a	3.322	1.300-8.489	0.012 ^a
Multiple metastasis	1.852	0.780-4.397	0.162			
Hematogenous metastasis	1.295	0.545-3.074	0.558			
Lymphogenous metastasis	1.355	0.575-3.191	0.487			
Treatment (Cx or PC)	12.115	1.625-90.298	0.015 ^a	5.588	0.680-45.943	0.109
NLR (>3.92)	6.422	2.156-19.125	0.001 ^a	2.332	0.457-11.894	0.308
PLR (>300.00)	5.19	1.897-14.199	0.001 ^a	1.475	0.348-6.252	0.598
PNI (<40.64)	7.205	2.887-17.987	<0.001 ^a	4.983	1.889-13.146	0.001 ^a
24 months survival						
Histology	0.595	0.310-1.140	0.118			
Treatment free interval	2.748	1.500-5.035	0.001 ^a	2.44	1.316-4.526	0.005 ^a
Multiple metastasis	2.3	1.258-4.206	0.007 ^a	1.099	0.565-2.139	0.781
Hematogenous metastasis	1.302	0.717-2.366	0.385			
Lymphogenous metastasis	1.301	0.718-2.357	0.386			
Treatment (Cx or PC)	6.772	2.649-17.314	<0.001 ^a	4.17	1.463-11.885	0.008 ^a
NLR (>2.90)	2.252	1.136-4.464	0.020 ^a	1.002	0.342-2.931	0.997
PLR (>265.00)	2.378	1.258-4.495	0.008 ^a	1.093	0.408-2.927	0.859
PNI (<46.70)	5.495	2.749-10.984	<0.001 ^a	3.767	1.750-8.109	0.001 ^a
Overall survival						
Histology	0.713	0.406-1.252	0.239			
Treatment free interval	2.446	1.421-4.209	0.001 ^a	2.244	1.285-3.918	0.004 ^a
Multiple metastasis	2.564	1.478-4.447	0.001 ^a	1.07	0.578-1.980	0.829
Hematogenous metastasis	1.245	0.726-2.136	0.426			
Lymphogenous metastasis	1.302	0.760-2.231	0.336			
Treatment (Cx or PC)	7.196	3.293-15.727	<0.001 ^a	5.709	2.297-14.190	<0.001 ^a
NLR (>2.80)	1.89	1.056-3.380	0.032 ^a	1.051	0.435-2.539	0.912
PLR (>260.00)	1.821	1.051-3.155	0.032 ^a	0.817	0.353-1.891	0.637
PNI (<46.90)	3.621	2.026-6.473	<0.001 ^a	3.229	1.689-6.173	<0.001 ^a

^aP<0.05. HR, hazard ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; Cx, chemotherapy; PC, palliative cares.

12-month, 24-month and overall survival for patients with lower PNI were significantly shorter than for patients with higher PNI. We not only found PNI to be an independent prognostic factor for 12-month, 24-month and overall survival in multivariate analysis, but PNI was also superior to NLR or PLR as a predictor of survival in all patient cohorts with recurrent cervical cancer.

Each patient underwent varied treatment combinations, some of which are subjected to alter the bone marrow hematopoietic function, further to affect the results of blood tests, like dosage of radiotherapy, coverage of irradiated field, numbers of chemotherapies, regimens of chemotherapies and different combination. In this study, pretreatment of SIR was also superior to during treatment as a predictor of survival

with recurrent cervical cancer. Therefore, the PNI may be useful in reflecting the frailty and nutritional decline in patients with recurrent cervical cancer. Our results suggest that the PNI will provide additional value to the routine assessment of survival of patients with recurrent cervical cancer.

We acknowledge that our study has some limitations. The number of patients was relatively few, and the duration of follow-up was relatively short. Further prospective studies with more patients and longer follow-up periods would provide more definitive data to clarify the significance of our findings.

In conclusion, our results show that PNI can serve as a useful indicator of survival in patients with recurrent cervical cancer.

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