

Pretreatment platelet-lymphocyte ratio is an independent predictor of cervical cancer recurrence following concurrent chemoradiation therapy

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Abstract. The aim of the present study was to identify the correlations between inflammation markers such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and C-reactive protein (CRP) and the prognosis in patients with recurrent cervical cancer. The associations among NLR, PLR and CRP and clinical characteristics and prognosis were examined in 32 patients receiving chemotherapy with recurrent cervical cancer following concurrent chemoradiation therapy (CCRT). The patient median survival time was 198 days (range, 42-1,022 days). Pretreatment NLR and PLR were significantly correlated with the recurrence of cervical cancer following CCRT ($R=-0.538$, $P=0.002$; and $R=-0.542$, $P=0.001$, respectively). Pretreatment PLR >322.0 was significantly associated with a poor prognosis for recurrent cervical cancer following CCRT by univariate and multivariate analyses ($P=0.015$ and $P=0.029$). These findings indicate that pretreatment PLR is an important predictor of prognosis in patients with recurrent cervical cancer following CCRT.

Introduction

Cervical cancer is the second most common gynecological malignancy (1). Concurrent chemoradiation therapy (CCRT) with platinum-based chemotherapy has been established as the standard of care for patients with stage IB2-IVA cervical cancer [International Federation of Gynecology and Obstetrics (FIGO) classification] (2,3). However, the recurrence rate of cervical cancer varies between 11 and 22%

in FIGO stage IB-IIA and between 28 and 64% in FIGO stage IIB-IVA (4).

Inflammation has been shown to enable various cancer characteristics, thus affecting prognosis. Recent evidence has indicated that relative differences in neutrophil, platelet and lymphocyte counts, and neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are systemic indicators of prognosis (5). C-reactive protein (CRP) also increases under inflammation in cancer (6). Pretreatment measurements of peripheral blood NLR, PLR and CRP are independent predictors of a poor prognosis in various types of cancer (7-12). However, their predictive role in recurrent cervical cancer is unknown. In the present study, the associations among NLR, PLR and CRP and the clinical characteristics and prognoses of patients with recurrent cervical cancer following CCRT were investigated.

Materials and methods

Study subjects. The clinicopathological characteristics of 32 patients with recurrent cervical cancer who had been treated in the Department of Obstetrics and Gynecology of Okayama University Hospital (Okayama, Japan) between April 2005 and June 2014 were retrospectively analyzed. The primary treatment of these patients was CCRT. All the patients were treated with a combination of external irradiation (50 Gy administered in 25 fractions over 5 weeks; 4-field box technique) and high-dose intracavitary brachytherapy (24 Gy/4 times); and concurrent chemotherapy of either cisplatin (40 mg/m² infusion weekly for 6 cycles) or nedaplatin (30 mg/m² infusion weekly for 8 cycles). Following the primary treatment, the patients underwent follow-up examinations approximately every 1-2 months for the first 6 months, and subsequently, every 3 months for the next 2 years. The study protocol was approved by the Institutional Review Board of Okayama University Hospital. Informed consent was obtained from all the patients.

Chemotherapy. The policy of the Department of Obstetrics and Gynecology requires a performance score ≤ 2 (World Health Organization criteria) prior to initiating second-line

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chemotherapy, involving 60 mg/m² TC-paclitaxel weekly and carboplatin [area under the plasma-concentration curve (AUC), 1.5] (Bristol-Myers Squibb, New York, NY, USA). Chemotherapy for recurrent disease was continued until complete response or progressive disease was observed. Third-line chemotherapy consisted of single-agent irinotecan (CPT-11; 70 mg/m² weekly for 3 weeks followed by 1 week off; Yakult, Tokyo, Japan); and fourth-line chemotherapy was single-agent gemcitabine (700 mg/m² weekly for 3 weeks followed by 1 week off; Eli Lilly and Co., Indiana, IN, USA). These patient objective responses were principally evaluated by the Response Evaluation Criteria in Solid Tumors (version 1.1).

NLR, PLR and CRP. Each subject had a complete blood cell count and differential white blood cell counts recorded within 7 days prior to chemotherapy. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was defined as the absolute platelet count divided by the lymphocyte count (Bayer HealthCare, Diagnostics Division, Tarrytown, NY, USA). Serum CRP was measured by latex nephelometry (LT Auto Wako, Osaka, Japan).

Statistical analysis. Statistical analyses were performed using the Mann-Whitney U test for comparisons with controls and one-factor analysis of variance followed by Fisher's protected least significant difference test for all the pairwise comparisons. Receiver operating characteristic (ROC) curves were generated for pretreatment NLR, PLR and CRP to determine cut-off values that predicted survival for <200 days (i.e., approximately the median survival period of 198 days for patients in the present study) that yielded optimal sensitivity and specificity; patients were subsequently grouped by these cut-off values. Univariate and multivariate analyses were performed using Cox's proportional hazards model to identify biomarkers that predict survival following adjustment for the effects of known prognostic factors. Analyses used SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics and treatments. Histological type, duration of recurrence-free survival and recurrence sites are listed in Table I. Tumors that were simultaneously found inside and outside the previously irradiated area were treated as extra-irradiation areas. Among the patients with recurrent disease, 32 (100%), 15 (46.9%) and 4 (12.5%) patients received second-, third- and fourth-line chemotherapy, respectively (Fig. 1A). Responses of patients who received second- to fourth-line chemotherapy are shown in Fig. 1B. Tumor response rate (RR) and disease control rate were 12.5 and 43.7% for second-line chemotherapy, 6.7 and 20.0% for third-line chemotherapy, and 0.0 and 25.0% for fourth-line chemotherapy, respectively. The median numbers of cycles of second-, third- and fourth-line chemotherapy received were 12 (range, 3-24), 8 (3-18) and 6 (2-12), respectively. Median survival time was 198 days (range, 42-1,022 days). Final chemotherapy regimens for the 32 patients were second-line for 17 patients (53.1%), third-line for 11 (34.4%) and fourth-line for 4 (12.5%). Their mean survival periods were 178.9, 483.0

Table I. Patient and tumor characteristics.

Baseline characteristics	All patients
Age at diagnosis, mean years (range)	52.6 (25-78)
Histology, n (%)	
SCC	27 (84.3)
AD	3 (9.4)
ADSQ	2 (6.3)
TFI, n (%)	
≤6 months	10 (31.2)
7-12 months	18 (56.3)
≥13 months	4 (12.5)
Recurrent site, n (%)	
Prior-irradiation area	18 (56.3)
Extra-irradiation area	11 (34.3)
Extra + prior-irradiation area	3 (9.4)

SCC, squamous cell carcinoma; AD, adenocarcinoma; ADSQ, adeno-squamous cell carcinoma; TFI, treatment-free interval.

and 493.5 days, respectively; thus patients whose final treatment was a second-line regimen had a significantly shorter survival time compared with those who reached third- and fourth-line regimens ($P=0.001$ and $P=0.001$) (Fig. 1C).

NLR, PLR and CRP. Median pretreatment NLR, PLR and CRP in these patients were NLR, 6.36 (range, 1.44-20.63); PLR, 426.06 (range, 154.77-1,227.6); and CRP, 3.64 mg/dl (range, 0.01-15.2 mg/dl). Patient pretreatment NLR ($R=-0.538$, $R_2=-0.289$, $P=0.002$) and PLR ($R=-0.542$, $R_2=-0.294$, $P=0.001$) were significantly and inversely correlated with their survival time (Fig. 2A). Pretreatment NLR and PLR for patients whose final regimen was second-line were significantly higher compared with for patients who survived to third- and fourth-line regimens ($P=0.006$, $P=0.007$, $P=0.019$ and $P=0.019$, respectively). However, CRP concentration showed no association with any line of chemotherapy (Fig. 2B).

Whether the cancer recurrence sites were correlated with NLR, PLR, CRP, treatment-free interval (TFI), final-line chemotherapy or survival period were examined. Recurrences in extra-irradiation areas were associated with lower final-line chemotherapy number ($P=0.011$) and shorter survival time ($P=0.021$). However, none of the inflammatory markers were correlated with the recurrence site (Fig. 3).

ROC curve analyses determined cut-off values for pretreatment NLR, PLR and CRP that predicted survival <200 days at NLR, 3.95 (AUC, 0.809; sensitivity 81.3%; specificity 56.2%); PLR, 322.0 (AUC, 0.816; sensitivity 81.3%; specificity 68.7%); and CRP, 0.7 mg/dl (AUC, 0.693; sensitivity 68.8%; specificity 56.2%) (Fig. 4).

Survival time analysis. Whether clinical factors correlated with survival <200 days was assessed by univariate and multivariate analyses. Univariate analyses were significantly associated with extra-irradiation area ($P=0.009$), second-line chemotherapy as final-line chemotherapy ($P=0.003$) and

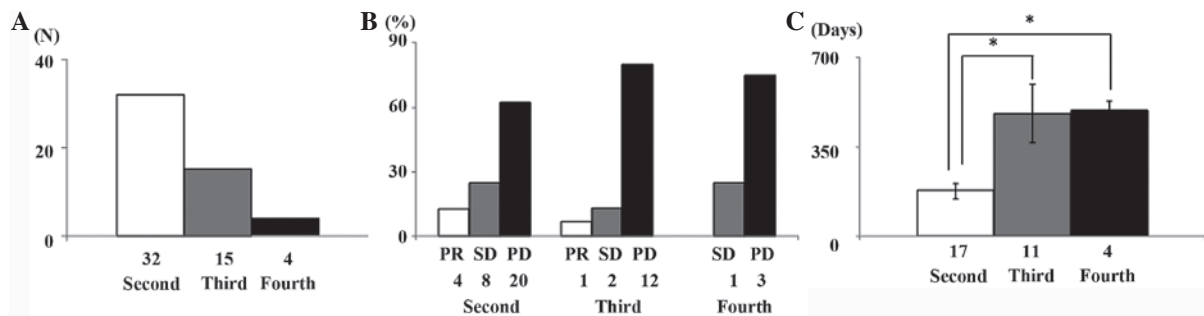


Figure 1. (A) Number of patients who received second- to fourth-line chemotherapy regimens for recurrent cervical cancer following first-line concurrent chemoradiation therapy. (B) Responses to second- to fourth-line regimens in these patients. (C) Survival time for these patients by their final chemotherapy lines. PR, partial response; SD, stable disease; PD, progressive disease. * $P < 0.05$.

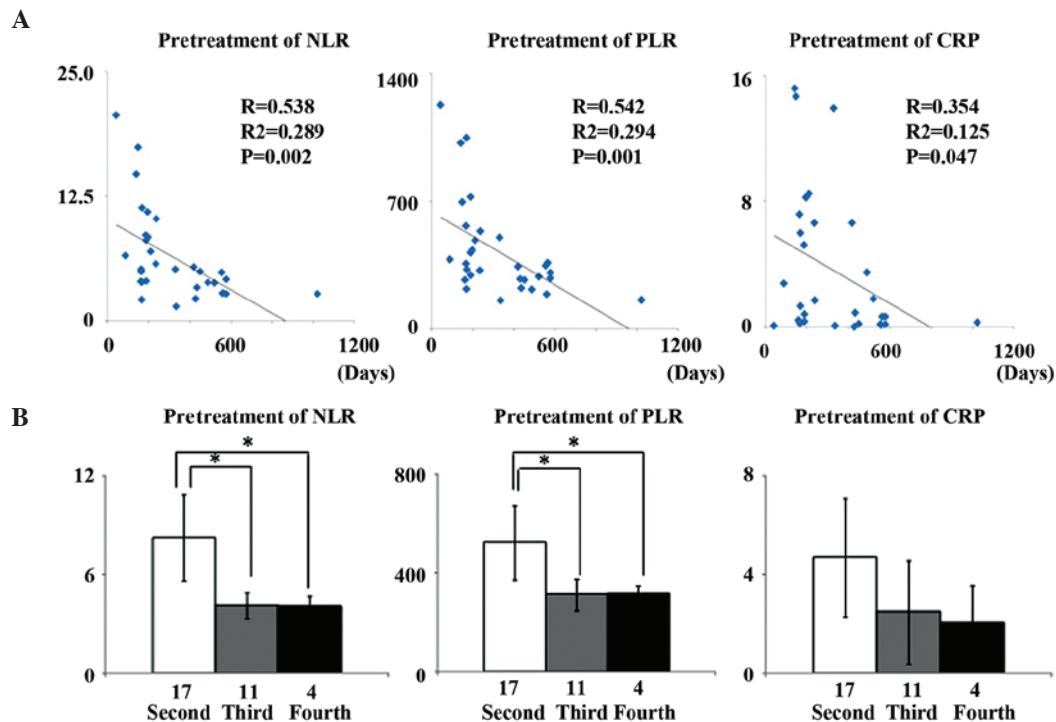


Figure 2. (A) Regression analysis for pretreatment neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP) and survival days in 32 patients whose cervical cancer recurred following first-line concurrent chemoradiation therapy. (B) Pretreatment NLR, PLR and CRP for patients whose second- to fourth-line regimen was their final line of chemotherapy. * $P < 0.05$.

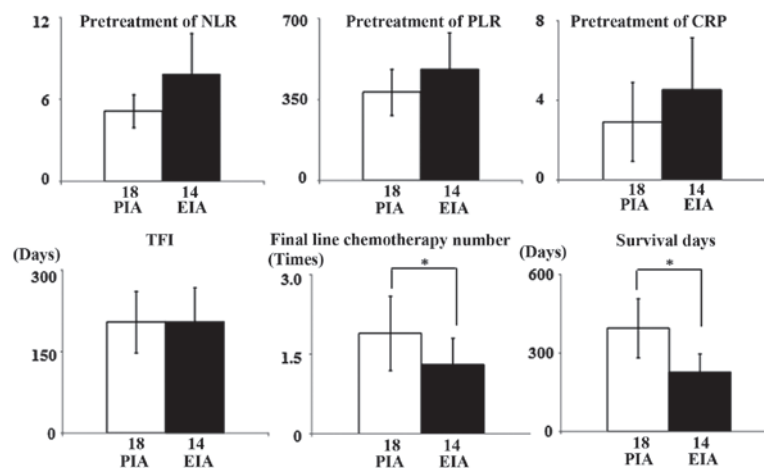


Figure 3. Pretreatment neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP), treatment-free interval (TFI), final-line chemotherapy number and survival days were compared with the extra- and prior-irradiation areas in patients whose cervical cancer recurred following first-line concurrent chemoradiation therapy. * $P < 0.05$.

Table II. Prognostic factors for survival within 200 days according to Cox's univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Histology (non-SCC)	1.202	0.339-4.264	0.776			
TFI (≤ 6 months)	3.339	0.423-26.376	0.253			
Extra-irradiation area	4.187	1.431-12.248	0.009 ^a	2.712	0.800-9.192	0.109
Second-line chemotherapy as final line chemotherapy	5.875	1.858-18.581	0.003 ^a	3.071	0.840-11.229	0.09
Pretreatment-NLR (>3.95)	2.564	0.826-7.961	0.103			
Pretreatment-PLR (>322.0)	4.814	1.364-16.988	0.015 ^a	4.204	1.158-15.268	0.029 ^a
CRP (>0.7 mg/dl)	1.858	0.644-5.357	0.252			

^aP<0.05. SCC, squamous cell carcinoma; TFI, treatment-free interval; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein; CI, confidence interval.

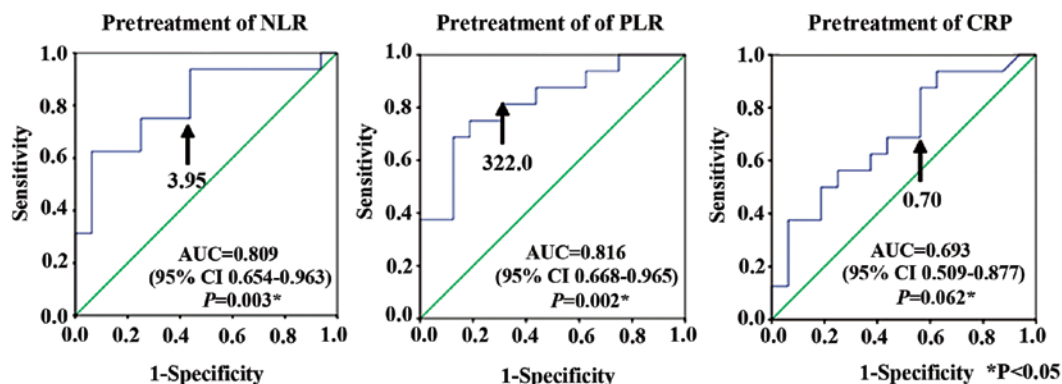


Figure 4. Receiver operating characteristic curves for optimal cut-off values to predict survival <200 days in patients whose cervical cancer recurred following first-line concurrent chemoradiation therapy, for pretreatment neutrophil-lymphocyte ratio (NLR) [3.95; area under the plasma-concentration curve (AUC), 0.809; 95% confidence interval (CI), 0.654-0.963; P=0.003], platelet-lymphocyte ratio (PLR) (322.0; AUC, 0.816; 95% CI, 0.668-0.965; P=0.002) and C-reactive protein (CRP) (0.70 mg/dl; AUC, 0.693; 95% CI, 0.509-0.877; P=0.062)].

pretreatment PLR >322.0 (P=0.015) with survival <200 days. Multivariate analyses showed that patients with high pretreatment PLR had a significantly higher hazard ratio (4.204) for survival <200 days compared to the patients with lower PLR (P=0.029) (Table II).

Discussion

Although treatment of recurrent cervical cancer depends on the site or extent of recurrence, disease-free interval and patient performance status (13,14), this condition has no standard chemotherapy regimen. The previous RR and median overall survival (OS) for second-line monotherapy regimens were cisplatin (50-100 mg/m²): 17-38%, 6.1-7.1 months (15,16); carboplatin (400 mg/m² every 4 weeks): 15-28%, 6.75 months (17,18); gemcitabine (800 mg/m², days 1, 8 and 15 every 4 weeks): 4.5-8%, 4.9-6.5 (19,20); paclitaxel (250 mg/m² every 3 weeks): 21-26%, 7.3 months (21,22); and irinotecan (125 mg/m²/week for 4 weeks every 6 weeks or 350 mg/m² every 3 weeks): 16-21%, 6.4-8.2 months (23,24). The previous RR and median OS for combination regimens were cisplatin (75 mg/m²) plus paclitaxel (135-175 mg/m²): 45-47%, 7-10 months, more efficient than either of them used as single agents (25-27); and

CBDCA (AUC, 5) plus paclitaxel (135-175 mg/m²): 40-78%, 9.6-13.0 months (28,29). As carboplatin plus paclitaxel versus cisplatin plus paclitaxel regimens do not differ in terms of RR and OS (30), the side effects and anticancer agent continuations were considered in selecting weekly carboplatin plus paclitaxel for second-line regimens, irinotecan for third-line regimens, and gemcitabine for fourth-line regimens. In the present study, RR was 12.5% for second-line chemotherapy, 6.7% for third-line and 0.0% for fourth-line. Median survival was 198 days for the cohort, and 178.9, 483.0 and 493.5 days for patients whose final regimens were second-, third- and fourth-line chemotherapy, respectively, i.e., significantly shorter for patients whose final therapy was a second-line regimen.

Systemic inflammatory processes have been examined as possible predictors of prognosis in various types of cancer. Neutrophils release inflammatory cytokines and leukocytic and other phagocytic mediators that would induce damage to cellular DNA, inhibit apoptosis and promote angiogenesis (31,32). Platelets can release potent mitogens or adhesive glycoprotein such as platelet-derived growth factor, transforming growth factor- β and vascular endothelial growth factor (VEGF). Lymphocytes, such as cluster of differentiation 3⁺ T cells and natural killer cells, can affect growth

and metastasis (33,34). CRP may be released as a result of producing inflammation-related cytokines, such as VEGF and interleukin-6 (35,36). Thus, NLR and PLR have attracted the interest of investigators as possible markers of systemic inflammation, and therefore of prognosis. High pretreatment NLR and PLR have been reportedly associated with mortality in various types of cancer type (7-11). High pretreatment NLR is an independent indicator of poor prognosis in patients with cervical cancer (37,38); and CRP levels are also a prognostic parameter in patients with cervical cancer (39).

However, to the best of our knowledge, no studies have previously reported the correlations between pretreatment NLR, PLR and CRP and the survival of patients with recurrent cervical cancer following first-line CCRT. In the present study, pretreatment NLR and PLR were significantly and inversely correlated with survival time in these patients. Furthermore, patients whose final regimen was second-line chemotherapy had significantly higher pretreatment NLR and PLR compared with those who survived to undergo third- and fourth-line chemotherapy. NLR, PLR, CRP, TFI, final-line chemotherapy and survival against recurrence sites were examined, and the patients whose recurrence spread to extra-irradiation areas had a significantly shorter survival rate compared with those whose tumors recurred in the prior-irradiation area. Higher inflammatory markers (NLR, PLR and CRP) were associated, but not significantly so, with recurrence sites.

One of the aims of the present study was to confirm whether pretreatment NLR, PLR or CRP could predict survival <200 days. ROC curve analyses showed that the optimal cut-off pretreatment values were NLR, 3.95; PLR, 322.0; and CRP, 0.70 mg/dl. Univariate and multivariate analyses were significantly associated with pretreatment PLR >322.0 with survival <200 days.

The study has certain limitations; including relatively few patients, followed up over a relatively short period. Further prospective studies with more patients and longer follow-up periods would verify the present findings and clarify their significance.

In conclusion, the present findings suggest that pretreatment PLR is an important predictor of prognosis in patients with recurrent cervical cancer following CCRT.

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