Prognostic significance of pre-treatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in non-surgically treated uterine cervical carcinoma

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Abstract. The aim of the present study was to assess the prognostic significance of the pre-treatment neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR) and other clinicopathological characteristics in patients with non-surgically treated uterine cervical carcinoma. The correlations of clinicopathological characteristics with overall and progression-free survival were determined in 98 Japanese patients who received non-surgical treatment for uterine cervical carcinoma between January 1997 and July 2013. Survival rates were calculated using the Kaplan-Meier method and potential prognostic indicators were assessed using a Cox proportional hazards model. A total of 68 patients (69.4%) had a high pre-treatment NLR (≥3.5) and 34 patients (34.7%) had a high pre-treatment PLR (≥212). Both NLR and PLR were found to be positively correlated with pre-treatment platelet counts. Multivariate analysis identified NLR and carcinoembryonic antigen level, but not PLR, as independent predictors of overall and progression-free survival. In conclusion, the present study identified two prognostic indicators for uterine cervical carcinoma, both of which can be easily and cost-effectively monitored via blood testing.

Introduction

Uterine cervical carcinoma is the second most common cancer in women and the fifth most common type of cancer worldwide (1), and it is a leading cause of cancer-related mortality among Japanese women.

Recent studies have identified the pre-treatment neutrophil-to-lymphocyte ratio (NLR) as an independent prognostic indicator in several types of malignancies, including colorectal cancer (2,3), hepatocellular carcinoma (4), pancreatic cancer (5) and non-small-cell lung cancer (6). The pre-treatment NLR was also found to be an independent prognostic factor in patients with uterine cervical carcinoma who have undergone radiation therapy or concurrent chemoradiation therapy (7). Although the pre-treatment platelet-to-lymphocyte ratio (PLR) may be used to predict the prognosis of colorectal (8), ovarian (9), prostate (10) and oral (11) cancers, its prognostic role in uterine cervical carcinoma remains unclear. The aim of the present study was to evaluate the prognostic significance of pre-treatment NLR and PLR, as well as that of other clinicopathological characteristics, in patients with uterine cervical carcinoma. The associations between NLR and PLR and these factors were also investigated.

Patients and methods

Patients. A total of 98 non-surgically treated patients with uterine cervical carcinoma at Shimane University School of Medicine (Izumo, Japan) between January 1997 and July 2013 were enrolled in this study. Patient data (e.g., baseline characteristics, laboratory findings and pathology reports) were collected from electronic medical records. Uterine cervical carcinoma was diagnosed via conventional morphological examination of hematoxylin and eosin-stained sections. Tumor type and stage were classified according to the classification systems of the World Health Organization (12) and the International Federation of Gynecology and Obstetrics (FIGO) (13), respectively.

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Table I. Associations between the pre-treatment NLR and the clinicopathological characteristics of patients with uterine cervical carcinoma (n=98).

Clinicopathological characteristics	NLR <3.5 (n=68)	NLR ≥3.5 (n=30)	P-value
Age at diagnosis (years), n (%)			0.369
<60	23 (23.5)	13 (13.3)	
≥60	45 (45.9)	17 (17.3)	
Histological type, n (%)			0.399
SCC	52 (53.1)	25 (25.5)	
Other	16 (16.3)	5 (5.1)	
FIGO stage, n (%)			0.950
I/II	23 (23.5)	10 (10.2)	
III/IV	45 (45.9)	20 (20.4)	
Platelet count (/μl), n (%)			0.002[a]
<35x10^4	57 (58.2)	17 (17.3)	
≥35x10^4	11 (11.2)	13 (13.3)	
CRP level (mg/dl), n (%)			0.460
<0.2	15 (15.3)	1 (1.0)	
≥0.2	53 (54.1)	29 (29.6)	

[a]P<0.05. NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

The study protocol was approved by the Ethics Committee of Shimane University School of Medicine (approval no.: 960) and all the patients provided written informed consent. The research was conducted in accordance with the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, effective December 13, 2001.

Definition of NLR and PLR. All laboratory data used in the present study were obtained at least 4 weeks prior to treatment initiation. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The mean pre-treatment NLR was 3.5, according to which patients were divided into high NLR (≥3.5) and low NLR (<3.5) groups. The PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. The mean pre-treatment PLR was 212, according to which patients were divided into high PLR (≥212) and low PLR (<212) groups.

Statistical analysis. Univariate analysis was performed using binomial logistic regression for ordered categorical variables. The following patient clinicopathological characteristics were included in this analysis: Age at diagnosis (<60 vs. ≥60 years), FIGO classification (stage I/II vs. III/IV), histological type [squamous cell carcinoma (SCC) vs. other], pre-treatment plasma D-dimer level (<1.0 vs. ≥1.0 μg/ml), plasma fibrinogen level (<450 vs. ≥450 mg/dl), white blood cell (WBC) count (<8.6 vs. ≥8.6x 10^3/μl), platelet count (<35 vs. ≥35x10^4/μl), NLR (<3.5 vs. ≥3.5), PLR (<212 vs. ≥212), C-reactive protein (CRP) level (<0.2 vs. ≥0.2 mg/dl), SCC antigen level (<1.5 vs. ≥1.5 U/ml) and carcinoembryonic antigen (CEA) level (<5.0 vs. ≥5.0 ng/ml). The endpoints of the analysis were overall survival (OS) and progression-free survival (PFS). OS was defined as the time interval between the date of diagnosis and the date of death. Patients who were alive at the last follow-up were censored. PFS was defined as the time interval between the date of diagnosis and the date of recurrence. Patients without recurrence at the last follow-up were censored. OS and PFS were calculated using the Kaplan-Meier method and statistical significance was determined using the log-rank test.

To identify significant prognostic factors, a multivariate analysis was performed using a Cox proportional hazards model. Variables shown to be significant (P<0.05) in the univariate analysis were entered into the multivariate analysis. All statistical analyses were conducted using Statistical Package for the Social Sciences for Windows, software version 19.0 (IBM Corp., Armonk, NY, USA). A two-sided P<0.05 was considered statistically significant.

Results

Patient clinicopathological characteristics. This study analyzed data from 98 patients with uterine cervical carcinoma. The median age at diagnosis was 65 years (range, 32-86 years), with 37.6% of the patients aged <60 and 63.3% ≥60 years. The majority of patients (78.6%) were diagnosed with SCC; 33 patients (33.7%) had FIGO stage I/II disease and 65 (66.3%) had FIGO stage III/IV disease.

A total of 68 patients (69.4%) were included in the high pre-treatment NLR group (≥3.5) and 30 (30.6%) were in the low pre-treatment NLR group (<3.5). A total of 34 patients (34.7%) were included in the high pre-treatment PLR group (≥212) and 64 (65.3%) were in the low pre-treatment PLR group (<212). The number (percentage) of patients with plasma D-dimer levels ≥1.0 μg/ml, plasma fibrinogen levels ≥450 mg/dl, WBC count ≥8.6x10^3/μl, platelet count ≥35x10^4/μl,

Table II. Associations between the pre-treatment (PLR) and the clinicopathological characteristics of patients with uterine cervical carcinoma (n=98).

Clinicopathological characteristic	PLR <212 (n=64)	PLR ≥212 (n=34)	P-value
Age at diagnosis (years), n (%)			0.136
<60	20 (20.4)	16 (16.3)	
≥60	44 (44.9)	18 (18.4)	
Histological type, n (%)			0.932
SCC	50 (51.0)	27 (27.6)	
Other	14 (14.3)	7 (7.1)	
FIGO stage, n (%)			0.115
I/II	25 (25.5)	8 (8.2)	
III/IV	39 (39.8)	26 (26.5)	
Platelet count (/μl), n (%)			<0.001[a]
<35x10^4	58 (59.2)	16 (16.3)	
≥35x10^4	6 (6.1)	18 (18.4)	
CRP level (mg/dl), n (%)			0.460
<0.2	15 (15.3)	1 (1.0)	
≥0.2	53 (54.1)	29 (29.6)	

[a]$P<0.05$. PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.
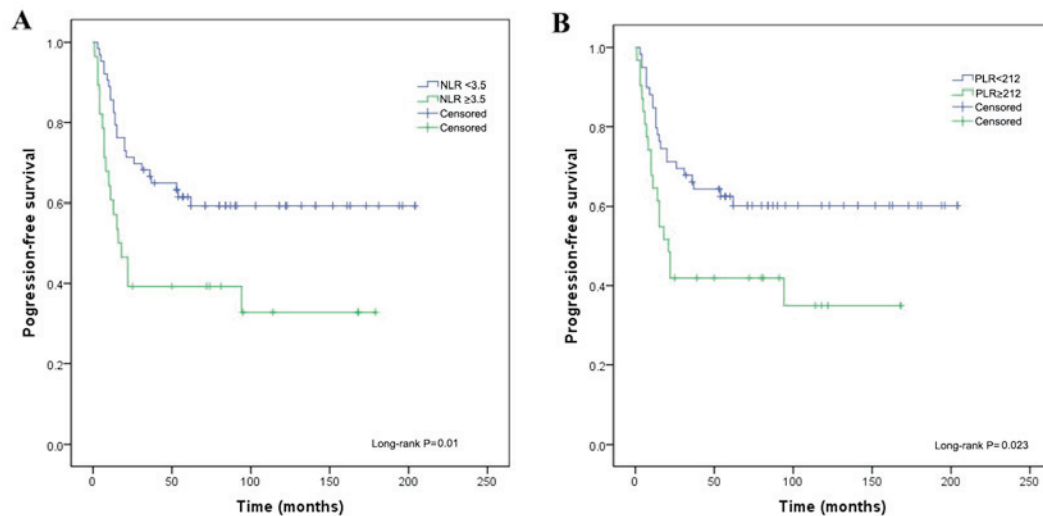

Figure 1. Kaplan-Meier estimates of the prognostic significance of: (A) A high pre-treatment neutrophil-to-lymphocyte ratio (NLR); and (B) a high pre-treatment platelet-to-lymphocyte ratio (PLR) on the progression-free survival rate of patients with uterine cervical carcinoma (n=98).

CRP levels ≥0.2 mg/dl, SCC antigen levels ≥1.5 U/ml and CEA levels ≥5.0 ng/ml were 72 (73.5%), 46 (46.9%), 32 (32.7%), 24 (24.5%), 82 (83.7%), 77 (78.6%) and 59 (60.2%), respectively.

Pre-treatment NLR and patient clinicopathological characteristics. The correlations between the pre-treatment NLR (<3.5 vs. ≥3.5) and patient clinicopathological characteristics were evaluated via binomial logistic regression analysis. Only the pre-treatment platelet count was found to be correlated with the pre-treatment NLR, and this correlation was positive. There was no significant association between age at diagnosis, FIGO stage or histological type and the NLR (Table I).

Pre-treatment PLR and patient clinicopathological characteristics. The correlations between the pre-treatment PLR (<212 vs. ≥212) and patient clinicopathological characteristics were also assessed via binomial regression analysis. Only the pre-treatment platelet count was found to be associated with the pre-treatment PLR (Table II).

Univariate and multivariate analysis of pre-treatment prognostic factors for uterine cervical carcinoma. In the univariate analysis, the NLR (P=0.010, Fig. 1A), PLR (P=0.023, Fig. 1B), platelet count (P=0.009) and CEA level (P=0.012) were significantly associated with PFS in patients with uterine cervical

Table III. Univariate and multivariate analysis of progression-free survival using a Cox proportional hazards model in patients with uterine cervical carcinoma (n=98).

Factors	Univariate analysis			Multivariate analysis		
	HR	95.0% CI	P-value	HR	95.0% CI	P-value
Age at diagnosis (years)	Ref.					
	0.885	0.472-1.650	0.702	-	-	-
	Ref.					
	0.641	0.323-1.270	0.204	-	-	-
	Ref.					
	0.525	0.259-1.066	0.075	-	-	-
	Ref.					
	0.449	0.245-0.826	0.010[a]	0.317	0.167-0.602	<0.001[a]
	Ref.					
	0.494	0.268-0.908	0.023[a]	N/A	N/A	N/A
Plasma D-dimer level (μg/ml)	Ref.					
	0.849	0.397-1.815	0.674	-	-	-
Plasma fibrinogen level (mg/dl)	Ref.					
	0.636	0.327-1.238	0.183	-	-	-
	Ref.					
	0.55	0.301-1.004	0.550	-	-	-
Platelet count (/μl)	Ref.					
	0.432	0.229-0.713	0.009[a]	N/A	N/A	N/A
	Ref.					
	0.537	0.210-1.372	0.194	-	-	-
SCC antigen level (ng/ml)	Ref.					
	0.938	0.445-1.977	0.866	-	-	-
	Ref.					
	0.422	0.215-0.830	0.012[a]	0.337	0.168-0.676	0.002[a]

[a]P<0.05. CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; N/A, not available; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Ref., reference; SCC, squamous cell carcinoma; WBC, white blood cell.
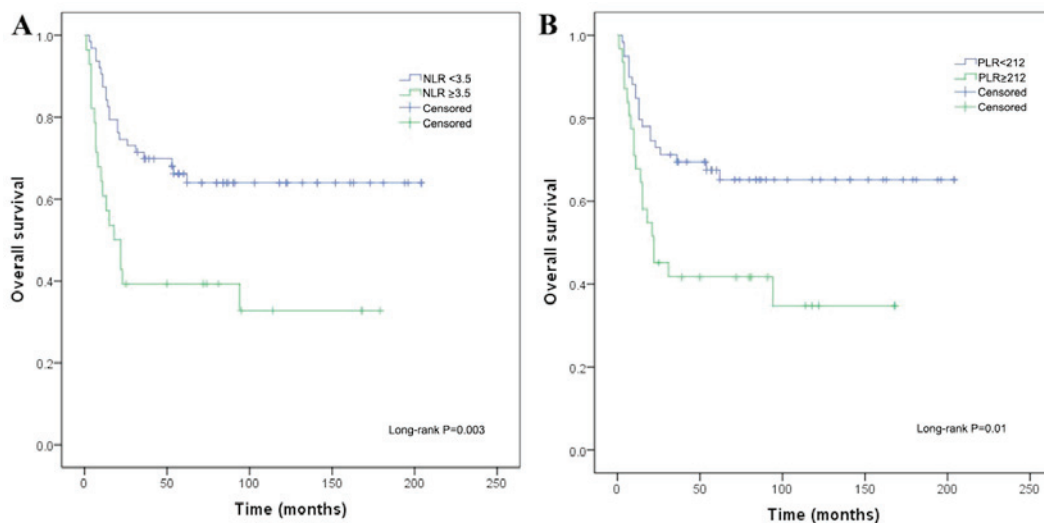

Figure 2. Kaplan-Meier estimates of the prognostic significance of: (A) A high pre-treatment neutrophil-to-lymphocyte ratio (NLR); and (B) a high pre-treatment platelet-to-lymphocyte ratio (PLR) on the overall survival rate of patients with uterine cervical carcinoma (n=98).

Table IV. Univariate and multivariate analysis of overall survival using a Cox proportional hazards model in patients with uterine cervical carcinoma (n=98).

Factors	Patients (n)	Univariate analysis			Multivariate analysis		
		HR	95.0% CI	P-value	HR	95.0% CI	P-value
Age at diagnosis (years)							
<60	36	Ref.					
≥60	62	0.882	0.460-1.689	0.704	-	-	-
Histological type							
SCC	77	Ref.					
Other	21	0.575	0.287-1.152	0.119	-	-	-
FIGO stage							
I/II	33	Ref.					
III/IV	65	0.565	0.276-1.157	0.119	-	-	-
NLR							
<3.5	68	Ref.					
≥3.5	30	0.391	0.209-0.732	0.003[a]	0.274	0.141-0.530	<0.001[a]
PLR							
<212	64	Ref.					
≥212	34	0.438	0.233-0.820	0.010[a]	N/A	N/A	N/A
Plasma D-dimer level (μg/ml)							
<1.0	26	Ref.					
≥1.0	72	0.832	0.372-1.858	0.654	-	-	-
Plasma fibrinogen level (mg/dl)							
<450	52	Ref.					
≥450	46	0.693	0.347-1.383	0.298	-	-	-
WBC count (/μl)							
<8.6x10^3	66	Ref.					
≥8.6x10^3	32	0.523	0.280-0.977	0.042[a]	N/A	N/A	N/A
Platelet count (/μl)							
<35x10^4	74	Ref.					
≥35x10^4	24	0.419	0.217-0.808	0.009[a]	N/A	N/A	N/A
CRP level (mg/dl)							
<0.2	16	Ref.					
≥0.2	82	0.521	0.203-1.339	0.176	-	-	-
SCC antigen level (ng/ml)							
<1.5	21	Ref.					
≥1.5	77	1.06	0.498-2.256	0.880	-	-	-
CEA level (ng/ml)							
<5.0	39	Ref.					
≥5.0	59	0.429	0.212-0.868	0.019[*]	0.334	0.162-0.689	0.003[*]

[a]P<0.05. CEA, carcinoembryonic antigen; CI, confidence interval; CRP, C-reactive protein; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; N/A, not available; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Ref., reference; SCC, squamous cell carcinoma; WBC, white blood cell.

carcinoma. In the multivariate analysis, only the NLR [hazard ratio (HR)=0.317, 95.0% confidence interval (CI): 0.167-0.602; P<0.001] and CEA level (HR=0.337, 95.0% CI: 0.168-0.676; P=0.002) were independently correlated with PFS (Table III).

The factors significantly associated with OS in the univariate analysis included the WBC count (P=0.042), NLR (P=0.003, Fig. 2A), PLR (P=0.01, Fig. 2B), platelet count (P=0.009) and CEA level (P=0.019). Of these, and similar to the results for PFS, only the NLR (HR=0.274, 95.0% CI: 0.141-0.530; P<0.001) and CEA level (HR=0.334, 95.0% CI: 0.162-0.689; P=0.003) were independently correlated with OS in the multivariate analysis (Table IV).

Discussion

A high pre-treatment NLR was recently recognized as a valid indicator of a poor prognosis in patients with various types of malignancies, including colorectal cancer (2,3), hepatocellular carcinoma (4), pancreatic cancer (5) and non-small-cell lung cancer (6). In the present study, a high pre-treatment NLR was correlated with a poor prognosis in patients with uterine cervical carcinoma, which is consistent with the findings of previous cancer studies (2-6).

The mechanism through which a high NLR adversely affects prognosis remains unclear. There are two possible explanations: First, the NLR is a measure of systemic inflammation, and the correlation between inflammation and cancer has been established, with inflammation considered to promote angiogenesis, lymphangiogenesis, invasion and tumor metastasis (14). Second, neutrophils release a number of angiogenic factors, such as vascular endothelial growth factor and matrix metalloproteinase-9. Matrix metalloproteinase-9 acts as an angiogenic switch that is critical for tumor progression (15). Lymphocytes, on the other hand, secrete interleukin-2, which inhibits tumor cell proliferation by activating and stimulating the proliferation of cytotoxic lymphocytes (16). Although pre-treatment neutrophil and lymphocyte counts are associated with systemic inflammation, there was no observed association between the pre-treatment CRP level and the NLR in this study. However, the NLR was associated with survival prognosis.

In a previous study (17), the pre-treatment PLR was an important predictor of prognosis in patients with recurrent cervical cancer following concurrent chemoradiation therapy. There is a potential explanation as to why this was the case: Tumors promote the activation and aggregation of platelets in their vasculature by inducing the expression of angiogenesis regulatory factors and their release from platelets (18). In the present study, the pre-treatment PLR was a prognostic factor in the univariate analysis, but not in the multivariate analysis. As there was a significant association between the NLR and platelet count (Table I), it is possible that the NLR may have affected the PLR. This may explain, at least in part, why the pre-treatment PLR was not found to be correlated with prognosis in this study.

In addition, a high pre-treatment CEA level was found to be a significant prognostic factor in uterine cervical carcinoma in the present study, whereas a high pre-treatment SCC antigen level was not. However, in two previous studies (19,20), both factors were useful for predicting prognosis in patients with uterine cervical carcinoma. It is well known that CEA levels are higher in patients with adenocarcinoma compared with those in patients with SCC, and a previous study (19) reported that the CEA level was a prognostic marker in patients with cervical SCC.

The limitations of the present study include its single-institution retrospective design.

In conclusion, the findings of the present study demonstrated that a high NLR, but not a high PLR, predicts a poor prognosis in non-surgically treated patients with uterine cervical carcinoma; they also suggested that pre-treatment CEA levels may independently predict OS and PFS. These findings may prove valuable, as both the NLR and CEA levels may be measured easily and cost-effectively via blood testing.

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