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Original Article

The prognostic role of the pretreatment peripheral neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in patients with cervical cancer

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Abstract

Aim: To investigate whether pretreatment peripheral neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) can be used as a prognostic indicator for predicting treatment response and survival outcomes in patients with cervical cancer.

Materials and Methods: Records of 141 patients with histologic confirmation of squamous cell carcinoma of the uterine cervix who were treated with radical radiotherapy or chemoradiotherapy in our clinic from 2010 to 2016 were retrospectively reviewed in this study. The relationship between pretreatment NLR/PLR with clinicopathological characteristics and therapeutic response and survival was analyzed. The cut-off values of NLR and PLR that predicted treatment response were determined using a receiver operating characteristic analysis.

Results: In the clinicopathological analysis, while pretreatment elevated NLR was associated with the tumor size and grade, elevated PLR was related to an advanced stage, tumor size and grade. Low NLR (<2.64) and PLR (<164) predicted treatment response significantly. However, there was no relationship between NLR/PLR and survival outcomes. The five-year overall survival (OS) and progression-free survival (PFS) rates for the whole study group were 67% and 74%, respectively. In multivariate analysis, the presence of the lymph node involvement and incomplete response to treatment was independent prognostic factors affecting both OS ($p = 0.013$, $p < 0.001$) and PFS ($p = 0.004$, $p < 0.001$).

Conclusion: Pretreatment NLR/PLR has predicted the treatment response significantly. The optimal cut-off values confirmed by further large-scale studies may be used in the future as a predictive marker for therapeutic response in cervical cancer.

Keywords: Cervical cancer; neutrophil/lymphocyte ratio; platelet/lymphocyte ratio; radiotherapy; concurrent chemoradiotherapy

INTRODUCTION

Cervical cancer is still one of the most common cancers that cause death in women in developing countries (1). The management of the early-stage disease is generally radical surgery. The unfavorable features remarked in the pathology report help determine the risk of relapse and adjuvant therapy decision. In locally advanced disease, the standard treatment is platinum-based chemotherapy and concomitant radiotherapy followed by intracavitary brachytherapy (2). The clinical stage is currently the most widely used prognostic factor worldwide. However, treatment response and prognosis are different in patients even at a similar stage. Approximately, one-third of patients relapse within the first two years after the end of treatment (3). In this patient group, there are no biological or molecular markers that can predict pretreatment prognosis and tumor response yet, except for known risk factors, such as clinical stage, age, bulky tumor and lymph node (LN) involvement.

The association between inflammation and cancer has been known for many years (4). Inflammation affects all steps in cancer development, from the initiation of the tumor to progression and metastasis (5). Currently, it has been shown in many studies that there is a relationship between several inflammatory markers such as C-reactive protein, neutrophil, thrombocyte, and lymphocyte count in the peripheral blood or their various combinations and the prognosis of various cancer (6,7). Neutrophil/lymphocyte

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ratio (NLR) and platelet/lymphocyte ratio (PLR) are the most frequently investigated parameters in these studies. Pretreatment elevated NLR and PLR values have been established to be related to worse survival in patients with many cancer types, such as esophageal, hepatocellular, colorectal, gastric, non-small cell lung and renal cancers (8-13). Recent studies have indicated the predictive and prognostic role of pre-treatment NLR and PLR values also in patients with cervical cancer (14-21). However, the data from these studies have conflicting results and the prognostic significance of NLR and PLR in cervical cancer is still uncertain.

Therefore, we aimed to investigate the relationship between pretreatment NLR/PLR values in peripheral blood and treatment response and survival outcomes in cervical cancer patients who underwent definitive radiotherapy alone or concurrent chemoradiotherapy.

MATERIALS and METHODS

Patients

This study included 141 patients with clinical stage IB1 to IVA uterine cervical cancer according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. All patients were histologically confirmed with squamous cell carcinoma (SCC) of the uterine cervix and received definitive radiotherapy or concurrent chemoradiotherapy in our clinic between 2010 and 2016. The patients' medical records, including history, physical examination, laboratory analysis, radiological reports, were retrospectively reviewed. The patients' age was ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance score of 0-2, and without distant metastasis were included in this study. The patients who had cervical adenocarcinoma and adenosquamous cell carcinoma, did not complete treatment, with missing follow-up data, and received palliative or adjuvant radiotherapy were excluded from this study. Ethical review and approval of the study were done by the local ethics committee of our university (No: A-22/2018). Also, written informed consent was obtained from all patients before treatment.

Pretreatment evaluation

Pretreatment clinical staging was performed by physical and gynecological examination. Also, pelvic MRI (Magnetic Resonance Imaging) and/or PET/CT (Positron Emission Tomography/Computed Tomography) were used to evaluate LN involvement and distant metastasis. The initial blood test performed within one week before the start of treatment was reviewed. Total white blood cell, neutrophil, lymphocyte, platelet counts and hemoglobin levels of each patient were recorded. The NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR was obtained by dividing the absolute platelet count by the absolute lymphocyte count. The median NLR and PLR values were 2.64 and 149.5, respectively. Patients were grouped according to their high NLR/PLR and low NLR/ PLR values.

Treatment

Pelvic radiotherapy was delivered by three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) technique with 6-10 MV X-rays in a linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). The total dose was median 45 Gy (45-59.4 Gy) with a daily dose of 1.8-2 Gy. High-dose-rate (HDR) intracavitary brachytherapy was performed using a Gammamed HDR with an Ir-192 source. A median dose of 27.5 Gy (11.2-30 Gy) prescribed to point A was performed twice a week.

Weekly 40 mg/m^2 cisplatin was administered concurrently with pelvic radiotherapy. All patients received a median of four cycles of chemotherapy.

Follow-up

All of the cases were followed up every week during the RT period, then every three months for the first two years, every six months for the next three years, and annually after the 5th year. During the routine follow-up physical and gynecologic examinations, including cervical smear, imaging studies, such as computed tomography (CT) or MRI were performed. When relapse was suspected based on gynecological examinations or imaging studies, a biopsy was performed. For assessment of treatment response, a gynecologic examination was performed at four weeks, pelvic MRI was administered at six weeks and positron emission tomography scan was administered at three months after completion of treatment. Complete response (CR) was defined as no evidence of disease on gynecological examinations and imaging studies. Progression-free survival (PFS) was considered the time from diagnosis to the date of the first event (recurrence, metastasis, or last follow-up). Overall survival (OS) was defined as the period from diagnosis to death for any reason or the last follow-up. Cancer-specific survival (CSS) was defined as the time from diagnosis to cancer-related death or the date of the last visit.

Statistical analysis

Descriptive statistics were used for the demographic and baseline characteristics of the patients. The patients were categorized by median NLR and PLR. The relationship between NLR/PLR and the clinicopathological characteristics of the patients was investigated using the non-parametric Mann-Whitney U test. The OS and DFS were estimated using the Kaplan-Meier method and were compared using a log-rank test. The univariate and multivariate analyses were performed using the Cox proportional hazard model to determine the prognostic value of clinicopathological and hematologic parameters on survival outcomes. A receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of NLR/PLR in predicting tumor response. For statistical significance, the p-value < 0.05 was accepted, and data analysis was processed using the SPSS software version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

We analyzed 141 patients with cervical cancer who underwent curative radiotherapy or concomitant chemoradiotherapy. The median age was 57 years, and the age range was from 28 to 86 years. According to the FIGO 2009 staging system, 12 (8.5%) of these cases were stage I, 113 (80.2%) were stage II, 12 (8.5%) were stage III, and the remaining four (2.8%) were stage IVA. Lymph node (LN) metastasis was present in 75 (53.2%) of the cases. Concurrent chemotherapy was administered to 127 (90.1%) patients. Radiotherapy was delivered to 86 (61%) patients with the IMRT technique, whereas 55 (39%) patients received 3DCRT. The patient, tumor characteristics and treatment details are listed in Table 1.

Table 1. Demographic data and other characteristics of the patients

Variables	Patients (n=141)	
	n	%
Age (median, range)	57 (28-86)	
≤57 years	76	53.9
>57 years	65	46.1
FIGO stage (2009)		
IB1-B2	12	8.5
IIA-B	113	80.2
IIIA-B	12	8.5
IVA	4	2.8
Histologic grade		
G I-II	61	43.1
G III	17	12.1
unknown	63	44.7
Tumor size		
≤ 4 cm	71	50.4
>4 cm	70	49.6
Lymph node involvement		
No	66	46.8
Yes	75	53.2
Concurrent chemotherapy		
No	14	9.9
Yes	127	90.1

The median follow-up time was 52 months (range, 8-102 months). By the last follow- up, recurrence was detected in 17 (12.1%) patients. Ten of them had only local recurrence, three had only pelvic and four had only paraaortic lymph node metastases. The five-year local control rate was 87.3%. Distant metastasis was detected in 27 (19.1%) patients. Of the 27 cases, three also had local recurrence, and 4 also had LN involvement. The most common sites of distant metastasis were the liver, lung, and bone.

ROC curves for treatment response

The complete response at 12 weeks after concurrent chemoradiotherapy was achieved in 122 patients (86.5%). A pretreatment NLR cut-off value of 2.64 was determined for predicting CR (area under the curve 0.660; 95% CI, 0.586-0.747; p=0.019), with a sensitivity of 73% and a specificity of 53%. This value was the same as the median NLR. For PLR, the cut-off value of 164 was determined for predicting CR (area under the curve 0.627; 95% CI, 0.541-0.707; p=0.0815), with a sensitivity of 68% and a specificity of 55%. ROC curves of pretreatment NLR and PLR that predicted CR are plotted in Figure 1. The correlation between treatment response and the patient's clinicopathological features is shown in Table 2. The group of patients with tumor size ≤4 cm, grade I-II and NLR <2.64, PLR <164, and hemoglobin level ≥ 11 g/dL had a significantly better therapeutic response. The low NLR and PLR were significantly predictive of CR (p=0.029 and p=0.036, respectively).

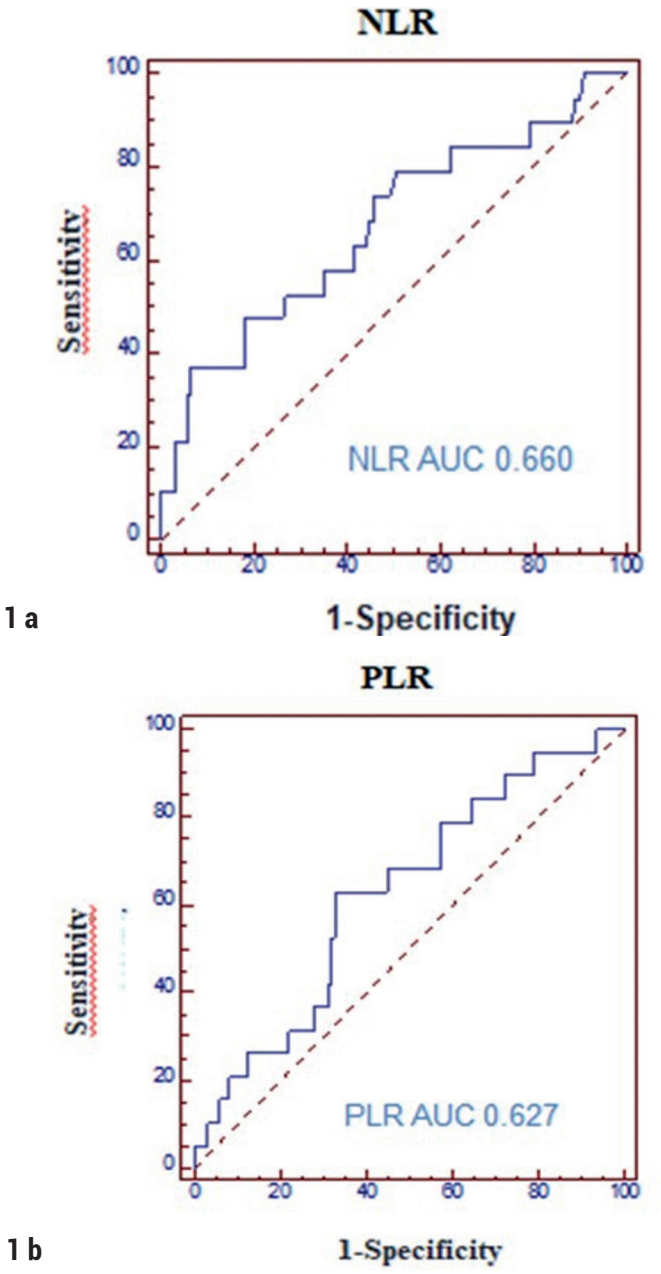

Figure 1a-b. Receiver operating characteristic (ROC) curves for optimal cut-off values to predict clinical complete response, for pretreatment NLR [2.64] and PLR [164]

Table 2. The correlation between treatment response and the patient's clinicopathological characteristics

Characteristics	n	Treatment response		p
		CR	Non-CR	
NLR*				
< 2.64	70	65 (53.3%)	5 (26.3%)	0.029
≥ 2.64	71	57 (46.7%)	14 (73.7%)	
PLR*				
<164	83	76 (62.3%)	7 (36.8%)	0.036
≥164	58	46 (37.7%)	12 (63.2%)	
FIGO stage				
IB-IIA	24	23 (18.9%)	1 (5.3%)	0.197
IIB-IVA	117	99 (81.1%)	18 (94.7)	
Tumor size				
≤4 cm	71	66 (54.1%)	5 (26.3%)	0.024
>4cm	70	56 (45.9%)	14 (73.7%)	
Grade				
Gr I-II	61	56 (86.2%)	5 (38.5%)	0.001
Gr III	17	9 (13.8%)	8 (61.5%)	
Hemoglobin level				
<11 g/dL	38	27 (22.1%)	11 (57.9%)	0.001
≥11g/dL	103	95 (77.9%)	8 (42.1%)	
Treatment				
Chemoradiotherapy	127	110 (90.2%)	17 (89.5%)	0.925
Radiotherapy	14	12 (9.8)	2 (10.5)	

* Cut-off values found by ROC analysis predicting treatment response

Relationship between NLR/PLR status and clinicopathological factors

There were 71 patients in a high NLR group (≥2.64) and 70 patients in a low NLR group (< 2.64). The higher NLR group was highly correlated with tumor size (p=0.016) and grade (p=0.036). Similarly, 71 patients were in the high PLR (≥149.5) group, and 70 patients were in the low PLR (<149.5) group. The higher PLR group was significantly associated with advanced stage (p=0.041), tumor size (p=0.024) and grade (p=0.023). The clinicopathological features of the patients and tumors by NLR and PLR subsets are summarized in Table 3.

Prognostic variables for OS and PFS

Forty-three (30.5%) patients died during the follow-up period. Twelve of these deaths are due to causes other than cancer. (Myocardial infarction in five patients, advanced old age in five patients, chronic obstructive pulmonary disease in one patient, lung cancer in one patient). The five-year progression-free survival, overall survival, and cancer-specific survival rates for the whole study group are 74%, 67%, and 78.1%, respectively. Since median survival values could not be reached in all groups, mean survival values are presented in Table 4. Univariate analysis showed that the presence of LN metastasis and the incomplete response was significantly associated with both poor OS and PFS (Table 5) Likewise, in multivariate analysis, the presence of LN metastasis and the incomplete response was independent poor prognostic factors for both OS and PFS (Table 6). No relationship was found between pretreatment NLR/PLR and survival.

However, there was a significant trend pre-treatment NLR (p=0.083) and PLR (p=0.054) values in univariate analysis for CSS; it could not be shown in multivariate analysis. Similarly, LN involvement and incomplete response were negative prognostic factors for CSS.

Table 3. The relationship between NLR / PLR status and clinicopathological characteristics (n=141)

Clinical characteristics	NLR*			PLR*		
	< 2.64 (n=70)	≥ 2.64 (n=71)	p	< 149.5 (n=70)	≥ 149.5 (n=71)	p
Age, n (%)						
≤57 years	36 (47.4)	40 (52.6)	0.687	36 (47.4)	40 (52.6)	0.321
>57 years	34 (52.3)	31 (47.7)		34 (52.3)	31 (47.7)	
FIGO stage, n (%)						
IB-IIA	18 (75)	6 (25)	0.080	17 (70.8)	7 (29.2)	0.041
IIB-IVA	52 (44.4)	65 (55.6)		53 (45.3)	64 (54.7)	
Tumor size, n (%)						
≤ 4 cm	42 (59.2)	29 (47)	0.016	40 (56.3)	31 (43.7)	0.024
> 4 cm	28 (46.7)	42 (53.3)		30 (42.9)	40 (57.1)	
Grade, n (%)						
Gr I-II	33 (54.1)	28 (45.9)	0.036	34 (55.7)	27 (44.3)	0.023
Gr III	5 (29.4)	12 (70.6)		4 (23.5)	13 (76.5)	
LN metastasis, n (%)						
No	35 (53)	31 (4)	0.113	34 (51.5)	32 (48.5)	0.938
Yes	35 (50)	40 (54.8)		36 (48)	39 (52)	
Local recurrence, n (%)						
No	61 (49.2)	63 (50.8)	0.307	61 (49.2)	63 (50.8)	0.535
Yes	9 (52.9)	8 (47.1)		9 (52.9)	8 (41.1)	
Distant mestastasis, n (%)						
No	57 (50)	57 (50)	0.316	57 (50)	57 (50)	0.260
Yes	13 (48.1)	14 (51.9)		13 (48.1)	14 (51.9)	

*Median NLR and PLR value

Table 4. The survival times in the whole group and subgroups

	PFS			OS			CSS		
	Mean (months)	Median (months)	p	Mean (months)	Median (months)	p	Mean (months)	Median (months)	p
Whole group	78.6 ± 3.2	---		77.4 ± 3.0	---		82.8 ± 2.9	---	
NLR									
<2.45	80.1 ± 4.4	---	0.665	80.2 ± 4.0	---	0.361	87.9±3.6	---	0.078
≥2.45	76.5 ± 4.7			74.2 ± 4.5			77.3±4.4		
PLR									
<149.5	86.7 ± 4.3	---	0.556	81.9 ± 3.8	---	0.154	88.4±3.5	---	0.049
≥149.5	76.4 ± 4.8			72.9 ± 4.6			76.8±4.5		
Treatment response									
nonCR	31.0 ± 6.5	14 ± 3.0	<0.001	24.3 ± 4.1	20 ± 4.1	<0.001	24.3 ± 4.1	20 ± 1.4	<0.001
CR	83.8 ± 3.1	---		84.4 ± 2.8			90.7 ± 2.5		

Table 5. Univariate and Multivariate analysis for overall survival

Variables	Univariate			Multivariate		
	HR	%95 CI	p	HR	%95 CI	p
Age ≤ 57 vs. >57	1.189	(0.653-2.162)	0.572			
FIGO stage <IIB vs. ≥ IIB	1.483	(0.625-3.515)	0.371			
Tumor size ≤ 4 cm vs.> 4cm	1.567	(0.858-2.862)	0.144			
LN metastasis No vs. Yes	2.467	(1.289-4.756)	0.006	2.353	(1.196-4.627)	0.013
NLR (median) <2.64 vs. ≥ 2.64	1.321	(0.725-2.406)	0.364			
PLR (median) <149.5 vs. ≥ 149.5	1.544	(0.845-2.824)	0.158			
Therapeutic response CR vs. non-CR	12.358	(6.111-24.989)	<0.001	12.601	(5.997-26.475)	<0.001

Table 6. Univariate and Multivariate analysis for progression free survival

Variables	Univariate			Multivariate		
	HR	%95 CI	p	HR	%95 CI	p
Age ≤ 57 vs. >57	0.881	(0.459-1.689)	0.702			
FIGO stage <IIB vs. ≥ IIB	0.804	(0.367-1.760)	0.586			
Tumor size ≤ 4 cm vs.> 4cm	1.268	(0.665-1.419)	0.470			
LN metastasis No vs. Yes	2.926	(1.413-6.060)	0.004	2.923	(1.405-6.079)	***0.004***
NLR (median) <2.64 vs. ≥ 2.64	1.152	(0.604-2.196)	0.667			
PLR (median) <149.5 vs. ≥ 149.5	1.212	(0.636-2.312)	0.559			
Therapeutic response CR vs. non-CR	6.047	(2.860-12.783)	***<0.001***	6.145	(2.853-13.237)	***<0.001***

DISCUSSION

The link between cancer and immunity is one of the most emphasized topics during the last decades. (4,5,22,23). Many studies have shown that systemic inflammation plays a major role in cancer development (23). Most cancers may arise from environmental factors and occur in chronic irritation and inflammation areas (5,18,24). Generally, the indicators of systemic inflammation in peripheral blood are neutrophilia, thrombocytosis and relative lymphopenia (5). These immune cells and inflammatory mediators are important components of the tumor microenvironment. Neutrophils release various inflammatory cytokines, causing damage to cellular DNA, inhibition of apoptosis, and promotion of angiogenesis. Platelets produce potent mitogens or adhesive glycoproteins that contribute to tumor progression and metastasis. Lymphocytes have an anti-tumorigenic effect and mediated antitumor immune responses (5,16). Therefore, different combinations of these inflammatory markers are being investigated as independent prognostic factors in determining the progression of several cancers. Recent findings suggest that higher NLR and PLR values are significantly associated with worse prognosis in many types of cancer, such as colorectal cancers, urinary tract cancers, non-small cell lung cancer and esophageal cancer (8,9,11,13).

In the present study, we observed that patients with high pretreatment NLR values had a more advanced stage, larger tumor size (> 4cm), and treatment response was worse. Similarly, the group with high PLR values included more advanced stage patients. However, a relationship with survival outcomes was not found. In most of the previous studies, increased NLR has been reported as an indicator of poor prognosis. Lee et al. have indicated that they could use NLR for estimating the mortality and the recurrence rates in patients with cervical cancer (14). In a meta-analysis, including 13 studies and 3729 patients, increased NLR was significantly associated with the bulky tumor, advanced disease, and lymph node involvement, and it was reported that these patients had a shorter survival. The author and colleagues have suggested that it can be used as a novel index to predict prognosis in patients with cervical cancer (18).

Similarly, pretreatment PLR values were used for improved risk stratification and survival prediction in various studies.

Zhang et al. established that preoperative NLR and PLR values were correlated with unfavorable histopathologic features in patients with cervical cancer who received primary radical surgery (15). Both Nakamura et al., as well as Chen et al., demonstrated that pretreatment PLR is an important prognostic factor for predicting the survival of cervical cancer (16,25).

On the other hand, in the study conducted by Nuchpramool et al., the link between preoperative PLR and NLR and oncologic outcomes in patients with early-stage (IA2-IB1) cervical cancer could not be demonstrated (19). Furthermore, Lee et al. reported that post-treatment hematological parameters rather than pre-treatment hematological parameters might be used as a prognostic indicator in patients with locally advanced cervical cancer treated with radical chemoradiotherapy (21). These contradictory results may be due to different patient characteristics and study designs and the small sample size. Perhaps the reason we could not find a significant relationship between survival outcomes and pre-treatment NLR/PLR in our study may be the relatively shorter follow-up period and the small patient group.

Also, there is not yet a validated threshold value for NLR and PLR. Different values (median value or cut-of value determined by ROC) are used in each study. Generally, the NLR and PLR values used in these studies vary between two to five and 150 to 300, respectively (6,7,11,18). These are non-specific inflammatory markers. At the same time, it may be confusing to evaluate the results in the presence of concomitant chronic illness, as they are systemic inflammation parameters.

However, we observed that the tumor response to treatment was better in patients with low NLR and PLR values. As mentioned in other studies, they may be useful as potential predictive and prognostic parameters in determining the best treatment strategy in patients with cervical cancer (17,19).

While interpreting the results of this study, it should be considered that this study has some limitations. This was a retrospective study, which may lead to a selection bias. Also, the number of patients is small, the follow-up period is relatively short, and it was a single-center experience. However, the strengths of this study include that our cohort consisted of only patients with a diagnosis of SCC who underwent definitive radiotherapy with or without chemotherapy.

CONCLUSION

In conclusion, we could not find a relationship between pre-treatment NLR and PLR values and survival outcomes in this study. However, low NLR and PLR significantly predicted the treatment response. Therefore, after determined the optimal cut-off value with further studies, the NLR and PLR can be used in the future as a simple and cost-effective prognostic factor to predict treatment response, especially in countries where cervical cancer is still prevalent.

Competing interests: The authors declare that they have no conflict of interest.

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Ethical approval: This study was approved by the local ethics committee of Istanbul University-Cerrahpasa (No: A-22).

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