

The Prognostic Value of Peripheral Inflammatory Cell Ratios in Patients with Cervical Cancer After Radiotherapy

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Research

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Abstract

Introduction: This study aimed to explore the values of the neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) as prognostic biomarkers in patients with cervical cancer.

Methods: In total, 172 cervical cancer patients treated with radiotherapy between January 2014 and December 2017 were retrospectively identified. We calculated the NLR and PLR and determined their cut-off points, known prognostic factors, and the association of these factors with overall survival (OS).

Results: The median follow-up period was 59 months (range 1–91 months, 95% confidence interval 53–63 months). The 3- and 5-year OS rates of patients who received postoperative adjuvant radiotherapy were 86.7% and 79.7%, respectively, while the 3- and 5-year OS rates of patients who received radical radiotherapy were 70.2% and 61.6%, respectively. Univariate analysis identified that OS was significantly correlated with tumor diameter, pelvic lymph node status, the NLR and PLR before radiotherapy, past diabetes, International Federation of Gynecology and Obstetrics (FIGO) stage, the purpose of radiotherapy, pathology type, and the OS rate (all $P < 0.05$). On multivariate analysis, the PLR before radiotherapy, past diabetes, FIGO stage, and pathology type were independently associated with OS (all $P < 0.05$).

Conclusions: The NLR and PLR before radiotherapy are correlated with the prognosis of cervical cancer. Furthermore, the PLR before radiotherapy is an independent risk factor related to OS.

Introduction

Cervical cancer is one of the most common malignant tumor that threatens women's health. The incidence and mortality rate of cervical cancer are ranked fourth among malignancies in women, and women in developing countries are particularly vulnerable.[1–2] Radiotherapy is one of the most important treatment methods for cervical cancer.[3] At present, the prognosis of patients with cervical cancer mainly depends on the International Federation of Gynecology and Obstetrics (FIGO) stage.[4–6] However, recent studies have found that chronic inflammation plays an important role in cancer cell proliferation, angiogenesis, and immunosuppression and is related to the prognosis of patients with cancer.[7] Pertinently, the ratios of peripheral blood neutrophils to lymphocytes (NLR) and of platelets to lymphocytes (PLR) are important prognostic indicators related to systemic inflammatory response.[8] A series of studies have shown that the NLR and PLR values can be used as biomarkers for predicting the prognosis of patients with malignant tumors, including non-small cell lung, liver, gastric, colorectal, and pancreatic cancers.[9–13] However, there are few studies concerning the prognostic significance of the NLR and PLR in cervical cancer. Therefore, this study evaluates the prognostic value of the NLR and PLR in peripheral blood before radiotherapy to provide a reference for clinical work.

Methods

Patients

A total of 172 patients with cervical cancer who presented to our department between January 2014 to December 2017 were included in this study. Their clinical characteristics are listed in Table 1. Approximately 38.95% of patients received radical radiotherapy, while 58.72% of patients received postoperative assistance radiotherapy. We reviewed records related to treatment, complete blood cell counts before radiotherapy, and death. The last follow-up was June 15, 2021. A total of 37 patients died during the follow-up period.

Table 1

Clinicopathological characteristics of 172 patients with cervical cancer who underwent radiotherapy

Characteristic	No. of patients (%)	Characteristic	No. of patients (%)
Age, years	47 (27.3)	Tumor size	87 (50.6)
≥60	125 (72.7)	≥4 cm	62 (36)
<60		<4 cm	23 (13.4)
		Unknown	
Pelvic lymph node	63 (36.6)	FIGO stage	124 (72.1)
Positive	98 (57)	I–II	31 (18.0)
Negative	11 (6.4)	III	12 (7.0)
Unknown		IV	5 (2.9)
		Unknown	
Past diabetes	9 (5.2)	Previous hypertension	32 (18.6)
Yes	160 (93.0)	Yes	137 (79.7)
No	3 (1.7)	No	3 (1.7)
Unknown		Unknown	
The purpose of radiotherapy	67 (38.95)	Pathological type	153 (89.0)
Radical	101 (58.72)	Squamous cell carcinoma	10 (5.8)
Postoperative assistance	4 (2.33)	Adenocarcinoma	8 (4.7)
Unknown		Other	1 (0.6)
		Unknown	
NLR before radiotherapy	29 (16.9)	PLR before radiotherapy	37 (21.5)
High NLR (>4.33)	98 (57)	High PLR (≥200.47)	90 (52.3)
Low NLR (<4.33)		Low PLR (<200.47)	
NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FIGO, International Federation of Gynecology and Obstetrics			

NLR and PLR

Peripheral venous blood was collected from patients before radiotherapy. The NLR and PLR were calculated as follows: NLR = neutrophil count / lymphocyte count and PLR = platelet count / lymphocyte count. Receiver operating characteristic (ROC) curves were used to determine the optimal critical value of

the NLR and PLR before radiotherapy. Patients were divided into a low NLR group, high NLR group, low PLR group, and high PLR group for analysis.

Statistical analyses

The endpoint of this study was overall survival (OS). The independent sample t-test or X^2 test was used to test the difference between continuous and categorical variables. The best cut-off values for the NLR and PLR were evaluated using ROC survival curve analysis. To investigate the relationships between the NLR or PLR and prognosis of cervical cancer, univariate and multivariate Cox regression models were used. Significance was defined as $P < 0.05$. Statistical analyses were performed with SPSS 26.0 (IBM, Chicago, IL, USA).

Results

Patient characteristics

In total, 172 patients with cervical cancer who received radiotherapy were included in this study, of whom 127 had NLR and PLR values evaluated before radiotherapy. The median age of the entire group at diagnosis was 49 years (range 29–88 years). Patients' characteristics are shown in Table 1.

Overall survival

The median survival time of all patients was 59 months (95% CI: 53–63 months). At the end of follow-up, 32 patients were lost and 37 died. The 3- and 5-year OS rates of patients who received postoperative adjuvant radiotherapy were 86.7% and 79.7%, respectively. The 3- and 5-year OS rates of patients who received radical radiotherapy were 70.2% and 61.6%, respectively (Fig. 1).

Univariate and multivariate analyses

Tumor diameter, pelvic lymph node status, the NLR before radiotherapy, the PLR before radiotherapy, past diabetes, FIGO stage, the purpose of radiotherapy, and pathology type were all significantly correlated with the OS rate of patients ($P < 0.05$). These parameters were also included in the multivariate analysis, which showed that the PLR before radiotherapy, past diabetes, FIGO stage, and pathology type were the factors that significantly affected OS rate ($P < 0.05$), as shown in Table 2.

Table 2
Univariate and multivariate analysis of the impact of clinical factors on overall survival

Clinical parameter	Univariate analysis		COX multivariate analysis		
	χ^2	P	HR	95% CI	P
Tumor size	4.878	0.027			
Pelvic lymph node metastasis	15.347	0.000			
age	3.369	0.066			
Pelvic lymph node metastasis	11.997	0.001			
PLR before radiotherapy	10.106	0.001	0.079	0.012–0.534	0.009
Previous hypertension	3.504	0.061			
Past diabetes	5.338	0.021	22.934	2.276–231.048	0.008
FIGO stage	39.014	0.000	2.837	1.325–6.077	0.007
The purpose of radiotherapy	6.258	0.012			
Pathological type	7.777	0.020	3.459	1.590–7.525	0.002

FIGO, International Federation of Gynecology and Obstetrics; HR, Hazard ratio, CI, confidence interval; PLR, platelet to lymphocyte ratio

Determination of NLR and PLR cut-off values

The range of the NLR was 0.55–19.80. The ROC curve of the NLR for cervical cancer prognosis was plotted according to the patient's NLR value and survival time. The area under curve (AUC) was 0.649, and the 95% confidence interval (CI) was 0.528–0.770 (Fig. 2A). The boundary value of the NLR for predicting tumor prognosis was 4.33. The sensitivity was 48.1%, and the specificity was 84.0%. The range of the PLR was 4.71–460. The ROC curve of the PLR for cervical cancer prognosis was similarly plotted according to the PLR value and survival time. The AUC was 0.705, and the 95% CI was 0.600–0.811 (Fig. 2B). The boundary value of the PLR for predicting tumor prognosis was 200.47. The sensitivity was 59.3%, and the specificity was 79.0%.

Correlation between the NLR or PLR before radiotherapy and prognosis of patients

All patients were divided into two groups according to the critical value of NLR: patients with NLR >4.33 were included in the high NLR group (29 cases) and patients with NLR <4.33 in the low NLR group (98 cases). The 3-year OS rates of the high and low NLR groups were 60.7% and 86.3%, respectively. The 5-year OS rates of the high and low NLR groups were 51.7% and 83.3%, respectively (χ^2 value 11.997, $P=0.001$). The survival curve is shown in Fig. 3A. According to the critical value of the PLR, all patients

were divided into two groups: a high PLR group with PLR >200.47 (37 cases) and a low PLR group with PLR <200.47 (90 cases). The 3-year OS rates of the high and low PLR groups were 61.1% and 89.0%, respectively. The 5-year OS rates of the high and low PLR groups were 57.9% and 83.8%, respectively (χ^2 value 10.106, $P=0.001$). The survival curve is shown in Fig. 3B.

Correlation between peripheral blood NLR and FIGO stage

The peripheral blood NLR values of the 127 patients with cervical cancer were included in a box diagram according to the FIGO stage (Fig. 4). Phases I–II and III–IV were divided into early and late stages, respectively. The average NLR was 2.859 in the early stage (95% CI 2.386–3.333) and 4.761 in the late stage (95% CI 3.540–5.981). There was a significant difference between the two phases ($P=0.005$). The NLR value of peripheral blood was higher when the FIGO stage was more advanced.

Discussion

FIGO stage typifies tumor progression according to the results of clinical and imaging examinations, and this is an important means for prognosis prediction of patients with cervical cancer.[14–15] Recent studies have shown that inflammation plays an important role in the occurrence and development of cervical cancer. Hematological markers related to inflammation in complete blood cell count may help in the evaluation of the prognosis of patients.[16]

Inflammatory response is caused by inflammatory cells and a series of inflammatory mediators. Chronic inflammation is an important cause of immunosuppression in the tumor microenvironment. Inflammatory cells and cytokines or chemokines are involved in almost every step of tumor development. [16] Inflammatory response caused by tumors can lead to hematological changes, including relative neutrophilia, thrombocytosis, and lymphocytopenia. Therefore, patients with high NLR and PLR usually have severe systemic inflammatory responses, poor antitumor activities, and strong tumor invasiveness. Moreover, assessment of the NLR and PLR has the advantages of low cost, simple operation, and high repeatability.[8] Several studies have shown that the NLR and PLR can be used to predict the prognosis of patients with malignant tumors.[10–13] Such indicators have also been proven to be clinically relevant for cervical cancer.[9] Lu et al. [17] analyzed the prognosis of 120 patients diagnosed with cervical cancer and found that the systemic immune inflammation index influences patient survival and that the NLR and PLR are important factors that affect the OS rate. Zhang et al. [18] also found the NLR was an independent prognostic indicator of progression-free survival(PFS) of patients with cervical cancer. Consistent with previous studies, this study confirmed that such indicators can be used to predict the prognosis of patients with cervical cancer. The results of this study showed that the survival times of the high NLR and PLR groups were significantly lower than those of the low NLR and PLR groups. The 3-year OS rates of the high and low NLR groups were 60.7% and 86.3%, respectively. The 5-year OS rates of the high and low NLR groups were 51.7% and 83.3%, respectively (χ^2 value 11.997, $P=0.001$). The 3-year OS rates of the high and low PLR groups were 61.1% and 89.0%, respectively. The 5-year OS rates of the high and low PLR groups were 57.9% and 83.8%, respectively (χ^2 value 10.106, $P=0.001$). Univariate analysis

showed that both the NLR and PLR before radiotherapy were factors that were significantly associated with the prognosis of patients with cervical cancer. However, multivariate analysis showed that the NLR before radiotherapy was not an independent risk factor for the prognosis of patients with cervical cancer. The reason may be that the NLR value is significantly affected by the tumor stage (Fig. 4). The later the FIGO stage the more serious the systemic inflammatory response and the higher the NLR in peripheral blood.

This paper has the following limitations. First, this was a retrospective study. Some information were missing or inaccurate, which may have introduced bias. Some patients were rechecked in different places or other hospitals, and the information could not be collected completely and accurately. This resulted in a small sample size. Therefore, the results need to be interpreted carefully. Even so, this study still reflects the possibility that the NLR and PLR can be used as biological indicators to predict the prognosis of patients with cervical cancer.

Conclusions

The PLR, past diabetes, FIGO stage, and pathology type before radiotherapy were independent risk factors that influenced OS. Therefore, the NLR and PLR are important indicators that predict the prognosis of patients with cervical cancer.

Declarations

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DISCLOSURE STATEMENT

There are no competing financial interests.

CONSENT FOR PUBLICATION

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ETHICAL APPROVAL STATEMENT

Data are collected from The Second Affiliated Hospital of Soochow University and are devoid of any personal identifiable information.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHORS' CONTRIBUTIONS

Ruizhe Xu, Haiyan Lu, and Qi Guo conceived the study, contributed to the study design, assisted with analysis, and wrote the first draft of the manuscript. Jianjun Qian, Qihong Fan, and Peifeng Zhao contributed to data preparation and analysis. Ye Tian contributed to the interpretation of the results and finalization of the report and reviewed and approved of the manuscript before submission. All authors agreed with the decision to submit.

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Figures

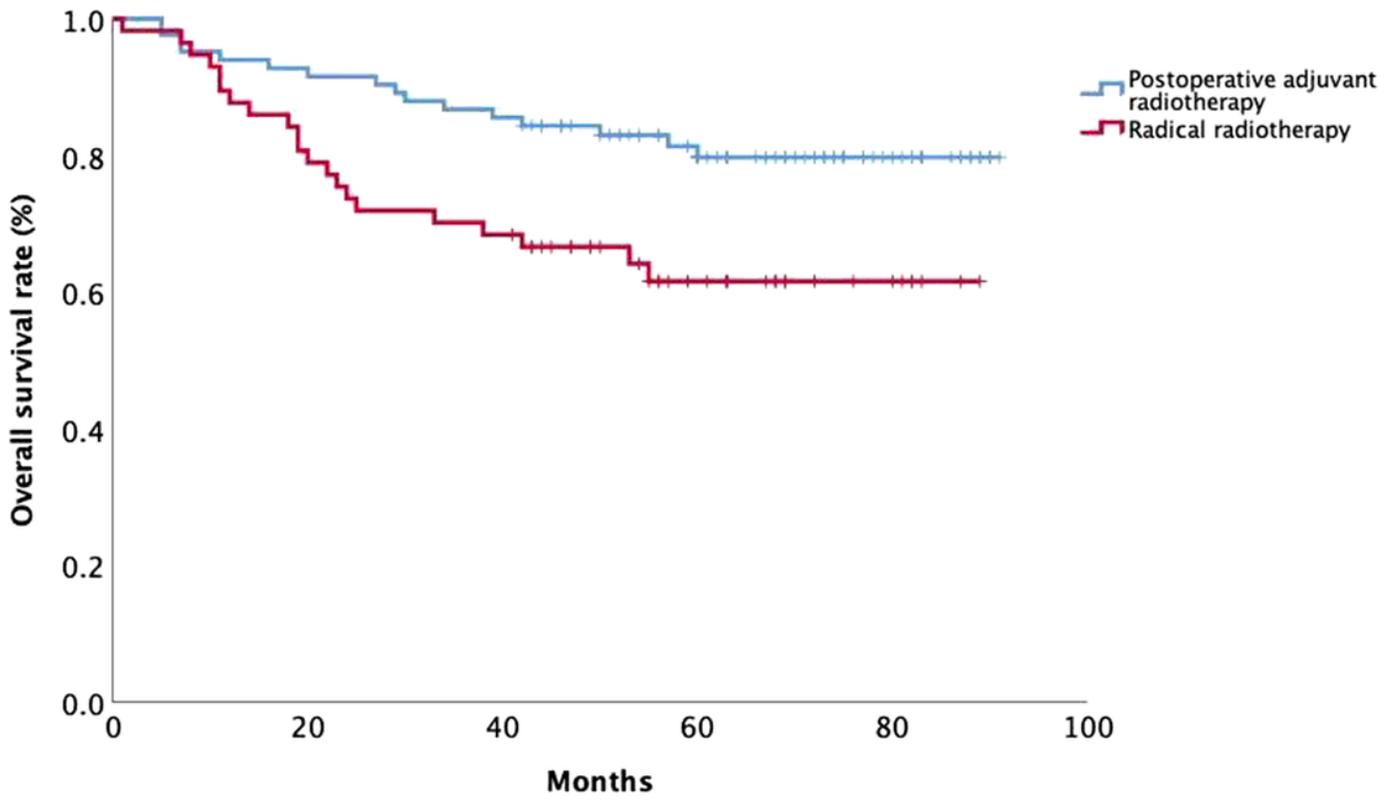


Figure 1

Overall survival curves of 172 patients with cervical cancer

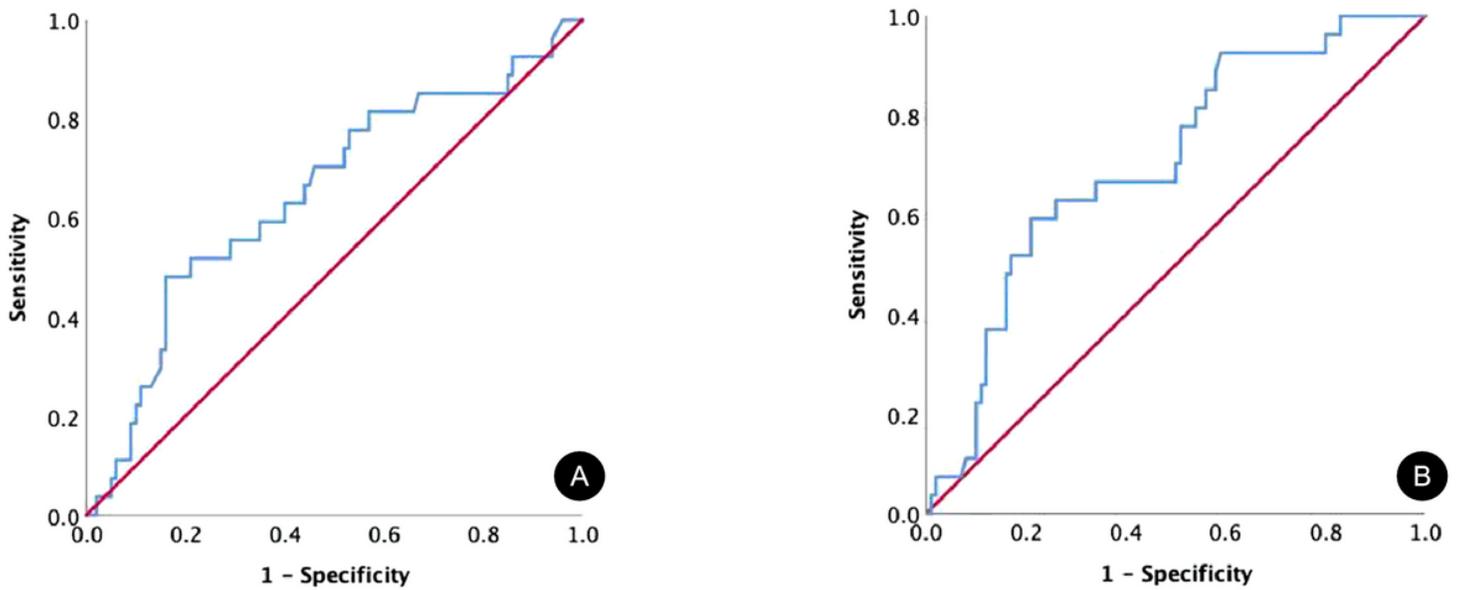


Figure 2

ROC curves for the NLR (A) and PLR (B) before radiotherapy in 127 patients with cervical cancer

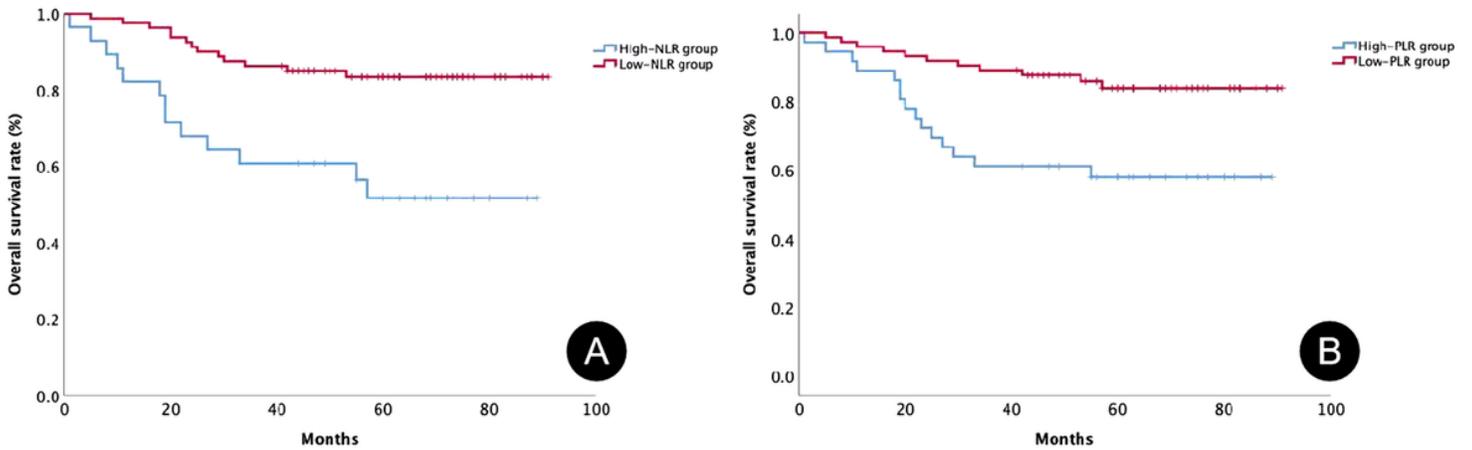


Figure 3

Survival curves of 127 patients with cervical cancer grouped according to the NLR and PLR before radiotherapy. Survival curves comparing patients in the high and low NLR groups (A) and the high and low PLR groups (B) are shown. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio

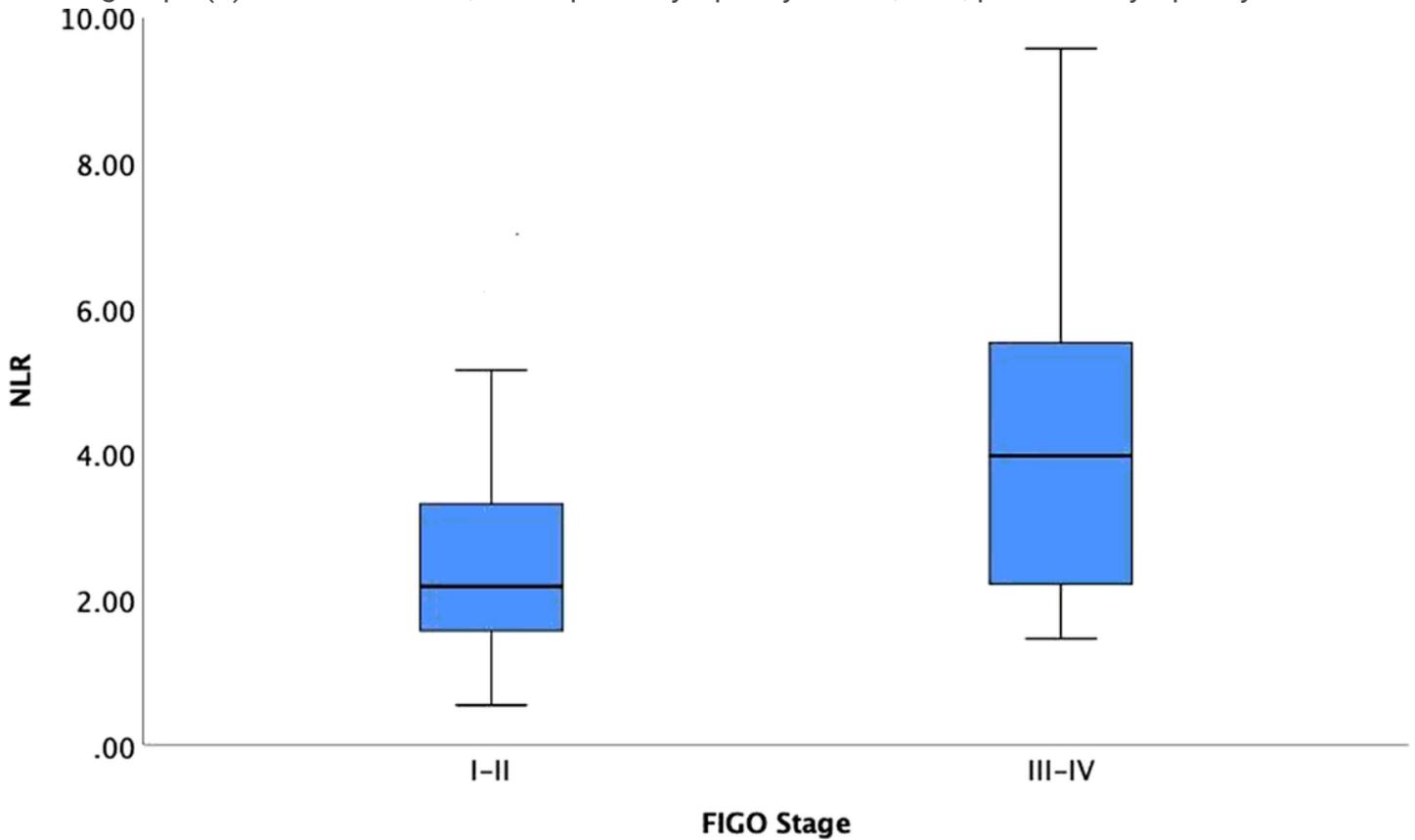


Figure 4

Box diagrams of the peripheral blood NLR and FIGO stages in 127 patients with cervical cancer. NLR, neutrophil to lymphocyte ratio; FIGO, International Federation of Gynecology and Obstetrics