

# Can preoperative neutrophil to lymphocyte and platelet to lymphocyte ratios predict cervical stromal involvement in endometrioid endometrial adenocarcinoma?

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## Summary

**Purpose:** To evaluate the possible relationships between preoperative inflammatory markers [neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)] and cervical stromal involvement in endometrioid endometrial adenocarcinoma. **Materials and Methods:** Charts and pathology results of 639 women who were operated on for endometrioid endometrial adenocarcinoma between 2000 and 2013 in the present clinic were retrospectively reviewed. Demographic, laboratory, and clinical parameters were evaluated. **Results:** 118 women (18.4%) had cervical stromal involvement. Lymph node positivity was significantly more frequent in the cervical stromal involvement group ( $p < 0.001$ ). A threshold value of 2.41 for NLR had a sensitivity of 62.7%, specificity of 60.1%, PPV of 61.1%, and NPV of 61.8% for the presence of cervical stromal involvement. In multivariate analysis, increased NLR had a significant predictive value for cervical stromal involvement ( $p = 0.006$ , OR = 2.03), although PLR remained non-significant ( $p = 0.77$ , OR = 1.08). **Conclusions:** The preoperative NLR assessment is a significant predictor for cervical stromal involvement in endometrioid endometrial adenocarcinoma.

**Key words:** Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio; Cervical stromal involvement; Endometrioid adenocarcinoma.

## Introduction

Endometrial adenocarcinoma is the most common gynecological malignancy [1], which is usually confined to the uterus at the time of diagnosis. The surgical staging of FIGO revised in 2009 determines the treatment methods and predicts the prognosis.

Myometrial invasion, cervical stromal infiltration, lymph node metastasis, and/or distant metastasis are important criteria for staging [2]. Among these criteria, “lymph node metastasis” is one of the most important factors affecting survival and prognosis, and it is closely associated with depth of myometrial invasion, presence of cervical stromal invasion, as well as histopathologic subtype and grade [1]. The rate of lymphatic metastasis may increase up to 35–40% in high risk patients such as cervical invasion.

Lymph node dissection (LND) is not routinely performed in every patient. Moreover, there is no common agreement on the limits of LND, since an extensive LND, including para-aortic lymph nodes, may cause short- or long-term complications.

The anatomic boundaries of the operation depend on the extension of disease. Preoperative identification of high risk patients with cervical stromal invasion is important to avoid excessive or insufficient procedures. Various techniques such as transvaginal ultrasonography, diagnostic

hysteroscopy, magnetic resonance, and endocervical curettage can be used for detecting cervical stromal invasion; however it is still controversial which of these is the best predictive marker for cervical stromal invasion. Invasive methods such as endocervical curettage and hysteroscopy constitute risks due to anesthesia; whereas non-invasive methods such as transvaginal sonographic examination lack accuracy. Magnetic resonance imaging is expensive and constitutes risk of allergic reactions against contrast substances.

We need a non-invasive, accurate, inexpensive, and easily performed method to determine which patients are at high risk for cervical invasion and may therefore benefit from LND. Considering the close association between cancer and inflammation, systemic inflammatory markers have been investigated for this purpose. Tumor cells suppress the immune system and cause inflammation, which, in turn, may further accelerate aggressive growth of the tumor and produce inflammation. The neutrophil to lymphocyte ratio (NLR) was shown to increase due to a mild decrease in lymphocyte counts [3, 4] and increase in neutrophil counts, possibly by increased secretion of granulocyte colony stimulating factor (G-CSF) [5, 6], interleukin 6 (IL-6), and/or tumor necrosis factor alpha (TNF- $\alpha$ ) from the tumor cells [7]. NLR has been shown to have significant prognostic

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**Table 1.** — Comparison of the clinicopathological features and laboratory values of the patients with and without cervical stromal involvement.

	Cervical stromal involvement Negative (n=521)	Cervical stromal involvement Positive (n=118)	p
Age, (years; mean±SD)	58.4±10.2	60.1±11.2	0.130
FIGO Stage, n (%)			
I	499 (95.8%)	0 (0.0%)	< 0.001
II-IV	22 (4.2%)	118 (100.0%)	
Lymph node			
Negative	367 (70.4%)	28 (23.7%)	< 0.001
Positive	154 (29.6%)	90 (76.3%)	
Neutrophil (cells/µL)	5.26±2.54	6.18±2.65	< 0.001
Lymphocyte (cells/µL)	2.34±1.26	2.17±1.35	0.204
Platelet (cells/µL)	266.13±67.17	278.81±83.48	0.078
NLR	2.73±2.23	3.59±2.75	< 0.001
PLR	135.36±65.09	164.82±107.13	0.005

p < 0.05 is significant; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SD: standard deviation.

value in resected colorectal cancer [8]. In addition to NLR, platelets have also been investigated, and platelet to lymphocyte ratio (PLR) was reported to be a significant prognostic factor in resected pancreatic cancer [9].

The objective of this study was to investigate the potential predictive role of neutrophil count, lymphocyte count, platelet count, NLR, and PLR for cervical stromal invasion in order to define endometrial cancer patients with a high risk for lymphatic spread.

## Materials and Methods

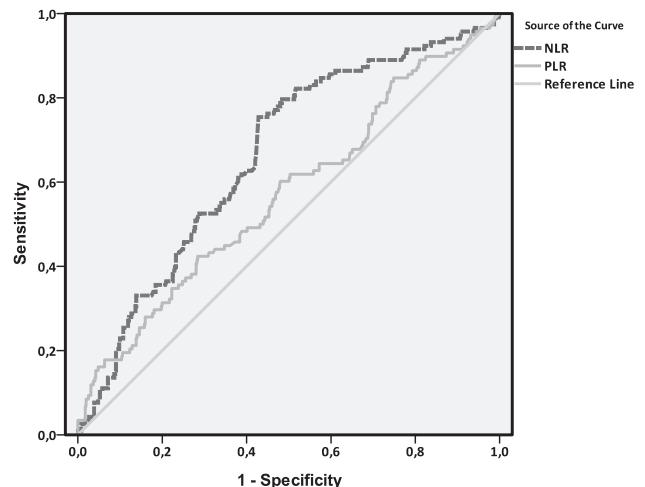
The patient records of 639 consecutive women who were operated on for endometrioid endometrial adenocarcinoma between January 2000 and June 2013 in the present clinic were evaluated retrospectively. This study was approved by the institutional review board of Cerrahpasa Medical Faculty (33961/03.12.2013).

Inclusion criteria were patients with histologically confirmed endometrioid endometrial adenocarcinoma and comprehensive surgical staging including total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and lymphadenectomy. Exclusion criteria were uterine sarcomas and other subtypes of endometrial cancer, prior chemotherapy or pelvic radiation therapy, concomitant malignancies, hematological diseases, and inflammatory diseases. Blood cell counts measured more than one week prior to surgery were also excluded.

Age, preoperative neutrophil, platelet and lymphocyte counts, postoperative stage, cervical stromal involvement, and lymph node status were evaluated. The stage of the cancer was determined (or re-evaluated if necessary) according to the 2009 FIGO endometrial cancer staging system.

In case of presence of more than one blood sample, blood samples measured closest to the date of surgery were used. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was defined as the absolute platelet count divided by the absolute lymphocyte count.

Demographic characteristics and risk factors of tumor progression were analysed according to cervical stromal involvement



**Figure 1.** — Receiver-operating curve for the relationship between NLR, PLR, and cervical involvement. Area under curve for NLR is 0.663 (95% CI 0.610–0.716) and for PLR is 0.570 (95% CI 0.511–0.630).

using Student's t-test for continuous variables and Chi-square test for categorical variables. Continuous variables were expressed as the mean ± standard deviation. Univariate and multivariate analysis were used to assess relationships between the various factors and cervical stromal involvement. Odds ratios (OR) were calculated by univariate or multivariate analysis using the logistic regression test. Sensitivity and specificity for different NLR and PLR cutoffs were calculated with receiver-operating curves. Receiver-operating curve analysis was plotted to investigate optimal cut-off values that maximized sensitivity and specificity. Statistical analyses were performed using Statistical Package for the Social Sciences Version 17.0 software. A p-value of < 0.05 was considered to indicate significance.

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Results

The mean age of 639 patients was 58.4 ± 7.78 years. The median time of blood count measurement was two days prior to surgery (range 1–6 days). According to FIGO 2009 criteria, 499 women (78%) had Stage I, 77 women (12%) had Stage II, 39 women (6.2%) had Stage III, and 24 women (3.8%) had Stage IV disease.

Histopathological evaluation showed that a total of 18.4% (118/639) of the women had cervical stromal involvement. Lymph node positivity was significantly higher in women with cervical stromal involvement compared to women without cervical stromal involvement (76.3% vs. 29.6%, p < 0.001). In logistic regression analysis, positive lymph node status was associated with cervical stromal involvement (p < 0.001, OR = 7.08, 95% CI 4.43–11.31).

Comparison of the clinicopathological features and lab-

**Table 2. — Uni- and multi-variate analysis of NLR, PLR, and lymph node status in association with cervical stromal involvement.**

Variables	OR	Univariate			Multivariate		
		95% CI	p	OR	95% CI	p	
≥ CO versus < CO	NLR	2.53	1.67–3.82	< 0.001	2.03	1.28–3.34	0.006
	PLR	1.76	1.16–2.66	0.005	1.08	0.65–1.80	0.77
Lymph node positive vs negative		7.66	4.81–12.18	< 0.001	7.08	4.43–11.31	< 0.001

*p* < 0.05 is significant. Cut-off value was 2.41 for NLR and 154.1 for PLR. CO: cut-off value; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

**Table 3. — Comparison of PLR and NLR combination values according to stromal and lymph node involvement status.**

		Double negative (n=315)		Single positive (n=168)		Double positive (n=155)		<i>p</i>
		n	%	n	%	n	%	
Stromal involvement	Absent (n=542)	284	52.4%	140	25.8%	118	21.8%	< 0.001
	Present (n=96)	31	32.3%	28	29.2%	37	38.5%	
Lymph node involvement	Absent (n=393)	213	53.9%	105	26.7%	76	19.3%	0.001
	Present (n=244)	102	41.8%	63	25.8%	79	32.4%	

oratory values of the patients with and without cervical stromal involvement are shown in Table 1. The mean neutrophil count, NLR, and PLR were significantly increased in women with cervical stromal involvement ( $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.005$ , respectively). No significant difference was found in the mean lymphocyte and platelet counts between the two groups.

The ROC curves of NLR and PLR for prediction of cervical stromal involvement are shown in Figure 1. A threshold value of 2.41 for NLR had a sensitivity of 62.7%, specificity of 60.1%, PPV of 61.1%, and NPV of 61.8% for the presence of cervical stromal involvement. A threshold value of 154.1 for PLR had a sensitivity of 40.7%, specificity of 72.1%, PPV of 59.4%, and NPV of 54.9% for the presence of cervical stromal involvement. In multivariate analysis, increased NLR had a significant predictive value for cervical stromal involvement ( $p = 0.006$ , OR = 2.03, 95% Confidence Interval (CI): 1.28–3.34), although PLR remained non-significant ( $p = 0.77$ , OR = 1.08, 95% CI: 0.65–1.8) (Table 2).

In patients with no stromal involvement (n=542), NLR and PLR were both negative in 52.4%, either NLR or PLR was positive in 25.8%, and NLR and PLR were both positive in only 21.8% of the women (ANOVA test,  $p < 0.001$ ). In patients with no lymph node involvement (n=393), NLR and PLR were both negative in 53.9%, either NLR or PLR was positive in 26.8%, and NLR and PLR were both positive in only 19.3% of the women (ANOVA test,  $p < 0.001$ ) (Table 3).

## Discussion

The current study evaluates the relationship between pre-operative inflammatory markers [(NLR) and (PLR)] and cervical stromal involvement in endometrioid endometrial adenocarcinoma with the largest population in the literature.

The present results showed that preoperative NLR represents a significant predictive factor of cervical stromal involvement in patients with endometrioid endometrial adenocarcinoma.

Endometrial adenocarcinoma is the most common gynecologic malignancy and has a worldwide increasing incidence. Although most endometrial cancers are limited to the uterus [3], 10% to 20% of women suffer from cervical invasion [10]. Morrow *et al.* [11, 12] showed that cervical stromal involvement was associated with an increase in the rate of lymphatic metastasis by 35–40%. In the present study, rates of lymph node metastasis were 29.6% vs. 76.3% in cervical stromal invasion negative and positive groups, respectively; this suggests a close association between lymphatic metastasis and cervical stromal involvement.

Tavares-Murta *et al.* [13] suggested that leukocyte alteration frequency is higher in advanced stage cervical cancer compared to preinvasive cervical cancer in patients with LVI and stromal involvement compared to patients without LVI and stromal involvement. Moreover, neutrophilia was suggested to be an indicator of cancer invasiveness. In the present study, neutrophil counts were higher in patients who had cervical stromal involvement compared to no cervical stromal involvement.

PLR and NLR are inflammatory markers showing “non-specific response to cancer-related inflammation” and significant predictors of prognosis in patients with small cell carcinoma of esophagus [14] and advanced gastric cancer [15]. Bhatti *et al.* [16] detected that NLR is a significant marker of prognosis in resected pancreatic ductal adenocarcinoma. Contrary to the well-defined associations between inflammatory processes and gastrointestinal cancers such as colorectal, hepatic, esophageal, pancreatic, and gastric cancer [17–20]; there are only a few studies in the literature about inflammation and en-

endometrial cancer. In the study of Dossus *et al.* [21], elevated C-reactive proteins, IL6, and IL1Ra were found to be associated with an increased risk of endometrial cancer. In the study of Suh *et al.* [22], NLR and PLR were found to be related with lymph node metastasis in endometrial cancer [22]. Moreover, Wang *et al.* [23] found that NLR and PLR can help identify the risk of cervical stromal involvement in endometrial cancer in 318 patients.

In the present study, a threshold value of 2.41 for NLR had a sensitivity of 62.7%, specificity of 60.1%, PPV of 61.1%, and NPV of 61.8% for the presence of cervical stromal involvement. In multivariate analysis, increased NLR had a significant predictive value for cervical stromal involvement although PLR remained non-significant. The latter finding differs from the findings of Wang *et al.* [23]. The present authors suggest that only NLR qualifies to be an independent predictive marker of cervical stromal involvement after other infections or inflammatory states were excluded. Neutrophilia, compared to thrombocytosis, is more sensitive in reflecting the response and better indicates the inflammatory activity of the tumor.

Regarding these relatively low sensitivity and specificity values, NLR and/or PLR cannot be used alone for preoperative evaluation of cervical stromal invasion. However, a combination of these markers with other additional diagnostic methods may provide a triple or quadruple panel with a better predictive value with low costs since neutrophil, lymphocyte, and platelet counts are already routinely performed preoperatively in endometrial cancer cases.

The retrospective nature, lack of comparison with other methods such as endocervical curettage, MRI and H/S and other markers such as C-reactive protein and CA125, are among the limitations of the present study.

Further studies may help clarify the potential predictive role of preoperative NLR and PLR on clinical outcomes as well as the pathogenetic relationship between NLR and PLR and endometrial cancer.

## Conclusion

In conclusion, preoperative NLR represents a significant predictive factor of cervical stromal involvement in patients with surgically treated endometrioid endometrial adenocarcinoma. NLR evaluation may help to select the patients who should be tested for cervical stromal involvement. The sensitivity and specificity values of NLR are not yet adequate alone to decide for LND, and further studies are needed to evaluate the potential role of NLR in combination with other methods in prediction of LND, as well as type of hysterectomy.

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