

# Clinical biomarkers to predict preoperative lymph node metastasis in endometrial cancer

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## Ethics Committee Approval

Canakkale Onsekiz Mart University Clinical Research Ethics Committee (date: 10.02.2021, number: 02-22)

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

## Conflict of Interest

No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** Although the evaluation of preoperative lymph node metastasis is very important for the appropriate approach of the surgeon, it cannot be determined precisely. We aimed to investigate preoperative systemic inflammatory markers and the value of CA 125 in the prediction of lymph node metastasis (LNM) in epithelial endometrial carcinoma.

**Methods:** In our retrospective cohort study, 327 patients were pathologically diagnosed with epithelial endometrial carcinoma and underwent surgical staging including lymphadenectomy. We investigated preoperative serum CA 125, neutrophil/lymphocyte (NLR) and thrombocyte/lymphocyte (PLR) values and their relationship with LNM. ROC analysis was performed to these variables for prediction of LNM.

**Results:** There was a significant difference between histological type ( $P=0.021$ ), myometrial invasion ( $P<0.001$ ), lymphovascular space invasion (LVSI) ( $P<0.001$ ), and peritoneal cytology ( $P=0.001$ ) in those with and without LNM. Among the NLR, PLR and CA 125 values, only CA 125 was significantly higher in the LN positive group compared to the LN negative group ( $P=0.516$ ,  $P=0.408$  and  $P=0.001$ , respectively). The optimal CA 125 cut-off value in the preoperative diagnosis of LNM was  $\geq 39.0$  U/ml. The diagnostic sensitivity, specificity, PPV, NPV, and accuracy values of CA 125 were 77%, 82%, 48%, 94%, and 81%, respectively.

**Conclusion:** While preoperative CA 125 value was a significant predictor for LNM in epithelial endometrial cancers, we did not detect this relationship in NLR, PLR and systemic inflammatory markers.

**Keywords:** Endometrial cancer, Systemic inflammatory markers, Serum CA 125 level, Lymph node metastasis

## Introduction

Endometrial cancer (EC) is the most common gynecological malignancy and the 6<sup>th</sup> most common cause of all female cancers in developed countries. Obesity and the increasing frequency of the elderly population gradually increase the prevalence of this cancer [1].

Endometrial cancer is often diagnosed at an early stage and has a good prognosis. However, lymph node metastasis (LNM) is observed in 10% of patients in the clinical early stage [2].

With prospective studies, it has been shown that lymph node dissection does not benefit overall and recurrence-free survival in patients with clinical early-stage endometrial cancer and is furthermore associated with surgical morbidity (prolonged operation time, deep vein thrombosis, leg edema) at a frequency of 15-20% [2-5]. On the other hand, pelvic or paraaortic LNM is associated with a poor prognosis, and detection of LNM is important for appropriate adjuvant therapy [6]. Although most gynecological oncologists do not consider pelvic/paraaortic lymphadenectomy as a standard procedure in patients with a low risk of lymph node involvement, it is also a fact that in most presumed early-stage patients, the surgeon is caught between overtreatment or under treatment as a therapeutic challenge [7]. Preoperative assessment of the risk of lymph node metastasis by the clinician would therefore be an appropriate approach.

Although tumor grade, histology and myometrial depth are considered the strong determinant criteria of LNM [8-10], there is no biochemical marker or radiological sign which can precisely predict lymph node metastasis preoperatively. In histological grade, a result discrepancy of up to 30% can be observed in preoperative and permanent pathology reports [11]. Additionally, access to magnetic resonance (MRI), computerized tomography (CT), and positron emission tomography (PET/CT) from radiological imaging are difficult and costly, and their value in lymph node involvement is limited [12]. The systemic inflammatory response is stimulated by the proliferation, metastasis, and angiogenesis of cancer cells [13]. Inflammation and immune response play a significant role in the progression of cancer. While neutrophil, thrombocyte and CRP levels increase due to the immune response, the lymphocyte count decreases. Interleukin-6 has been shown to cause thrombocytosis by increasing hepatic thrombopoietin synthesis [14]. Many inflammatory response markers, such as CRP, neutrophil/lymphocyte ratio (NLR), thrombocyte/lymphocyte ratio (PLR), have been investigated as prognostic factors in different cancer types [15, 16].

We aimed to investigate the values of NLR and PLR, which are the routinely examined hemocytometric measurements in preoperative evaluation, and CA125, which we commonly use in the diagnosis and follow-up of gynecological malignancies, in the prediction of lymph node metastasis in endometrial cancer.

## Materials and methods

Our retrospective study reviewed the medical records of 327 patients who were diagnosed with endometrial adenocarcinoma between February 2010 and February 2019 and underwent surgical staging with pelvic lymph node dissection

(PLND) ± paraaortic lymph node dissection (PALND). Our study was approved by the clinical research ethics committee of Çanakkale Onsekiz Mart University and conducted in accordance with the Helsinki Declaration principles (10.02.2021 approval date and 02-22 number).

Preoperative complete blood count and CA 125 measurement were performed one week before at the latest. NLR was defined as the ratio of absolute neutrophil count to absolute lymphocyte count, whereas PLR was defined as the ratio of absolute thrombocyte number to absolute lymphocyte count. Quantitative measurement of CA125 concentration was conducted with the Abbott Architect 2000i Analyzer (Abbott Diagnostics, Abbott Park, IL).

Patients who were not diagnosed with epithelial endometrial carcinoma, who did not undergo pelvic lymphadenectomy, those who had any acute or chronic inflammatory disease, received preoperative chemotherapy or had other synchronous malignancies were excluded from the study.

### Surgical procedure

First, peritoneal cytology samples were obtained with median laparotomy or laparoscopy, and all intra-abdominal organs and peritoneal surfaces were examined. Biopsies were taken from suspicious areas, and total hysterectomy and retroperitoneal lymphadenectomy were then performed. For pelvic lymphadenectomy, the external iliac artery and vein were mobilized; the obturator nerve was then protected, and the external iliac vessels, internal iliac, and lymphatic tissue were excised from the obturator fossa. In paraaortic lymphadenectomy, precaval, aortocaval and paraaortic lymphatic tissues were dissected up to the level of the left renal vein. The endometrial cancer 2009 FIGO staging system was used in surgical staging.

### Statistical analysis

Categorical variables were expressed as frequencies and percentages (%) whereas continuous variables were expressed as mean (SD), and median and interquartile range (IQR) due to non-normality. The Shapiro–Wilk test was used to assess the normality assumption of continuous variables. Differences between two independent groups for continuous variables were evaluated by Student's t-test and Mann–Whitney U test accordingly. The differences in proportions between the groups were compared using Chi-Square or Fisher Exact tests as appropriate. ROC analysis was used to calculate the areas under the receiving operator curves (AUC) and 95% confidence intervals for study parameters to predict LNM (positive). Sensitivity, specificity, PPV, NPV and accuracy were calculated. All statistical analyses were conducted using SPSS 19.0 for Windows Version 19.0 software (IBM Corp., Armonk, NY, USA) and *P*-values of less than 0.05 were considered to indicate statistical significance.

## Results

With the implementation of our exclusion criteria, we reached 327 patients who underwent surgical staging for endometrial cancer. While only pelvic lymphadenectomy was performed in 69 of our 327 patients (21.1%), pelvic and paraaortic lymphadenectomy were performed in 258 patients (78.9%). No patients underwent paraaortic lymphadenectomy without pelvic lymphadenectomy.

LNM was detected in 54 of our 327 patients (16.5%). There was a significant relationship between histological type, myometrial invasion, LVSI, peritoneal cytology and the presence of LNM. Age and pathological characteristics of our study population are given in Table 1.

Among NLR, PLR and CA 125, only CA 125 was found to have a significant relationship with LNM ( $P=0.001$ , Table 2).

Table 1: Patient characteristics according to lymph node status

Characteristics	n	LNM (negative) n=273	LNM (positive) n=54	P-value
Age	327	61.63 (9.20) <sup>**</sup> (31-86)	61.22 (8.57) <sup>**</sup> (45-80)	*0.762
Grade	1	244 83.60%	204 16.40%	0.615
	2	56 80.40%	45 11	
	3	27 88.90%	24 11.10%	
Type	Endometrioid	225 86.70%	195 13.30%	0.021
	Non-endometrioid	102 76.50%	78 23.50%	
Tumor size(cm)	<2	43 90.70%	39 9.30%	0.166
	≥2	276 82.20%	227 17.80%	
MI	<50 %	207 92.30%	191 7.70%	<0.001
	≥50 %	120 68.30%	82 31.70%	
LVSI	no	210 91.00%	191 9.00%	<0.001
	yes	112 68.80%	77 31.30%	
Peritoneal cytology	negative	287 84.70%	243 15.30%	0.001
	positive	9 44.40%	4 55.60%	

\*Student t test, mean (SD), n: number; LNM: lymph node metastasis; MI: myometrial invasion; LVSI: Lymphovascular space invasion

Table 2: Comparing median of study variables according to their association with LNM

Biomarker	n1/n2	LNM (negative)	LNM (positive)	P-value
CA 125	184/39	17.9 (11.42 – 30.7) U/ml	51.45 (40.4-128.4) U/ml	0.001
NLR	272/53	2.12 (1.67 -2.95)	2.43(1.61-3.35)	0.516
PLR	272/53	125.23 (96.91-159.81)	149.89 (97.38-171.50)	0.408

Mann Whitney U-test, median (interquartile range), n:number, LNM: lymph node metastasis, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio.

ROC analysis was performed to compare the predictive diagnostic performances of our variable values. CA 125 significantly predicted the LNM positivity rate (ROC AUC = 0.80,  $P<0.001$ ), while NLR and PLR did not (AUC=0.60,  $P=0.052$  and AUC=0.59,  $P=0.086$ , respectively). Our cutoff value for CA 125 was 39 U/ ml. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy values of CA 125, which were significant and superior to others, were 77%, 82%, 48%, 94% and 81%, respectively (Figure 1, Table 3).

Figure 1: Receiver operating characteristics curves for serum CA 125, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio for lymph node metastasis.

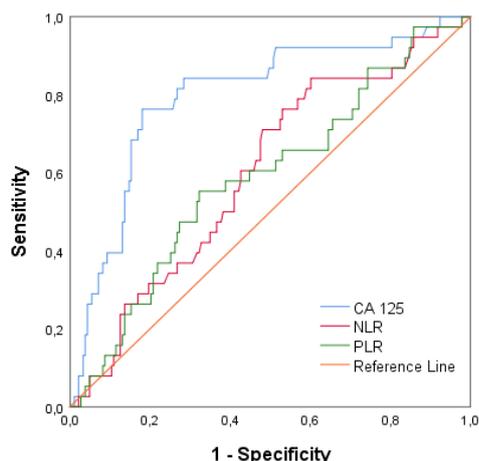


Table 3: Area under curve (AUC) and cut-off values in the receiver operating characteristic curve and sensitivity, specificity of CA 125, NLR and PLR to predict LNM

	Cut-off	AUC	%95 CI	P-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CA 125	39.00	0.80	0.715-0.878	<0.001	0.77	0.82	0.48	0.94	0.81
NLR	2.03	0.60	0.505-0.695	0.052	0.64	0.46	0.19	0.87	0.48
PLR	149.35	0.59	0.489-0.688	0.086	0.45	0.68	0.22	0.87	0.65

NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

## Discussion

Our objective is to avoid unnecessary lymphadenectomies by accurately predicting metastatic or nonmetastatic lymph nodes in EC preoperatively. We know that the known LNM risk factors (grade, mycobacterial invasion, lymphovascular invasion, cervical involvement, positive peritoneal cytology) can only be determined after surgery [2]. While preoperative and permanent mismatches can be seen at high rates for histological grade, the sensitivity and specificity of the pelvic MRI that we use in the evaluation of myometrial invasion can vary between 63-100% and 56-100% [17, 18]. The sensitivity and specificity of MRI for detecting LNM is 45% and 80.8%, respectively [19]. Therefore, many studies have focused on non-invasive, highly accurate and sensitive methods in the preoperative detection of possible LNM.

A systemic host response occurs against malignant tumors that alters the tumor's microenvironment. Leukocytosis and neutrophilia are the most common systemic changes. Lymphocytopenia associated with increased leukocytes is a response of systemic inflammation and the immune system [20]. Inflammatory cytokines released by tumor and adenosine diphosphate (ADP) also stimulate megakaryocytes and increase thrombocyte count and aggregation. Thrombocytosis reflects systemic inflammation and induces tumor invasion and metastasis [21]. Based on this theory, the prognostic value of many systemic inflammatory markers (WBC, CRP, neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio, fibrinogen, etc.) has been demonstrated in various malignancies [22, 23].

NLR and CRP increase and thrombocytosis predict survival in epithelial ovarian tumors [24, 25,26]. Although the correlation of preoperative thrombocyte count with cervical involvement in endometrial cancer and grade 3 histology has been demonstrated in numerous studies [27, 28], the predictive effect of systemic inflammatory markers in the detection of LNM in endometrial cancers has been evaluated in very few.

While Casper et al. [29] stated that preoperative leukocytosis and thrombocytosis increased the risk of LNM at a low-moderate degree in their meta-analysis, Tuomi et al.[30] stated that thrombocytosis could be used at a moderate impact degree in the preoperative scoring system in the detection of LNM in advanced ECs. Suh et al. [31] found that NLR, PLR and CA 125 values were significantly higher in the LNM positive group compared to the negative group in 319 patients with endometrioid type endometrial carcinoma who underwent surgical staging and that SIR markers were not, however, more effective markers for detecting LNM than serum CA 125. Although we found the negative predictive effect of both NLR and PLR to be high in our study, we could not find a significant relationship between the median or cut off values in terms of detecting LNM.

Several guidelines, including the consensus statement of the European Society for Medical Oncology and the European

Society of Gynecologic Oncology, describe the search for lymphadenopathy mediated by CA 125 antigen measurement and imaging methods in endometrial cancers as part of preoperative research [5,32].

Elevated Serum CA 125 levels are an indicator of lymph node involvement and poor prognosis in EC [33].

In a study in which all patients were surgically staged, as in our study, preoperative CA 125 had 77.8% sensitivity and 81% specificity in determining LNM [34]. Our results were 77% and 82%, respectively, very close to these values. Chung et al. [35] found that the CA 125 value had a low sensitivity of 61.5% in predicting LNM but emphasized that it was still an important independent predictor. When Todo et al. [36] combined the CA 125 value with commonly used preoperative pathological findings (histology, grade, myometrium invasion), they found a false negative rate of 3.6% in detecting LNM.

In our study, while tumor histology, myometrial invasion, LVSI, abdominal cytology and preoperative CA125 value were significant predictors for LNM, we did not find this relationship in NLR and PLR systemic inflammatory markers.

### Limitations

Our limitations include the retrospective nature of the study and that other inflammatory markers such as CRP and fibrinogen were not included due to insufficient data. The exclusion of patients who did not undergo lymphadenectomy increases the reliability of our study.

As our knowledge of the sentinel lymph node (SNL) increases, the morbidity associated with surgery will decrease and a more appropriate staging will be possible. Today, sufficient expert surgeons and large oncological centers are needed for the SNL procedure, which is costly.

### Conclusion

CA 125 value was an effective marker for lymph node metastasis in endometrial cancer. Contrary to many studies mentioned in the literature, we did not find the NLR and PLR values to be significant in the prediction of lymph node metastasis. More studies involving combined risk scoring systems with high sensitivity rates are needed.

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