

Can Preoperative Complete Blood Count Parameters Be Used as Predictive Markers for Lymph Node Metastasis in Endometrial Carcinomas?

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BACKGROUND/AIMS

To investigate the clinical utility of complete blood count (CBC) parameters in the preoperative diagnosis of lymph node involvement (LNI) in endometrial carcinomas (ECs).

MATERIAL and METHODS

We conducted a retrospective study of 159 patients with ECs who underwent complete staging surgery at a tertiary center between 2007 and 2017. After demographic characteristics and preoperative CBC parameters were retrieved from the patients' medical records, the patients were grouped according to lymph node status (positive and negative) and compared. Variables with $p < 0.05$ were included in the logistic regression analysis, and receiver operating characteristic curve analysis was used to determine the cut-off values for predicting LNI.

RESULTS

The mean age of the patients was 59.1 years, and 14 (8.8%) patients had LNI. The mean white blood cell, neutrophil, and platelet counts; plateletcrit level; and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were significantly higher in patients with LNI. Logistic regression analysis identified an independent association between increased neutrophil count and LNI (odds ratio 5.12; $p < 0.05$). The optimal cut-off value was $4.85 (\times 10^3 / \mu\text{L})$ (sensitivity, 77.4% and specificity, 74.2%). A cut-off of $6.25 (\times 10^3 / \mu\text{L})$ was used to identify LNI with 100% specificity.

CONCLUSION

An increased neutrophil count can be considered a useful additional tool for the preoperative diagnosis of LNI.

Keywords: Blood cell count, endometrial neoplasms, lymphatic metastasis, lymph node excision, neutrophils

INTRODUCTION

Endometrial carcinoma (EC) is the most common gynecological cancer among women in developed countries (1). Based on the GLOBOCAN estimates, which are produced by the International Agency for Research on Cancer, in 2012, there were approximately 160,000 new cases worldwide (1). Moreover, as risk factors, including obesity and advancing age, become more prevalent, the incidence will likely increase. Fortunately, an early diagnosis can be made in many patients (approximately 75%) based on signs and symptoms (abnormal uterine bleeding) (2).

Endometrial carcinoma is staged surgically and was first recognized by the International Federation of Gynecology and Obstetrics (FIGO) in 1988 (3). The staging guidelines were last revised in 2009, and total extrafascial hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection remain the standard staging procedures (3). Among the many clinical and pathological factors (FIGO stage, age, histological type and grade, tumor size, presence of lymphovascular space invasion (LVSI), lymph node involvement (LNI), and positive peritoneal cytology), the FIGO stage is the most important variable that influences the likelihood of EC recurrence and the survival rate (2). Therefore, the American Congress of Obstetricians and Gynecologists recommended surgical staging, including lymph node sampling, for all women with EC, except for those at increased risk of mortality because of secondary co-

morbidities (4). Despite these recommendations, recent studies have generated much debate on the benefit of lymph node sampling in low-risk ECs (5-8). Owing to this debate, staging practices vary widely based on the individual physician and institutional practices. Nevertheless, it is difficult to identify ECs with LNI preoperatively. In an attempt to resolve this challenge, various tools, including serum carcinoma antigen I25 measurement and magnetic resonance imaging, have been used; however, the sensitivity and specificity of these techniques are varied (7, 9).

In contrast, studies of gynecological and non-gynecological cancers have shown that preoperative complete blood count (CBC) is a useful diagnostic tool for predicting LNI and prognosis (10, 11). Similarly, studies conducted on ECs revealed that preoperative CBC parameters were not only able to predict cancerous lesions but might also be related to poor prognostic factors, including tumor stage and grade, LVSI, and LNI (12-20). However, the clinical utility of CBC parameters for predicting LNI has not yet been widely investigated.

The aim of the present study was to determine whether there is any significant relationship between LNI and CBC parameters in ECs. Furthermore, we investigated the clinical utility of these parameters in the preoperative diagnosis of LNI.

MATERIAL and METHODS

The medical files of 184 patients with EC who were staged surgically according to the recommendations of FIGO at a tertiary hospital between 2007 and 2017 were retrospectively analyzed. Patients who had acute inflammatory disease, myeloproliferative disorders, concomitant gynecological and other cancers, or autoimmune disease; were using any drug that affects CBC parameters including anticoagulants or hormonal contents; or

reported smoking were excluded from the study. A total of 159 patients were enrolled in the study. Informed oral consent was obtained from all participants. The study was approved by the Ethical Review Board of Ankara Atatürk Training and Research Hospital (approval no.: 26379996/152) and was conducted in accordance with the World Medical Association Declaration of Helsinki (2000 revision).

Data on demographic and pathological characteristics (age, gravidity, parity, histological type, FIGO stage, and LNI status) and preoperative CBC parameters (white blood cell (WBC), neutrophil, lymphocyte, and platelet counts; hemoglobin levels; mean corpuscular volume; mean platelet volume (MPV); platelet distribution width (PDW); plateletcrit levels; and neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios) were retrieved from the patient's medical files and hospital records. Blood samples were collected when the patients were admitted to the hospital for surgery and before receiving any medications. Specimens were analyzed within 2 h using a Sysmex XE-2100 Automated CBC Analyzer (Sysmex Europe, Germany).

After patients were grouped according to lymph node status (lymph node positive and lymph node negative), the groups were compared in terms of the examined CBC parameters. Once CBC parameters significantly associated with LNI were determined, the clinical utility of those parameters in the preoperative diagnosis of LNI was investigated.

Statistical Analysis

Data were expressed as mean \pm standard deviation. The groups (lymph node positive vs. lymph node negative) were compared using independent sample t-tests. Variables with $p < 0.05$ were included in the binary logistic regression analysis, and the influence of each factor on the preoperative diagnosis of LNI was evaluated. The receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of the serum neutrophil level for diagnosing LNI. Statistical analyses were made using Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Odds ratios (ORs) and 95% confidence intervals (CIs) were determined. A $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 summarizes the demographic and pathological characteristics and preoperative CBC parameters of 159 patients with EC.

In the study group, 14 (8.8%) patients had LNI. While the mean serum WBC, neutrophil, and platelet counts; plateletcrit level; and NLR and PLR ratios were significantly higher in the lymph node positive group than in the lymph node negative group ($p < 0.05$), the mean serum lymphocyte count and hemoglobin, hematocrit, MPV, and PDW levels did not differ significantly between the groups ($p > 0.05$) (Table 2).

Binary logistic regression analysis revealed that among variables that differed significantly between the lymph node positive and lymph node negative groups, only an increased neutrophil count was independently associated with LNI (OR 5.12,

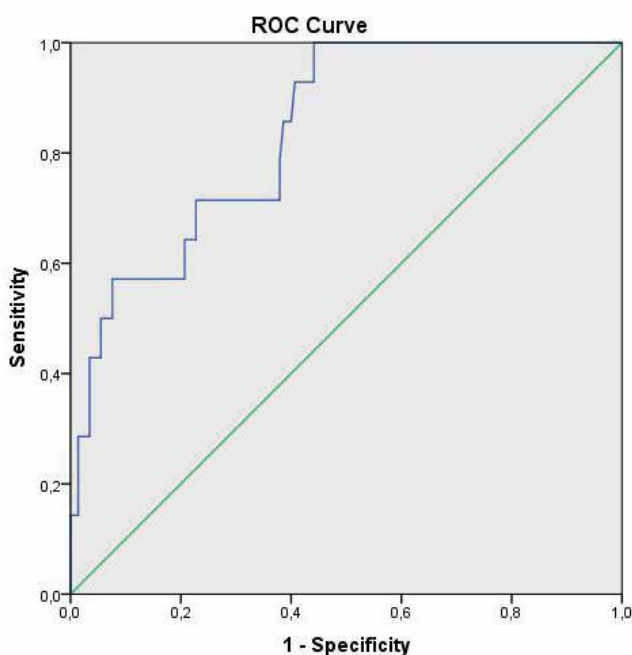


FIGURE I. Receiver operating characteristic curve of serum neutrophil levels for discriminating lymph node positive from lymph node negative patients with endometrial carcinoma (area under the curve: 0.838; standard error: 0.048)

95% CI 1.168-22.452; -0.03) (Table 3). The ROC curve analysis revealed that the optimal cut-off value of the serum neutrophil level for predicting LNI was $4.85 (\times 10^3/\mu\text{L})$. The sensitivity was 71.2%, and the specificity was 74.2% (Fig. 1). When the groups (lymph node positive vs. lymph node negative) were assessed in the ROC curve analysis using the $6.25 (\times 10^3/\mu\text{L})$ cut-off value, the sensitivity was 51.1%, and the specificity was 100%.

TABLE 1. Demographic and surgical characteristics and preoperative CBC parameters of 159 patients with endometrial carcinoma

Characteristics	Patients (n=159)
Demographic and surgical, mean \pm SD (range)	
Age (years)	59.1 \pm 10.0
Gravidity	4.45 \pm 3.02
Parity	3.54 \pm 2.51
Histological type, n (%)	
Type 1 (endometrioid type)	132 (83.0)
Type 2 (other types) ^a	27 (17.0)
FIGO stage, n (%)	
IA	97 (61.0)
IB	36 (22.6)
II	9 (5.7)
IIIA	2 (1.3)
IIIB	1 (0.6)
IIIC1	4 (2.5)
IIIC2	6 (3.7)
IVA	2 (1.3)
IVB	2 (1.3)
Lymph node involvement, n (%)	
Yes	14 (8.8)
No	145 (91.2)
CBC parameter, mean \pm SD (range)	
WBC count ($\times 10^3/\mu\text{L}$)	7.772 \pm 1.975
Neutrophil count ($\times 10^3/\mu\text{L}$)	4.426 \pm 1.535
Lymphocyte count ($\times 10^3/\mu\text{L}$)	2.231 \pm 0.645
Hemoglobin (g/dL)	12.858 \pm 1.56
Hematocrit (%)	38.91 \pm 4.312
MCV (fL)	84.67 \pm 6.27
Platelet count ($\times 10^3/\mu\text{L}$)	288.415 \pm 81.072
MPV (fL)	10.33 \pm 1.41
PDW (fL)	14.0 \pm 2.57
Plateletcrit (%)	0.293 \pm 0.830
NLR (%)	2.180 \pm 1.193
PLR (%)	140.155 \pm 60.59
^a Type II tumors include serous, clear cell, mucinous, mixed, and undifferentiated histological subtypes. CBC: complete blood count; FIGO: International Federation of Gynecology and Obstetrics; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PDW: platelet distribution width; SD: standard deviation; WBC: white blood cell	

DISCUSSION

The present study has shown that various CBC parameters, including WBC, neutrophil, and platelet counts; plateletcrit level; and NLR and PLR ratios, were significantly higher in ECs with LNI. Furthermore, it revealed that the neutrophil count was an independent predictor of a preoperative diagnosis of LNI, and a value $>6.25 (\times 10^3/\mu\text{L})$ was able to identify ECs with LNI with a specificity of 100%. To our knowledge, this is the first study that widely investigates the clinical utility of CBC parameters for diagnosing ECs with LNI.

The influence of inflammation, caused by inflammatory cells and their mediators, in various aspects of cancer, including cancer initiation, promotion, progression, and metastasis, has recently been demonstrated (21). Similarly, it is suggested that changes in serum CBC parameters, including cell counts, cell size and shape, and cell-to-cell ratios, may reflect cancer and cancer-related characteristics. Studies of ECs revealed that various CBC parameters, such as WBC count, platelet count, PDW,

TABLE 2. The CBC parameters of patients with endometrial carcinoma according to lymph node status (positive or negative)

Characteristics, mean (\pm SD)	Lymph node positive (n=14, 9.8%)	Lymph node negative (n=145, 91.2%)	p
WBC count ($\times 10^3/\mu\text{L}$)	9.492 \pm 2.123	7.611 \pm 1.887	0.001*
Neutrophil count ($\times 10^3/\mu\text{L}$)	6.307 \pm 1.541	4.244 \pm 1.402	<0.001*
Lymphocyte count ($\times 10^3/\mu\text{L}$)	2.067 \pm 0.598	2.247 \pm 0.649	0.321
Hemoglobin (g/dL)	12.342 \pm 1.364	12.904 \pm 1.572	0.199
Hematocrit (%)	38.0 \pm 4.655	38.996 \pm 4.284	0.414
MCV (fL)	86.535 \pm 6.047	84.495 \pm 6.047	0.246
Platelet count ($\times 10^3/\mu\text{L}$)	358.642 \pm 76.436	281.634 \pm 78.476	0.001*
MPV (fL)	10.385 \pm 1.224	10.325 \pm 1.43	0.879
PDW (fL)	13.964 \pm 2.45	14.0 \pm 2.595	0.953
Plateletcrit (%)	0.34 \pm 0.11	0.288 \pm 0.079	0.026*
NLR (%)	3.285 \pm 1.155	2.075 \pm 1.145	<0.001*
PLR (%)	192.723 \pm 84.075	135.044 \pm 55.602	0.001*
*p<0.05. CBC: complete blood count; MCV: mean corpuscular volume; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PDW: platelet distribution width; SD: standard deviation; WBC: white blood cell			

TABLE 3. Binary logistic regression analysis of CBC variables of patients with respect to lymph node involvement

Variables	p	OR	95% CI
WBC count	0.855	1.052	0.613-1.804
Neutrophil count	0.03*	5.12	0.168-22.452
Platelet count	0.675	0.996	0.975-1.016
Plateletcrit	0.155	0.001	0.001-33.417
NLR	0.214	0.202	0.016-2.516
PLR	0.095	1.033	0.994-1.074
*p<0.05. CBC: complete blood count; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; WBC: white blood cell			

MPV, plateletcrit, and NLR, were significantly higher in ECs than in healthy and precancerous controls (12-17). Furthermore, some studies reported that serum WBC count, platelet count, and MPV may reflect both tumor stage and grade in ECs (12, 13, 17, 18). As a result, the authors proposed that CBC is a useful diagnostic tool for the preoperative early diagnosis of ECs in patients at a high risk of EC (i.e., those with abnormal uterine bleeding) (12-16).

Furthermore, several recent studies have investigated the relationship between CBC and LNI in ECs (13, 18-20). However, their results were inconsistent. For instance, Ekici et al. (13) found that both WBC and platelet counts are significantly higher in ECs with LNI than in others. Conversely, Takahashi et al. (18) found a significant relationship between increased platelet count and LNI, whereas there was no significant relationship between WBC count and LNI (19). In contrast, in their study, Suh et al. (20) found significant relationships between both NLR and PLR ratios and LNI, whereas there was no significant relationship between WBC count and LNI. In the present study, we found that preoperative serum WBC, platelet, and neutrophil counts; plateletcrit level; and PLR and NLR ratios were significantly higher in ECs with LNI. Furthermore, our study revealed that the neutrophil count was an independent predictor of the preoperative diagnosis of LNI.

An increased serum neutrophil count has been observed in many cancers with an advanced tumor stage and a poor prognosis (22, 23). Although the precise mechanism is still unknown, this condition was proposed to provide evidence for the concept of cancer-related inflammation inducing tumor progression (23, 24). Takahashi et al. (18) also found significant relationships between an increased neutrophil count and various poor prognostic factors associated with ECs (advanced surgical stage, LVSI, and cervical stromal involvement). In contrast to the previous study, the present study showed a significant and independent relationship between an increased neutrophil count and LNI. The inconsistency between studies may be the result of the diverse surgical and histological characteristics of the study populations, including FIGO stage and histological type and grade. It may also be the result of many variable characteristics of the study populations (i.e. race and harvested lymph node count).

Currently, there is no consensus on the benefit of lymph node sampling in all patients with ECs. Although a population-based retrospective study stated that lymph node sampling improved the survival of patients with ECs, another recent prospective study found no evidence of benefit from lymph node sampling in terms of overall or recurrence-free survival in women with early stage disease (3, 4). Thus, identification of patients with a high risk of LNI may improve survival by determining the extent of the lymph node sampling area and the administration of a suitable adjuvant therapy. With this aim, the usability of various diagnostic tools has been investigated. However, the sensitivity and specificity of commonly used preoperative diagnostic tools for LNI, such as serum carcinoma antigen 125 and magnetic resonance imaging, have been reported to be approximately 61.5%-77.8%/81.0%-94.9% and 50.0%-62.2%/92.0%-94.9%, respectively (7, 9). Similarly, the present study showed that the neutrophil count had 71.2% sensitivity and 74.2% specificity for diagnosing ECs with LNI preoperatively. Additionally, a cut-off value of 6.25 ($\times 10^3/\mu\text{L}$) was able to identify patients with EC with LNI with 100% specificity.

In conclusion, although the present study has its limitations, such as its retrospective single-center design and relatively small sample size, it revealed the potential predictive role of CBC for selecting patients with EC with LNI. To our knowledge, the present study is also the first to report the usability of the neutrophil count for diagnosing ECs with LNI. As the neutrophil level can be routinely determined using CBC tests preoperatively, this low cost and readily available parameter may be a new and promising marker to select patients with ECs for extended lymph node sampling. However, comprehensive studies on different histological subtypes are necessary to determine the utility of this marker for patients with ECs.

Ethics Committee Approval: Ethics committee approval was received for this study from Ankara Atatürk Training and Research Hospital. (Approval Date: 28/05/2018, Approval Number: 26379996/152).

Informed Consent: Oral informed consent was taken from the patients prior to the study.

Peer-review: Externally peer-reviewed.

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