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The Influence of Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Platelet Distribution Width on Myometrial Invasion in Endometrial Carcinoma: A Retrospective Study

Endometriyal Karsinomda Nötrofil-Lenfosit Oranı, Trombosit-Lenfosit Oranı ve Trombosit Dağılım Genişliğinin Miyometrial İnvazyon Üzerindeki Etkisi: Retrospektif Bir Çalışma

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ABSTRACT Objective: To estimate the stage of endometrial carcinoma, an easily reproducible and simple marker is needed. We aimed to find out whether the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, platelet distribution width (PDW) values have an impact on the degree of myometrial invasion in endometrial carcinoma. **Material and Methods:** The study was planned as a retrospective cross-sectional study between 2007 and 2014 in Ankara, Türkiye. After reviewing the patients' pathology reports, a total of 88 patients with adenocarcinoma of the endometrium were included in the study. **Results:** The age of the 88 women included in the study ranged from 44 to 92 years, with a mean age of 56.00 (inter quantile range=16.0) years. The ROC analysis showed that only the PDW and NLR values could statistically significantly differentiate between patients with less than half the depth of invasion and patients with more than half the depth of invasion (p=0.025, p=0.003). Accordingly, the significance of the PDW was 64.5% (95% confidence interval: 51.6-77.4); when the PDW value is less than 15.05, it predicts that the depth of invasion is more than half with 67.7% sensitivity and 61.4% selectivity. **Conclusion:** We found that preoperative PDW and NLR values can predict myometrial invasion in endometrial cancer.

Keywords: Neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; myometrial invasion; platelet distribution width; endometrial cancer

ÖZET Amaç: Endometriyal karsinomun evresini tahmin etmek için kolayca tekrarlanabilir ve basit bir belirteç gereklidir. Nötrofil lenfosit oranı [neutrophil-to-lymphocyte ratio (NLR)], trombosit lenfosit oranı, trombosit dağılım genişliği [platelet distribution width (PDW)] değerlerinin endometriyal karsinomda miyometrial invazyon derecesi üzerinde etkisi olup olmadığını bulmayı amaçladık. **Gereç ve Yöntemler:** Çalışma, 2007-2014 yılları arasında Ankara'da retrospektif kesitsel bir çalışma olarak planlandı. Hastaların patoloji raporları incelendikten sonra endometriyum adenokarsinomu olan toplam 88 hasta çalışmaya dâhil edildi. **Bulgular:** Çalışmaya alınan 88 kadının yaşları 44-92 arasında değişmekte olup, ortalama yaşları 56,00'dır (çeyrekler arası aralık=16,0). ROC analizi, yalnızca PDW ve NLR değerlerinin, invazyon derinliğinin yarısından az olan hastalar ile invazyon derinliğinin yarısından fazla olan hastalar arasında istatistiksel olarak anlamlı bir ayrım yapabildiğini gösterdi (p=0,025, p=0,003). Buna göre, PDW'nin anlamlılığı %64,5 (%95 güven aralığı: 51,6-77,4); PDW değeri 15,05'ten küçük olduğunda %67,7 duyarlılık ve %61,4 seçicilik ile invazyon derinliğinin yarıdan fazla olduğunu tahmin eder. **Sonuç:** Preoperatif PDW ve NLR değerlerinin endometriyal kanserde miyometrial invazyonu tahmin edebileceğini bulduk.

Anahtar Kelimeler: Nötrofil-lenfosit oranı; trombosit-lenfosit oranı; myometriyal invazyon; trombosit dağılım genişliği; endometriyal kanser

Endometrial adenocancer is the one of common genital tract cancer.[1] Its prevalence has increased over the years and now accounts for approximately 4.8% of all cancers in women.[2] The cumulative risk of developing endometrial cancer by the age of 75 years is about 1%.[2] The main risk factors are endogenous or exogenous uncontrolled estrogen exposure due to certain factors, including early menarche, late

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menopause, diabetes, obesity, nulliparity, advanced age (≥55 years), and tamoxifen use.[3] The average 5-year survival rate for all stages is approximately 80%.[4] There are several theories for the development of cancer, with one of the most widely accepted theories being that auto-traumatization triggers the chronic inflammatory response.[1,2] The resulting cytokines (interleukins), chemokines, and growth factors likely promote tumor development and spread.[5] Mutations in the signaling pathway that regulates cell proliferation have been detected in endometrial carcinomas.[6] The most important factors for prognosis are the stage, histologic type, and grade of the cancer. Therefore, a simple and inexpensive marker is needed to provide information about the prognosis of endometrial cancer and allow early diagnosis.

Numerous researchers have explored possible links between chronic inflammation and cancer, although the exact mechanisms are still unclear. Current evidence suggests a reciprocal induction between chronic inflammation and cancer.[5] Blood levels indicative of an inflammatory response have been the subject of numerous studies on tumorigenesis and have been shown to reach significant levels in the blood of various cancers.[7-9] White blood cell count is considered markers of systemic inflammation. The neutrophil to lymphocyte ratio (NLR) is considered an index indicating both acute inflammation and the negative effects of chronic processes.[7,9] Platelet to lymphocyte ratio (PLR) is a parameter that can help predict survival. Elevated PLR has been shown as a risk factor for lower survival in gastrointestinal system cancers.[10,11] Platelet count is known to have prognostic significance in many cancers, such as endocrine cancers. Platelet distribution width (PDW) is the platelet equivalent of the red cell distribution width (RDW) measurement.[7-11] A low PDW is an indicator of a homogeneous platelet population. With abnormal thrombopoiesis, platelet heterogeneity increases and PDW also increases. There are numerous recent studies on PDW in the literature.[12,13]

Based on this information, we aimed to determine whether NLR, PLR, and PDW values have an impact on the degree of myometrial invasion in endometrial cancer.

MATERIAL AND METHODS

The study was planned as a retrospective cross-sectional study in the Department of Gynecology of Yıldırım Beyazıt Hospital in Ankara between 2007 and 2014 for seven years. The study was approved by the board of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (date: February 11, 2015, no: 26379996/73). Because it was a study with human participants, it complied with the principles of the Declaration of Helsinki. All women (n=441) who had undergone total abdominal hysterectomy in the gynecology department were included in the study. We excluded three hundred and fifty-three patients because of benign diseases (including systemic diseases, infectious diseases, rheumatologic diseases), discontinuation of follow-up in our hospital or inaccessibility of patient data, presence of another tumor with metastases in the endometrium, presence of a synchronous tumor, hematologic cancer, or neoadjuvant chemotherapy. After reviewing the patients' pathology reports, a total of 88 patients were enrolled in the study. This center is one of the largest oncology facilities in our city and also accepts patients from surrounding areas. Therefore, we can assume that the size of this study is comparable to the total number of patients in Ankara province. Patients participating in this study were divided into 2 groups according to whether myometrial invasion was less or more than 50%. Group 1 (n=57) are those with myometrial invasion depth of 50% or less. Group 2 (n=31) are those with myometrial invasion depth greater than 50%.

We collected data on the descriptive demographic and clinical characteristics of the patients. We also evaluated preoperative and postoperative histopathologic findings: Probe/curettage, histopathologic diagnosis, carcinoma type, disease stage, tumor diameter, tumor grade, depth of myometrial invasion, cervical stromal invasion, lymphatic invasion, adnexal involvement, presence of lymph node involvement, uterine leiomyoma or coexistence of endometriosis, presence of endometrial hyperplasia, presence of distant metastases, cytology positivity.

Transvaginal ultrasonography was performed in all patients to exclude the presence of other diseases

and to assess the thickness of the endometrium. This examination was performed in all patients by the BDC using the same ultrasound machine. Venous blood (10 cc) was collected from the antecubital vein for routine blood tests such as human chorionic gonadotropin and blood count during hospitalization on the day before the day of surgery. Automated blood counts were performed with a Coulter instrument (LH 780 Hematology Analyzer, USA). The remaining biochemical parameters were analyzed with a hormone analyzer and a chemiluminescence immunoassay [Immulite 1000 device (Siemens Health Diagnostics, USA)]. Inflammatory markers were determined in blood samples taken from patients the day before surgery. NLR was determined by dividing the neutrophil count by the lymphocyte count. Similarly, PLR was calculated by dividing the platelet count by the lymphocyte count.

All histological sections were examined by two experienced pathologists at our hospital. Sections of the uterus, cervix, lower uterine segment, and uterus were divided into at least 6 parts, anterior and posterior corpus, and each segment was examined in detail for deepest tumor invasion. Grouping by depth of invasion was performed to determine whether these complete blood count parameters had an impact.

STATISTICAL ANALYSIS

The Statistical Package (SPSS 22.0, Inc., Chicago, IL, USA) was used to analyze the data. Receiver operating characteristic curve analysis (ROC) was used to determine the optimal cut-off value for the independent markers, and sensitivity and specificity were calculated. Data were expressed as arithmetic mean, standard deviation, median, and minimum-maximum values. For normally distributed data, the independent-samples t test was used, and for nonnormally distributed variables, the Mann-Whitney U test was used. For analysis of categorical variables, the chi-square test or the Fisher extract test was used. In the study, a p value of less than 0.05 was considered statistically significant.

RESULTS

The ages of the 88 women included in the study ranged from 44 to 92 years, with a mean age of 56.00 [inter quantile range (IQR)=16.0] years. Table 1 shows the demographic datas of the two groups, ranked by depth of myometrial invasion. The mean age of the patients was 63.07±11.29 years in the group with myometrial invasion equal to or less than 1/2 (group 1) and 67.13±10.29 years in the group with myometrial invasion greater than 1/2 (Group 2). There were 49 patients (90.7%) in Stage 1 in Group 1 and 37.1% in the other group. The number of patients with Grade 3 tumors in Group 2 was 10 (41.7%). The incidence of menopause was also

TABLE 1: Distribution of study characteristics according to depth of invasion.

	Myometrial invasion	
	≤50% (Group 1) n=57	>50% (Group 2) n=31
Age (years)		
X̄±SD	63.07±11.29	67.13±10.29
Minimum-Maximum	44.00-92.00	44.00-88.00
Stage [n (%)]		
Stage 1	49 (90.7)	10 (37.1)
Stage 2	5 (9.3)	9 (33.3)
Stage 3	0 (0.0)	6 (22.2)
Stage 4	0 (0.0)	2 (7.4)
Grade [n (%)]		
Grade 1	35 (67.3)	8 (33.3)
Grade 2	12 (23.1)	6 (25.0)
Grade 3	5 (9.6)	10 (41.7)
Histology [n (%)]		
Endometrioid	56 (98.2)	28 (90.3)
Non-endometrioid	1 (1.8)	3 (9.7)
Tumor diameter [n (%)]		
<2 cm	54 (94.8)	24 (77.5)
≥2 cm	3 (5.2)	7 (22.5)
Lymph node involvement [n (%)]		
No	47 (90.4)	10 (40.0)
Yes	5 (9.6)	15 (60.0)
Cervical involvement [n (%)]		
No	49 (90.7)	16 (61.5)
Yes	5 (9.3)	10 (38.5)
Distant metastasis [n (%)]		
No	54 (100.0)	23 (88.5)
Yes	0 (0.0)	3 (11.5)
Cytology positivity [n (%)]		
No	44 (100.0)	15 (83.3)
Yes	0 (0.0)	3 (16.7)
Menopause [n (%)]		
No	15 (26.8)	1 (3.2)
Yes	41 (73.2)	30 (96.8)

SD: Standard deviation.

higher in this group than in Group 1 (96.8% versus 73.2%). When comparing outcomes, patients were similar in all areas except PDW and NLR (p>0.05, Table 2). Median PDW values were 16.00 (IQR=4.25) and 13.50 (IQR=5.30), respectively; median NLR values were 1.79 (IQR=1.10) and 3.00 (1.65), respectively. PDW values were significantly higher in patients with less than half the depth of in-

TABLE 2: Comparison of findings according to depth of invasion.

	Myometrial invasion			
	≤50% (Group 1) n=57	>50% (Group 2) n=31		p value
Endometrial thickness				
Median (IQR)	17.50 (10.98)	21.00 (18.50)	1.764	0.078
Minimum-Maximum	3.00-50.00	4.60-65.00		
WBC				
Median (IQR)	7.40 (2.99)	7.50 (2.13)	0.533	0.594
Minimum-Maximum	4.29-18.68	5.08-13.03		
NEU				
Median (IQR)	3.91 (2.42)	5.23 (2.26)	1.485	0.138
Minimum-Maximum	1.70-16.27	2.58-9.32		
LYM				
Median (IQR)	2.22 (0.94)	1.85 (1.24)	1.887	0.059
Minimum-Maximum	0.43-4.40	0.74-3.36		
MON				
Median (IQR)	0.50 (0.30)	0.54 (0.16)	1.551	0.121
Minimum-Maximum	0.20-3.30	0.24-1.06		
EOSINO				
Median (IQR)	0.10 (0.13)	0.10 (0.11)	1.046	0.296
Minimum-Maximum	0.00-0.42	0.00-0.30		
HGB				
Median (IQR)	13.40 (1.90)	12.90 (1.90)	1.595	0.111
Minimum-Maximum	7.80-15.80	9.30-14.90		
HCT				
Median (IQR)	39.10 (5.65)	37.40 (5.40)	1.415	0.157
Minimum-Maximum	26.30-46.30	26.30-44.80		
RDW				
Median (IQR)	14.10 (2.10)	14.10 (1.90)	0.546	0.585
Minimum-Maximum	11.70-22.30	12.40-16.80		
PLT				
Median (IQR)	257.00 (88.00)	267.00 (81.00)	0.149	0.882
Minimum-Maximum	109.00-493.00	140.00-848.00		
MPV				
Median (IQR)	10.20 (2.60)	9.90 (1.54)	0.127	0.899
Minimum-Maximum	0.08-13.80	7.60-12.10		
PDW				
Median (IQR)	16.00 (4.25)	13.50 (5.30)	2.241	**0.025**
Minimum-Maximum	10.80-20.60	9.60-18.60		
NLR				
Median (IQR)	1.79 (1.10)	3.00 (1.65)	2.974	**0.003**
Minimum-Maximum	0.66-31.30	0.88-11.58		
PLR				
Median (IQR)	122.78 (54.51)	133.92 (56.29)	1.848	0.065
Minimum-Maximum	47.39-469.77	68.75-446.25		

WBC: White blood cell; NEU: Neutrophil; LYM: Lymphocyte; MON: Monocytes; EOSINO: Eosinophil; HGB: Hemoglobin; HCT: Hematocrit; RDW: Red cell distribution width; PLT: Platelet; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

TABLE 3: ROC analysis results for depth of invasion.

Variables	AUC±SE	95 CI%	Cut-off	p value	Sensitivity	Specificity
PDW	0.645±0.066	0.516-0.774	≤15.05	**0.025**	0.677	0.614
NLR	0.693±0.063	0.570-0.816	≥2.88	**0.003**	0.548	0.860

PDW: Platelet distribution width; NLR: Neutrophil to lymphocyte ratio; AUC: Area under the curve; SE: Standard error; CI: Confidence interval.

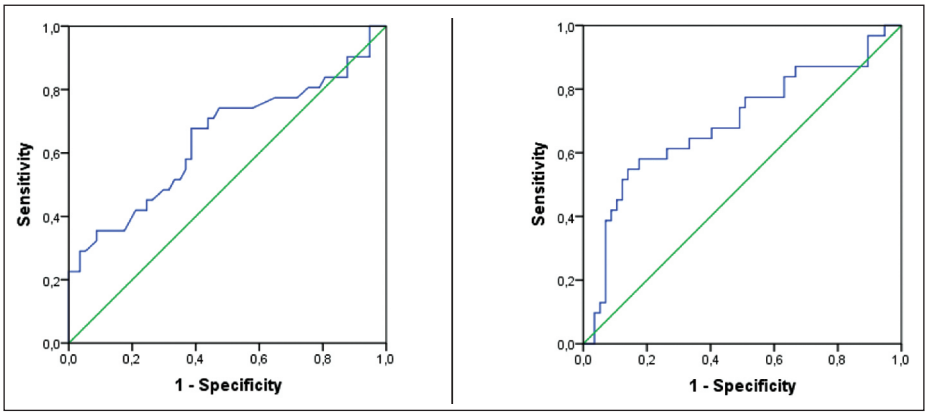

FIGURE 1: ROC curve of count blood parameters. **a)** ROC curve of platelet distribution width; **b)** ROC curve of neutrophil-to-lymphocyte ratio.

vasion (Z=2.241, p=0.025); NLR values were significantly lower (Z=2.974, p=0.003). The ROC analysis showed that only the PDW and NLR values could statistically significantly differentiate between patients with less than half the depth of invasion and patients with more than half the depth of invasion (p=0.025, p=0.003) (Table 3). Accordingly, the significance of the PDW was 64.5% (95% CI: 51.6-77.4); when the PDW value is less than 15.05, it predicts that the depth of invasion is more than half with 67.7% sensitivity and 61.4% selectivity. The plots of ROC, obtained for both readings, are shown in Figure 1a and Figure 1b.

DISCUSSION

Complete blood count is a routine and inexpensive laboratory test. White blood cell count is one of the useful biomarkers of inflammation that we commonly use in clinical practice.[14] Numerous studies have been conducted to investigate the relationship between these parameters, namely inflammation and cancer.[15,16] In this study, we investigated whether these parameters are important in predicting myometrial invasion, which is particularly used in staging endometrial cancer and is associated with poor prognosis. As a result, we found that preoperative PDW and NLR values can predict invasion.

NLR and PLR, cellular components of systemic inflammation and coagulation, have been shown to be important predictors of prognosis in various malignancies.[17] In colorectal carcinoma, pretreatment NLR is an independent risk factor for prognosis associated with recurrence after surgery and chemotherapy.[18] These results were also confirmed in advanced gastric cancer, hepatocellular carcinoma, and lymphoma.[19]

Inflammation is an important risk factor for endometrial cancer.[17] Chronic inflammation associated with hyperinsulinemia and hyperestrogenemia may mediate the increased risk of endometrial cancer associated.[20] One study reported that high prediagnostic levels of inflammatory markers are associated with an increased risk of endometrial cancer.[21] Tumor formation in endometrial cancer is due to genetic mutations such as phosphatase and tensin homolog and K-ras, which lead to tumorigenesis and trigger an inflammatory state.[22] As a result of growth factors, neutrophilia and leukocytosis de-

velop, and tumor invasion and metastasis are promoted by the release of angiogenic factors.[23] Lymphocyte numbers decrease in response to tumor cells.[22] Neutrophils can release a variety of chemokines and mediators that promote tumor progression, angiogenesis, and metastasis.[24] In contrast to neutrophils, lymphocytes function as components of host defense against tumor cells.[16] Lymphocytopenia may occur as a consequence of systemic inflammation.

High NLR and PLR levels are likely a secondary response to cancer-related inflammation.[25] This has been demonstrated in many studies.[15,16,26] NLR and PLR have also been associated with lymphatic metastasis in cancer.[27] The increase in platelet activity in patients with solid tumors has been demonstrated in previous studies.[28,29] Similarly, there is an association between increased platelet size and malignancy.[29] Mean platelet volume and platelet activity can be indirectly demonstrated. Large platelets are denser, recruit more rapidly in response to collagen, have a higher capacity for thromboxane B2 production, release more serotonin and ß-thromboglobulin, have more GPIb and GPIIb-IIIa receptors, and have higher thrombotic potential.[30] The relationship between this blood parameter and cancer is confusing in the literature.[31] Some authors have stated that high preoperative platelet counts mean a poor prognosis for patients.[32] It has been shown that platelets can interact with tumor cells, which activates platelets by releasing thrombin.[33] Angiogenesis provides oxygen and nutrients and removes toxic substances from the tumor microenvironment.[34] Studies have shown that PLR better predicts prognosis, especially in cancer patients.[35]

The retrospective nature of the study and the availability of all data from only 88 women are limitations of this study. In addition, only menopausal status was assessed in the study. Whether these parameters change with age could not be assessed because of the small size of the study group. However, this study gave us the opportunity to biochemically assess proinflammatory processes in cancer patients independent of surgery. Multicenter, larger studies are needed to provide a personalized roadmap to cancer patients in the preoperative period.

CONCLUSION

Thus, with some inexpensive, readily available tests, we can get an idea of the prognosis and stage of the disease before determining the treatment for the patient diagnosed with cancer. In this study, we have seen that we can predict the cancer stage with PDW and NLR values.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Büşra Demir Çendek, Müjde Can İbanoğlu;* ***Design:*** *Büşra Demir Çendek;* ***Control/Supervision:*** *Müjde Can İbanoğlu, Ayşe Filiz Yavuz;* ***Data Collection and/or Processing:*** *Büşra Demir Çendek;* ***Analysis and/or Interpretation:*** *Melahat Yıldırım;* ***Literature Review:*** *Müjde Can İbanoğlu;* ***Writing the Article:*** *Müjde Can İbanoğlu;* ***Critical Review:*** *Ayşe Filiz Yavuz;* ***References and Fundings:*** *Büşra Demir Çendek;* ***Materials:*** *Büşra Demir Çendek.*

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