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Predictive Role of Delta Neutrophil Index in Endometrial Cancer: A Promising Biomarker for Diagnosis

Endometriyal Kanserde Delta Nötrofil İndeksinin Öngörücü Potansiyeli: Tanı için Yeni Bir Biyobelirteç

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ABSTRACT

Aim: This study aimed to explore the potential of delta neutrophil index (DNI) as a predictive biomarker for the development of endometrial cancer (EC) in women with endometrial intraepithelial neoplasia (EIN).
Material and Methods: This retrospective study included 139 women diagnosed with EIN who underwent surgery between 2019 and 2022. Demographic data, medical history, and laboratory parameters, including DNI, were collected from the patients' medical records. Patients with other types of cancer, a history of steroid use, inflammatory, hematologic, or autoimmune diseases, or missing data were excluded. The patients' pathology reports were reviewed, and patients were divided into three groups by the final pathological diagnosis, benign (n=64), EIN (n=66), and EC (n=39).
Results: The mean DNI level of the EC group was found to be significantly higher than the EIN and benign groups (4.85±2.31, 2.31±0.89, 1.48±1.03, p<0.001, respectively). The optimal cut-off value of DNI was determined as 2.75% with 82.1% sensitivity and 73.8% specificity. DNI levels >2.75% were found to be associated with an 11.56-fold (95% CI: 4-59-29.09, p<0.001) increased risk of EC. Smoking and postmenopausal status were also identified as independent risk factors for EC. Patients with smoking had a 4.13-fold (95% CI: 1.54-11.01, p=0.005), and postmenopausal status had a 2.8-fold (95% CI: 1.87-9.04, p=0.034) increased risk of EC.
Conclusion: The results of this study suggest that DNI may be a useful biomarker for predicting the risk of EC. The results also confirm that smoking and postmenopausal status are independent risk factors for EC.
Keywords: Biomarker; endometrial cancer; endometrial hyperplasia.

ÖZ

Amaç: Bu çalışmanın amacı, endometriyal intraepitelyal neoplazi (EIN) tanısı almış olan kadınlarda delta nötrofil indeksi'nin (DNI) endometriyal kanser (endometrial cancer, EC) gelişimi için bir öngörücü biyobelirteç olarak potansiyelini değerlendirmektir.
Gereç ve Yöntemler: Bu retrospektif çalışmaya, 2019 ve 2022 yılları arasında EIN tanısı almış ve cerrahi geçirmiş olan 139 kadın dahil edilmiştir. Demografik veriler, tıbbi öykü ve DNI da dahil olmak üzere laboratuvar parametreleri hastaların tıbbi kayıtlarından toplanmıştır. Başka kanser türüne sahip olan hastalar, steroid kullanım öyküsü olanlar, enflamatuar, hematolojik veya otoimmün hastalığı olanlar ve eksik verisi olan hastalar çalışmadan çıkarılmıştır. Hastaların patoloji raporları incelenmiş ve hastalar nihai patoloji tanılarına göre benign (n=64), EIN (n=66) ve EC (n=39) olmak üzere üç gruba ayrılmıştır.
Bulgular: EC grubunun ortalama DNI düzeyi, EIN ve benign gruplarına göre anlamlı olarak daha yüksek bulundu (sırasıyla 4,85±2,31; 2,31±0,89 ve 1,48±1,03; p<0,001). DNI için optimal kesim değeri %82,1 sensitivite ve %73,8 spesifite ile %2,75 olarak belirlendi. DNI düzeyi >%2,75 olmanın 11,56 kat (95% GA: 4,59-29,09; p<0,001) artmış EC riski ile ilişkili olduğu bulundu. Sigara içmek ve postmenopozal durum da EC için bağımsız risk faktörleri olarak belirlendi. Sigara içen hastalarda 4,13 kat (95% GA: 1,54-11,01; p=0,005) ve postmenopozal durumda ise 2,8 kat (95% CI: 1,87-9,04; p=0,034) daha fazla EC riski vardı.
Sonuç: Bu çalışmanın sonuçları DNI'nin EC riskini öngörmede kullanılabilir bir biyobelirteç olabileceğini öne sürmektedir. Sonuçlar ayrıca sigara içmenin ve menopoz sonrası durumun da EC için bağımsız risk faktörleri olduğunu doğrulamaktadır.
Anahtar kelimeler: Biyobelirteç; endometriyal kanser; endometriyal hiperplazi.

INTRODUCTION

Endometrial cancer (EC) is one of the most common gynecologic cancers affecting women globally (1). The incidence of EC is increasing, and a significant number of deaths in women worldwide are due to this disease (2). Therefore, early diagnosis and accurate prognosis are crucial for the successful treatment of EC (3,4).

In recent years, researchers have been exploring the potential of biomarkers as a tool to improve the diagnosis and prognosis of EC. Biomarkers are measurable indicators that can be used to identify and diagnose a disease, predict its progression, and evaluate its response to treatment (5-7). One such biomarker that has shown promise in the diagnosis and prognosis of EC is delta neutrophil index (DNI) (8,9).

DNI is a laboratory parameter that measures the difference between the fraction of immature granulocytes and mature granulocytes in the bloodstream (8-10). DNI is a sensitive marker of systemic inflammation and infection and has been shown to be a promising prognostic biomarker in various cancers, including EC (10-14).

Furthermore, DNI can be used as a predictive biomarker for the development of EC in women with endometrial hyperplasia. In our study, it was aimed to explore the predictive role of DNI in EC.

MATERIAL AND METHODS

This retrospective study examined the data of 169 female patients diagnosed with endometrial intraepithelial neoplasia (EIN) who underwent surgery at Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital between January 2019 and December 2022. Ethical approval was obtained from the local institutional review board of Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital (10.08.2022, 103), and the study was conducted in accordance with the Declaration of Helsinki. Measures were taken to ensure patient confidentiality and privacy throughout the study. Demographic data, medical history, and laboratory parameters including DNI were collected from the medical files of the patients who underwent surgery for EIN. The DNI was measured from the complete blood count (CBC) test results prior to surgery to minimize any potential confounding factors. The DNI was calculated as the difference between the fraction of immature granulocytes (bands and metamyelocytes) and mature granulocytes (segmented neutrophils). Patients who had a history of cancer other than EC, a history of steroid use, inflammatory, hematologic, or autoimmune diseases, or had missing data in their medical records were excluded from the study. Patients' pathology reports were reviewed, and the final pathological diagnosis was classified as benign, EIN, or EC, based on the World Health Organization (WHO) criteria. Patients were divided into three groups as benign (n=64, 37.8%), EIN (n=66, 39%), and EC (n=39, 23.2%), according to the final pathologic findings.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics v.25.0 software (IBM Corporation, Armonk, NY, USA). The normality of the data was assessed visually by histogram and with Skewness and Kurtosis values. The mean and standard deviation (SD) were calculated for continuous variables, and the frequencies and percentages were calculated for categorical variables. The ANOVA test was used to examine group differences. Post-hoc multiple comparison tests, such as Bonferroni and Tukey correction, were conducted to identify specific group differences if a significant overall difference was found. The Kruskal-Wallis test and chi-square test were used to compare continuous and categorical variables, respectively. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value, sensitivity, specificity, and the area under the curve (AUC) for DNI in predicting EC. Univariate logistic regression analysis was performed to determine the independent risk factors for EC. After univariate analysis, a model for multivariate logistic regression analysis was formed. 95% confidence interval (CI) and a p value of <0.05 were considered significant.

RESULTS

The comparison of demographic, clinical, and blood outcomes of the three groups was shown in Table 1. Age and body mass index (BMI) were found significantly different among the groups (p<0.001, and p=0.003, respectively). There was also a statistically significant difference in smoking status (p=0.001), and menopausal status (p=0.018).

Table 1. Comparison of demographic and clinical characteristics of the groups

	Benign (n=64)	EIN (n=66)	Malign (n=39)	p
Age (year), mean±SD	47.40±6.54[a]	48.72±8.00[a,b]	54.30±9.25[c]	**<0.001**
Body mass index (kg/m^2), mean±SD	29.65±3.68[a]	31.28±4.24[a,b]	32.76±5.70[b,c]	**0.003**
Gravidity, median (range)	3 (0-7)	3 (0-12)	3 (0-9)	0.059
Parity, median (range)	2 (0-6)	2 (0-7)	2 (0-7)	0.085
Endometrial thickness (mm), mean±SD	10.09±5.27	11.51±5.79	12.61±7.72	0.116
Preoperative leukocyte (x1/μL), mean±SD	7.55±2.16	7.64±2.53	7.35±1.96	0.817
Preoperative hemoglobin (x1/μL), mean±SD	12.03±1.81[a]	12.61±1.60[a,b]	13.00±1.89[b,c]	**0.020**
Preoperative platelet (x1/μL), mean±SD	291.92±82.92[a]	264.93±50.52[a,b]	327.69±63.11[c]	**<0.001**
Delta neutrophil index (%), mean±SD	1.48±1.03[a]	2.31±0.89[b]	4.85±2.31[c]	**<0.001**
Smoking, n (%)	5 (7.8)[a]	9 (13.6)[b]	14 (35.9)[c]	**0.001**
Postmenopausal, n (%)	13 (20.3)[a]	18 (27.3)[b]	18 (46.2)[c]	**0.018**

EIN: endometrial intraepithelial neoplasia, SD: standard deviation, [a,b,c]: groups with different letters are significantly different from each other

Preoperative hemoglobin (p=0.020), preoperative platelet count (p<0.001), and DNI levels (p<0.001) were significantly different among the groups. The highest values were observed in the cancer group and this difference was statistically significant (Table 1).

The optimal predictive value of DNI was calculated using ROC curve analysis (Figure 1). The cut-off value was calculated to be 2.75%, and AUC was 0.894 with 82.1% sensitivity and 73.8% specificity.

Patients were divided into two groups based on the cut-off value of DNI, median age, and BMI. Univariate logistic regression analyses revealed that age >48 years had 2.51 fold (95% CI: 1.22-5.17, p=0.012), DNI level >2.75% had 10.44 fold (95% CI: 4.52-24.12, p<0.001), being a smoker had 4.87 fold (95% CI: 2.07-11.43, p<0.001) and menopause had 2.67 fold (95% CI: 1.28-5.55, p=0.009) increased risk of having EC. After univariate logistic regression analyses, the multivariate logistic regression model was created. While patients with DNI >2.75% had an 11.56-fold (95% CI: 4.59-29.09, p<0.001) increased risk of having EC, patients who were postmenopausal had a 2.8-fold (95% CI: 1.87-9.04, p=0.034) and patients who smoke had a 4.13-fold (95% CI: 1.54-11.01, p=0.005) increased risk of having EC (Table 2).

DISCUSSION

In our study, we investigated the use of DNI as a potential biomarker for EC. The ability to diagnose EC is essential for timely and effective treatment. Our results showed that patients with high DNI levels had a significantly increased risk of EC, with an odds ratio of 11.5.

Our study also identified smoking status and menopausal status as independent risk factors for EC. These findings are consistent with previous research linking these factors to increased risk of EC and suggest that these factors should be considered when assessing a patient's risk of developing EC (15-18). Lou et al. (15) reported that preoperative-EIN patients who are postmenopausal or have an elevated level of CA125 may have a higher risk of concurrent EC. According to the Danish Gynecological Cancer Database (16), postmenopausal women have an almost 3-fold higher risk of final diagnosed EC compared with the premenopausal group, with 80% of postmenopausal women being affected. A systematic review that included 13 studies has shown women who were postmenopausal and smoking more than 15 cigarettes daily have higher circulating levels of estradiol than nonsmoker women (17). In contrast to these findings in the observational analysis, smoking was found associated with a low risk of EC (18).

The use of biomarkers, such as DNI, may have several clinical implications for the diagnosis and management of various cancers. According to Bozan et al. (13), DNI had a sensitivity of 86.5% and specificity of 80.4%, and the immature granulocyte (IG) count had 100% sensitivity and 82.6% specificity in detecting axillary metastasis of breast cancer. The study suggests that to detect axillary metastasis of breast cancer DNI and IG count may be helpful.

In another study, which evaluated the relationship between DNI and neutrophil-to-lymphocyte ratio (NLR) in the preoperative differentiation of benign and malign thyroid neoplasms, preoperative NLR, DNI, and IG count were found to be statistically significant between benign and malignant groups (19). Additionally, DNI levels were compared between patients with renal cell carcinoma and healthy individuals, and DNI and NLR were found to be predictors of renal cell carcinoma (14). It is important to note that different threshold values have been found for DNI in these studies, which can be attributed to the fact that different types of diseases have been examined. In our study, a DNI level >2.75% was the strongest independent risk factor for EC. Preoperative DNI may be used to identify patients who are at high risk of developing EC and who may benefit from more frequent screening or prophylactic measures such as chemoprevention. DNI may also be useful in monitoring the progression and response to treatment in patients with EC.

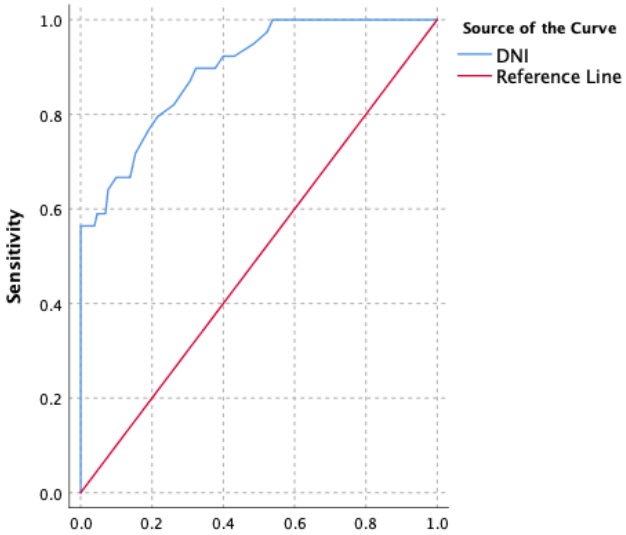

Figure 1. Receiver operating characteristics curve of delta neutrophil index for predictability of endometrial cancer

Table 2. Univariate and multivariate logistic regression analysis of the variables for endometrial cancer

	Univariate			Multivariate		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (>48 years)	2.51	1.22-5.17	**0.012**	-		-
BMI (>30.82 kg/m^2)	1.87	0.91-3.82	0.085	-		-
DNI (>2.75%)	10.44	4.52-24.12	**<0.001**	11.56	4.59-29.09	**<0.001**
Smoking	4.87	2.07-11.43	**<0.001**	4.13	1.54-11.01	**0.005**
Menopause	2.67	1.28-5.55	**0.009**	2.80	1.87-9.04	**0.034**

BMI: body mass index, DNI: delta neutrophil index, OR: odds ratio, CI: confidence interval

Our study has several limitations, including the relatively small sample size and the retrospective nature of the study design. The inclusion of patients who underwent surgery for EIN may introduce selection bias and single-center conduction may limit generalizability. On the other hand, the study explores the potential of a novel biomarker (DNI) for the diagnosis of EC, which could have significant clinical implications.

CONCLUSION

DNI may be a useful biomarker for predicting the risk of EC. Our results also confirm smoking and postmenopausal status as independent risk factors for EC, consistent with previous research. Further studies are needed to support the use of DNI as a biomarker for EC.

Ethics Committee Approval: The study was approved by the Ethics Committee of the Etlik Zübeyde Hanım Women's Health Training and Research Hospital (10.08.2022, 103).

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REFERENCES

1. Hecht JL, Ince TA, Baak JP, Baker HE, Ogden MW, Mutter GL. Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. Mod Pathol. 2005;18(3):324-30.
2. Weiderpass E, Antoine J, Bray FI, Oh JK, Arbyn M. Trends in corpus uteri cancer mortality in member states of the European Union. Eur J Cancer. 2014;50(9):1675-84.
3. Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, et al. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. Cancer. 2005;103(11):2304-12.
4. Auclair MH, Yong PJ, Salvador S, Thurston J, Colgan TTJ, Sebastianelli A. Guideline No. 390-classification and management of endometrial hyperplasia. J Obstet Gynaecol Can. 2019;41(12):1789-800.
5. Weis SM, Cheresh DA. Tumor angiogenesis: molecular pathways and therapeutic targets. Nat Med. 2011;17(11):1359-70.
6. Shiao SL, Ganesan AP, Rugo HS, Coussens LM. Immune microenvironments in solid tumors: new targets for therapy. Genes Dev. 2011;25(24):2559-72.
7. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99.
8. Kratz A, Maloum K, O'Malley C, Zini G, Rocco V, Zelmanovic D, et al. Enumeration of nucleated red blood cells with the ADVIA 2120 Hematology System: an International Multicenter Clinical Trial. Lab Hematol. 2006;12(2):63-70.
9. Nahm CH, Choi JW, Lee J. Delta neutrophil index in automated immature granulocyte counts for assessing disease severity of patients with sepsis. Ann Clin Lab Sci. 2008;38(3):241-6.
10. Bhansaly P, Mehta S, Sharma N, Gupta E, Mehta S, Gupta S. Evaluation of immature granulocyte count as the earliest biomarker for sepsis. Indian J Crit Care Med. 2022;26(2):216-23.
11. Güler Ö, Bozan MB, Alkan Baylan F, Öter S. The utility of immature granulocyte count and percentage on the prediction of acute appendicitis in the suspected acute appendicitis according to the Alvarado scoring system: a retrospective cohort study. Turk J Gastroenterol. 2022;33(10):891-8.
12. Shin IS, Gong SC, An S, Kim K. Delta neutrophil index as a prognostic factor for mortality in patients with Fournier's gangrene. Int J Urol. 2022;29(11):1287-93.
13. Bozan MB, Yazar FM, Kale IT, Topuz S, Bozan AA, Boran OF. Immature granulocyte count and delta neutrophil index as new predictive factors for axillary metastasis of breast cancer. J Coll Physicians Surg Pak. 2022;32(2):220-5.
14. Barut O, Demirkol MK, Kucukdurmaz F, Sahinkanat T, Resim S. Pre-treatment delta neutrophil index as a predictive factor in renal cell carcinoma. J Coll Physicians Surg Pak. 2021;31(2):156-61.
15. Lou Y, Liao J, Shan W, Xu Z, Chen X, Guan J. Menopausal status combined with serum CA125 level significantly predicted concurrent endometrial cancer in women diagnosed with atypical endometrial hyperplasia before Surgery †. Diagnostics (Basel). 2021;12(1):6.
16. Antonsen SL, Ulrich L, Høgdall C. Patients with atypical hyperplasia of the endometrium should be treated in oncological centers. Gynecol Oncol. 2012;125(1):124-8.
17. Endogenous Hormones and Breast Cancer Collaborative Group; Key TJ, Appleby PN, Reeves GK, Roddam AW, Helzlsouer KJ, Alberg AJ, et al. Circulating sex hormones and breast cancer risk factors in postmenopausal women: reanalysis of 13 studies. Br J Cancer. 2011;105(5):709-22.
18. Dimou N, Omiyale W, Biessy C, Viallon V, Kaaks R, O'Mara TA, et al. Cigarette smoking and endometrial cancer risk: observational and Mendelian randomization analyses. Cancer Epidemiol Biomarkers Prev. 2022;31(9):1839-48.
19. Bozan MB, Yazar FM, Kale İT, Yüzbaşıoğlu MF, Boran ÖF, Azak Bozan A. Delta neutrophil index and neutrophil-to-lymphocyte ratio in the differentiation of thyroid malignancy and nodular goiter. World J Surg. 2021;45(2):507-14.