ORIGINAL ARTICLE

Relationship between endometrial thickness and neutrophil/lymphocyte ratio with endometrial malignancy in 386 postmenopausal uterine bleeding cases

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Abstract

Introduction: In our study, endometrial thickness with neutrophil/lymphocyte ratio and endometrial sampling results were compared in terms of outcome in women with postmenopausal bleeding. In addition, we aimed to determine the predictive value of endometrial thickness and neutrophil/lymphocyte ratio for predicting endometrial carcinoma.

Material and methods: Our single-centered study was performed retrospectively. The study included 386 postmenopausal women admitted to our gynecology outpatient clinic for abnormal uterine bleeding between January 2015 and June 2017 and subjected to endometrial sampling.

Results: The mean endometrial thickness for endometrial hyperplasia was calculated as 13 mm (min. 4 mm, max. 20 mm) and for endometrial carcinoma 17.19 mm (min. 8 mm, max. 27 mm). The neutrophil count and neutrophil/lymphocyte ratio (NLR) were significantly higher and the lymphocyte count was lower in the group with endometrial malignancy ($p = 0.002$, $p < 0.001$ and $p = 0.011$, respectively). None of the patients with endometrial thickness < 8 mm received an endometrial carcinoma diagnosis. The optimal cut-off value of endometrial thickness for detecting endometrial carcinoma was ≥ 13.50 mm, at which the sensitivity was 75% and specificity was 83.6%. The optimal cut-off value of NLR for detecting endometrial carcinoma was ≥ 2.20, at which the sensitivity was 81.3% and specificity was 60.5%.

Conclusions: Co-evaluation of NLR with endometrial thickness determined by transvaginal sonography might be useful for predicting endometrial carcinoma.

Key words: endometrial cancer, endometrial thickness, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, postmenopausal uterine bleeding.

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Introduction

Abnormal uterine bleeding appears to be one of the most common gynecological problems affecting the quality of life of women [1]. The approach to this clinical problem that arises as a result of structural or functional pathologies of the endometrium varies according to whether the patient is in the pre-, peri-, or postmenopausal period [2, 3]. Endometrial cancer should be suspected especially in a woman with abnormal uterine bleeding during the postmenopausal period. The presence of abnormal uterine bleeding increases the endometrial cancer incidence about 10-fold in the postmenopausal period [2, 3].

Endometrium is a readily available tissue for histopathological evaluation in women who describe abnormal uterine bleeding. The diagnostic approach to women with abnormal bleeding has evolved over the years, from dilatation and curettage (D + C) in operating room conditions, to vacuum-aspiration curettage and Pipelle plastic catheter curettage in outpatient clinics [3–5]. Evaluation of the endometrium with transvaginal sonography has recently emerged as the imaging method used to investigate abnormal uterine bleeding. In postmenopausal women, ≤ 4 mm endometrial thickness has a negative predictive value of 99% for endometrial cancer [6–8]. Above 4 mm endometrial thickness is a nonspecific finding and may be associated with endometrial polyp, submucous myomas or endometrial hyperplasia [9–13].

Although inflammation is known to play a critical role in the etiopathogenesis of cancer by many pathways such as initiation, progression and metastasis, the underlying mechanism between chronic inflammation and cancer has not yet been fully elucidated [14–17]. Tumor cells weaken the immune system and accelerate the inflammatory process. This leads to tumor growth and progression of inflammation. Considering this vicious circle between inflammation and cancer, many systemic inflammatory markers have recently been investigated in relation to malignancies. There are very few studies in the literature that examine the relationship between cancerous and precancerous endometrial pathologies and white blood cells, lymphocytes, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) [18–20].

There are studies that relate endometrial sampling results in postmenopausal uterine bleeding to endometrial thickness and complete blood count parameters separately. In our study, we evaluated both endometrial thickness and complete blood count parameters with NLR for the same patients and compared them with endometrial sampling results. Additionally, we aimed to determine the predictive value of endometrial thickness and NLR for predicting endometrial carcinoma.

Material and methods

Our single-centered and retrospective study was conducted between January 2016 and July 2017 with patients who were admitted to Bursa Yuksek Ihtisas Research and Training Hospital with postmenopausal bleeding and underwent endometrial sampling. Hematologic diseases, all types of malignancy, diabetes, hepatic diseases, hypertension, autoimmune diseases, infectious diseases and inflammatory diseases were accepted as criteria for exclusion and 386 postmenopausal women who met the appropriate criteria were included in the study.

Demographic data such as age, gravida, parity, height, weight, and clinical data from endometrial sampling results, transvaginal ultrasonography findings (endometrial thickness) and complete blood count results were obtained from medical records. Body mass index (BMI) was calculated using height and weight parameters.

Menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause.

All patients underwent routine gynecological examination by the same clinician, including vaginal ultrasonography with a 6.5 MHz vaginal transducer (model EUB-415: Hitachi Medical Corp., Tokyo, Japan). NLR and PLR were calculated from the same blood samples.

Ethical approval

All procedures performed in studies 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.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Statistical analysis was performed with SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to verify whether the variables follow a normal distribution or not. Variables were presented as mean ± standard deviation. While parametric tests were used for normally distributed variables, nonparametric tests were used for non-normally distributed ones. For group comparisons, the independent t test or Mann-Whitney U test was used according to normality of the test results. A logistic regression analysis was performed to assess the risk of endometrial carcinoma. We calculated odds ratios (ORs) with respective 95% CIs. P-values were obtained for each variable to determine statistical significance, with $p < 0.05$ considered significant. Receiver operating curve (ROC) analysis was used to determine the predictive role of endometrial thickness and NLR for endometrial cancer. A p-value < 0.05 was considered as statistically significant.

Results

The mean age of the study population was 56.99 (min. 41; max. 82) and the mean BMI was 30.79 kg/m² (min. 19.3, max. 48.9). The demographic characteristics of the subjects and endometrial sampling results are presented in Table 1.

The most common endometrial pathology in the study population was endometrial polyp (n = 122; 11.2%). Endometrial cancer was detected in 32 (3%) patients. Of these, 2 were diagnosed with clear cell carcinoma and 30 were diagnosed with endometrioid adenocarcinoma. Patients in the study group were divided into two subgroups, malignant (n = 32) and benign (n = 354). The demographic and clinical characteristics of the subgroups and the laboratory parameters are presented in Table 2. Age and parity were significantly higher in patients with an endometrial carcinoma diagnosis. In addition, endometrial thickness was also found to be statistically higher in the malignant group compared to the benign group (17.19 (min. 8; max. 27), 8.67 (min. 1; max. 22) respectively and p < 0.001). When the laboratory parameters were examined, it was determined that neutrophil count and NLR were significantly higher and lymphocyte count was significantly lower in the malignant group (p = 0.002, p < 0.001 and p = 0.011, respectively).

Logistic regression analysis was performed to evaluate the independent predictors of endometrial carcinoma in postmenopausal women. In multivariate regression analysis, after adjusting for other confounding factors, age, endometrial thickness and NLR were found to be independent predictors of endometrial cancer (Table 3).

We also evaluated the endometrial thickness according to endometrial sampling results. The mean endometrial thickness was 7.07 mm (min. 3; max. 19) for nonspecific endometrium; 13 mm (min. 4; max. 20) for hyperplasia; 10.43 mm (min. 3; max. 22) for endometrial polyp; 7.24 mm (min. 1; max. 18) for a nondiagnostic result and 17.19 mm

Table 1. Characteristics and endometrial sample results of the study population

Parameter	Postmenopausal (N = 386) Mean (min.–max.)
Age [years]	56.99 (41–82)
Parity, n (%):	
Nullipara	8 (0.7)
Primipara	18 (1.7)
Multipara	360 (33.1)
Body mass index [kg/m²]	30.79 (19.3–48.9)
Endometrial thickness [mm]	9.37 (1–27)
Endometrial sampling histopathology, n (%):	12 (3.1)
Secretory endometrium	62 (16.1)
Proliferative endometrium	54 (14)
Atrophic endometrium	6 (1.6)
Chronic endometritis	122 (31.6)
Endometrial polyp	12 (3.1)
Simple hyperplasia without atypia	4 (1)
Simple hyperplasia with atypia	2 (0.5)
Complex hyperplasia without atypia	6 (1.6)
Complex hyperplasia with atypia	30 (7.8)
Endometrioid adenocarcinoma	2 (0.5)
Clear cell adenocarcinoma Nondiagnostic	74 (19.2)
Total	386 (100)

Table 2. Clinical and laboratory parameters of benign and malign group

Parameter	Benign group (n = 354) Mean (min.–max.)	Malign group (n = 32) Mean (min.–max.)	P-value
Age [years]	56.25 (41–82)	65.19 (53–76)	< 0.001*
Gravida	3.58 (0–10)	3.69 (2–7)	0.357
Parity	3.03 (0–10)	3.44 (2–7)	< 0.029*
Body mass index [kg/m²]	30.69 (19.3–48.9)	31.97 (21.5–41.7)	0.083
Endometrial thickness [mm]	8.67 (1–22)	17.19 (8–27)	< 0.001*
WBC [× 10³/mm³]	7688.14 (3600–19200)	9193.75 (5600–26000)	0.118
Hgb [g/dl]	12.31 (5.7–15.4)	12.10 (8.9–14.2)	0.354
Hct (%)	37.04 (20.4–45.2)	36.41 (27.2–41.9)	0.433
MPV [fl]	8.63 (6.4–11.5)	8.78 (7.3–11.6)	0.837
PCT (%)	0.23 (0.08–0.55)	0.2400 (0.14–0.47)	0.612
PDW (%)	16.62 (15.5–26.6)	16.68 (15.9–17.8)	0.226
Platelet count [× 1000/mm²]	277.08(103–576)	273.06 (160–518)	0.485
Neutrophil count [× 1000/mm²]	4.73 (1.6–17.1)	6.72 (3.6–25)	0.002*
Lymphocyte count [× 1000/mm²]	2.16 (0.3–5)	1.81 (0.4–3.2)	0.011*
NLR	2.74 (0.77–29.33)	6.85 (1.5–62.5)	< 0.001*
PLR	145.25 (49.50–463.33)	182.85 (50–600)	0.052

WBC – white blood cell, Hgb – hemoglobin, Htc – hematocrit, MPV – mean platelet volume, PCT – platecrit, PDW – platelet distribution width, NLR – neutrophil lymphocyte ratio, PLR – platelet lymphocyte ratio, *p-value of < 0.05 was considered significant (*).

Table 3. Logistic regression assessing independent predictors of endometrial malignancy in menopausal women

Parameter	OR	95% C.I. for exp(B)		P-value
		Lower	Upper	
Age	1.115	1.071	1.162	< 0.001*
Endometrial thickness	1.374	1.255	1.505	< 0.001*
BMI	1.057	0.981	1.139	0.145
NLR	1.073	1.019	1.129	0.007*

Results of multivariate binary logistic regression analysis are presented. OR – odds ratio; CI – confidence interval; a p-value of < 0.05 was considered significant (*).

Table 4. Mean endometrial thickness for each histopathological result

Endometrial sampling histopathology	Endometrial thickness (min.–max.) [mm]
Nonspecific endometrium	7.07 (3–19)
Hyperplasia	13 (4–20)
Polyp	10.43 (3–22)
Nondiagnostic	7.24 (1–18)
Cancer	17.19 (8–27)

(min. 8; max. 27) for endometrial cancer in postmenopausal women (Table 4). The effect of endometrial thickness for detecting endometrial carcinoma was evaluated by the ROC curve. The area under the ROC curve was 0.891 (95% CI: 0.841–0.941, p < 0.001) for endometrial thickness (Figure 1). Sensitivity of endometrial thickness was 75% and specificity was 83.6% at a threshold ≥ 13.50 mm. The effect of NLR for detecting endometrial carcinoma was evaluated by the ROC curve (Figure 2). The area under the ROC curve was 0.712 (95% CI: 0.627–0.797, p < 0.001) for NLR. The optimal cut-off value of NLR for detecting endometrial carcinoma was ≥ 2.20, at which the sensitivity was 81.3% and specificity was 60.5%.

Discussion

Abnormal uterine bleeding appears to be one of the most common gynecological problems affecting women's quality of life, especially in the postmenopausal period [1]. The diagnostic approach to women with abnormal bleeding has evolved over the years, from dilatation and curettage (D + C) in operating room conditions, to vacuum-aspiration curettage and Pipelle plastic catheter curettage in outpatient clinics [3, 5]. Pipelle biopsy is always preferred for initial assessment of women with suspicious bleeding for malignancy [21]. However, if sampling techniques fail to provide ade-
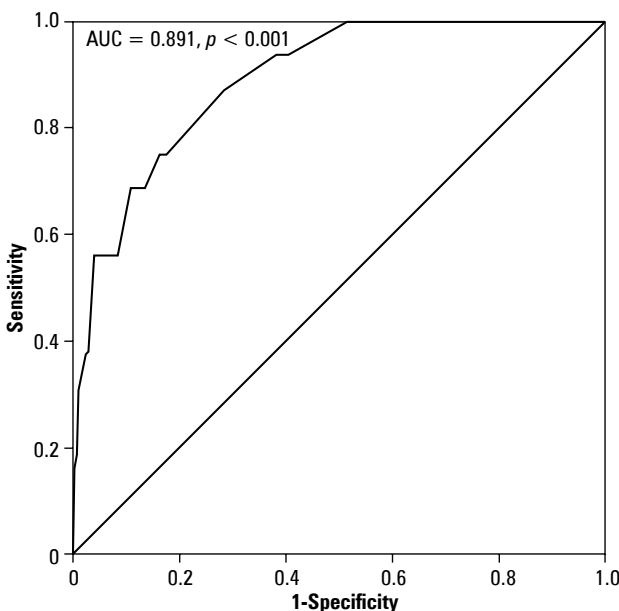

Figure 1. Receiver operating characteristic (ROC) curve for endometrial thickness for the prediction of endometrial malignancy. The estimate of the area under the ROC curve and its 95% confidence interval is shown. Cut-off value of endometrial thickness was ≥ 13.50 mm (sensitivity 75% and specificity 83.6%) for prediction of endometrial malignancy

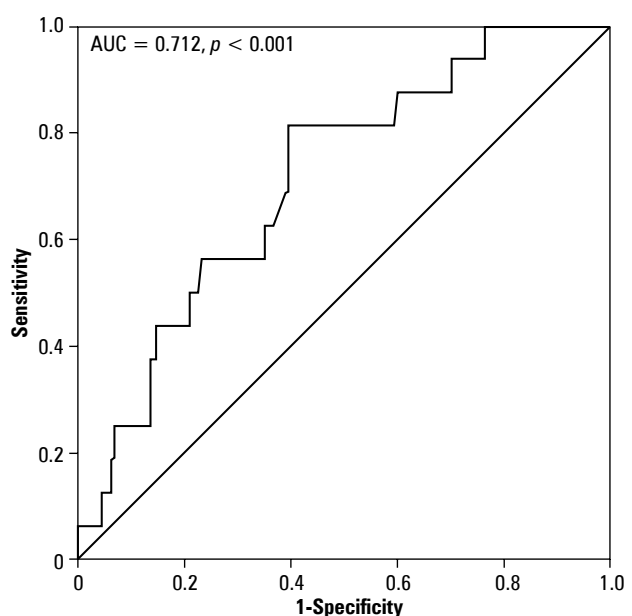AUC – area under curve, p-value of < 0.05 was considered significant (*).

Figure 2. Receiver operating characteristic (ROC) curve for NLR for the prediction of endometrial malignancy. The estimate of the area under the ROC curve and its 95% confidence interval is shown. Cut-off value of NLR was ≥ 2.20 (sensitivity 81.3% and specificity 60.5%) for prediction of endometrial malignancy

AUC – area under curve, p-value of < 0.05 was considered significant (*).

quate diagnostic evaluation or if abnormal uterine bleeding continues, D + C may be required to ascertain the diagnosis [22]. Nevertheless, recent studies on Pipelle biopsy and D + C results revealed different histopathologic results. In their study, Conoscenti *et al.* reported 6.7% endometrial hyperplasia without atypia, 2.7% endometrial hyperplasia with atypia, and 10.7% endometrial cancer in postmenopausal women with abnormal uterine bleeding [23]. Cho *et al.* reported that proliferative endometrium was found in 17.8%, secretory endometrium in 7.4%, endometritis in 6.7% and atrophic endometrium in 32% of patients among 163 postmenopausal women. In the same study, the frequency of endometrial polyp was found to be 9.2%, of endometrial hyperplasia 10.4%, and of endometrial cancer 10.4% [24]. In our study with 386 postmenopausal women, we found the frequency of 16.1% for proliferative endometrium and 3.1% for secretory endometrium. In addition, rates of 1.6% endometritis, 31.6% endometrial polyp, 14% atrophic endometrium and 6.2% endometrial hyperplasia were detected in our study group. Of the 386 postmenopausal women included in the study, 8.3% were diagnosed with endometrial cancer. We suggest that the distribution of pathology results may vary according to demographic characteristics, ethnicity, dietary habits, and endometrial sampling standards.

Some studies suggest that inflammation may play a role in the etiopathogenesis of endometrial cancer [14, 15, 18]. In recent studies, some inflammatory markers have been investigated [18–20]. Ural *et al.* reported that NLR and platelet distribution width (PDW) were found to be higher in endometrial cancer [20]. Similar to this study, Acmaz *et al.* reported that NLR is higher in endometrial cancer. They also found that PLR and white blood count (WBC) are higher in endometrial cancer [19]. Contrary to these studies, Kurtoglu *et al.* demonstrated no difference for PLR, NLR and WBC between benign and malignant groups in their study [18]. Cakmak *et al.* examined these parameters for endometrial hyperplasia with and without atypia and they reported higher NLR and PLR values in hyperplasia with atypia [25]. On the other hand, our study also showed that the NLR values were higher in the malignant subgroup. Similar to the study by Kurtoglu *et al.*, we also did not find a significant difference between the benign and malignant subgroups in terms of PLR values. Our study also demonstrated that NLR may be associated with endometrial cancer, paralleling other studies of the subject with ≥ 2.20 cut-off value for NLR. The low number of patients in our malignant subgroup is considered a limitation of the study, and larger studies may lead to more powerful outcomes than ours.

Evaluation of the endometrium with transvaginal sonography has recently emerged as the imaging method used to investigate abnormal uterine bleeding. In postmenopausal women, ≤ 4 mm endometrial thickness has a negative predictive value of 99% for endometrial cancer [6, 8]. Above 4 mm endometrial thickness is a nonspecific finding and may be associated with endometrial polyp, submucous myomas or endometrial hyperplasia [9–12]. Recently, endometrial thickness determination with transvaginal ultrasound has been established in our daily practice to predict

endometrial pathologies, and has become one of the investigated topics, especially in endometrial cancer-related studies. Conoscenti *et al.*, for example, found that endometrial thickness is higher in premalignant and malignant endometrial pathologies than in benign lesions [23]. Güner *et al.* found an endometrial thickness average of 22.7 mm for endometrial cancer and did not encounter malignant endometrial pathologies in subjects with endometrial thickness < 8 mm [10]. Another study found that endometrial thickness determined by transvaginal ultrasonography has 92.3% sensitivity and 95% specificity for endometrial cancer detection in cases with endometrial thickness ≥ 19.50 mm [13]. In our study, we found that endometrial thickness increased in malignant endometrial pathologies, and we did not encounter endometrial carcinoma in cases where the endometrial thickness was < 7 mm. The ROC analysis of our study showed that the sensitivity of endometrial thickness for detecting endometrial carcinoma was 75% and specificity was 83.6% at a threshold ≥ 13.50 mm.

Conclusions

Endometrial thickness is increased in malignant endometrial pathologies and NLR levels show a significant increase in endometrial cancer. Co-evaluation of NLR with endometrial thickness determined by transvaginal sonography might be useful for predicting endometrial carcinoma. Further studies with a larger number of participants are required in order to obtain more precise results.

Conflict of interest

The authors declare no conflict of interest.

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