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Platelet to lymphocyte and neutrophil to lymphocyte ratios in endometrial pathologies

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ABSTRACT

Objectives: Aim of this study was to evaluate the relationship between platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and endometrial pathologies.

Material and methods: The database of our institution was reviewed. Cases with endometrial pathology including endometrial cancer (EC), endometrial hyperplasia with atypia and without atypia, normal endometrial findings, between January 2015 to January 2020, were collected. Their CBC results and clinicopathologic data were determined. The relation between the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and endometrial pathologies was evaluated.

Results: NLR was significantly higher in patients with endometrial cancer compared to other endometrial pathologies including endometrial hyperplasia with and without atypia and patients with normal endometrial findings. NLR cut-off value was determined 3.55 to discriminate cancer among other endometrial pathologies. PLR had not a significant difference between the endometrial pathologies.

Conclusion: NLR seems to be an effective and simple marker to discriminate endometrial cancer among endometrial pathologies by contrast with PLR.

Key words: neutrophil to lymphocyte ratio; platelet to lymphocyte ratio; endometrial cancer; endometrial pathologies

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INTRODUCTION

Inflammation and related parameters have a crucial role in cancer development and spread [1]. Relation between inflammation and cancer is a focused issue for investigators to explain the interaction between them. However, precise pathophysiologic mechanisms have not been definitely determined yet. It is a well-known fact that there is mutual induction between cancer and inflammation [2]. Endometrial hyperplasia (EH) which is usually a result of continuous unopposed estrogen exposure is a predisposing factor for the development of endometrial carcinoma (EC) with rates of up to 30% [3]. Relation between inflammation markers and cancer progression was investigated previously in different studies. Neutrophil-lymphocyte ratio (NLR) was determined as an inflammation marker. Increased neutrophil to lymphocyte ratio was found to be related to worse overall-survival in EC and malign mesothelioma patients [4, 5]. Platelet-lymphocyte ratio (PLR) is another parameter that was used to evaluate the prognosis of certain cancer types including colorectal and EC [4, 6]. Hereby, a cheap, easy, simple, and reproducible marker is a need to distinguish the endometrial pathologies including normal, hyperplasia without atypia, hyperplasia with atypia, and endometrial cancer. To our knowledge, there has not been any study that aims to distinguish all four endometrial pathologies by using all three parameters including NLR and PLR. The present study aims to investigate the association between NLR, PLR, and endometrial pathologies.

MATERIAL AND METHODS

Study population

Clinicopathological data of the patients with the diagnosis of EC, EH (with and without atypia), normal endometrial results (proliferative, endometrium, secretuar endometrium, atrophic endometrium, endometrial cells) as a result of endometrial biopsy who applied to the Dokuz Eylul University Hospital from January 2015 to January 2020 were collected from the hospital database retrospectively. The ethics committee approval was obtained for this study from the local ethics committee

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Table 1. Clinicopathologic data of the patients among groups

		Endometrial cancer	Hyperplasia with atypia	Hyperplasia without atypia	Normal endometrium	Total (n = 431)	p value
Age (mean ± SD)		58.2 ± 10.7	50.3 ± 9.3	47.9 ± 7.6	44.4 ± 6.8	50.2 ± 10.1	< 0.01*
Parity (mean ± SD)		2.2 ± 1.6	2.1 ± 1.4	2.2 ± 1.5	1.6 ± 0.9	2.0 ± 1.4	< 0.01*
Diabetes, n (%)	Absent	79 (18.3)	63 (14.6)	111 (25.8)	108 (25.1)	361 (83.8)	< 0.01*
	Present	42 (9.7)	8 (1.9)	12 (2.8)	8 (1.9)	70 (16.2)	
Family history of cancer, n (%)	No	111 (25.8)	70 (16.2)	122 (28.3)	115 (26.7)	418 (97)	< 0.01*
	Yes	10 (2.3)	1 (0.2)	1 (0.2)	1 (0.2)	13 (3)	
Menopausal status, n (%)	Pre-menopause	28 (6.5)	44 (10.2)	96 (22.3)	99 (23)	267 (61.9)	< 0.01*
	Post-menopause	93 (21.6)	27 (6.3)	27 (6.3)	17 (3.9)	164 (38.1)	

SD — standard deviation

of Dokuz Eylul University. Eligible patients had undergone detailed gynecological examination and preoperative assessment including radiological imaging, histopathological examination of endometrial biopsy, and full blood count (FBC). Patients whose FBC assessment two weeks before surgery were excluded from the study. Besides, patients with insufficient clinicopathological data, irregular follow-up information, with granulocyte colony-stimulating factor use, inflammatory disease, carcinoid tumor, other malignancies or disorders that affect hematologic parameters, or those that were given a blood transfusion during the last two weeks before the blood sampling or treated with radiotherapy and chemotherapy were excluded.

Data collection

The hospital's electronic medical record database was used to obtain patients' clinicopathological data: (i) Basic information including age, menopause age, reproductive history, and comorbidities; (ii) FBCs including neutrophil, lymphocyte, and platelet counts were expressed in $\times 10^9$/L. NLR and PLR were calculated as the absolute neutrophil, and platelet count divided by the absolute lymphocyte count, respectively. Pathologic results of the endometrial biopsies were classified by the World Health Organization 2014 classification system which divides hyperplasia into two categories defined as hyperplasia with atypia and hyperplasia without atypia.

Statistical analysis

The normality of distributions of the variables was determined by the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation whether it had a normal distribution. However, variables without normal distribution were presented as median values (minimum–maximum). Association between continuous and categorical variables was evaluated by one-way ANOVA or Kruskal-Wallis test and additionally, Mann-Whitney U test was used for further evaluation of the preliminary results. Post-hoc tests were performed to determine the group which led to statistically significant differentiation among the four groups. Univariable and multivariable analyses were used to estimate the odd's ratio (OR) and 95% confidence intervals (CIs) between variables. Receiver operating characteristics (ROC) curve analysis was used to calculate a cut-off value to distinguish groups from each other. The comparison of proportions was calculated by the Chi-square test. P value < 0.05 was considered statistically significant. All analyses were performed by using IBM SPSS Statistics Version 25.

RESULTS

The mean age of the patients was 50.2 ± 10.1 years. The mean age of the EC patients was found 58.2 ± 10.7 years. Endometrial carcinoma patients were older than the other groups of the patients ($p < 0.01$), however, no significant difference was found between hyperplasia with atypia and without atypia groups. Postmenopausal patients, family history of cancer, and diabetes were determined higher in the EC patients as expected ($p < 0.01$; $p < 0.01$; $p < 0.01$, respectively). Clinicopathologic data of the patients were summarized in Table 1.

Median neutrophil to lymphocyte ratio of endometrial cancer, hyperplasia with atypia, hyperplasia without atypia, and patients with normal endometrial findings groups were 2.4 (0.7–12.2), 2.1 (0.01–18), 2.1 (0.1–148), and 2 (0.4–6); respectively. The neutrophil to lymphocyte ratio was found significantly higher in the endometrial cancer patients rather than other groups of the patients ($p = 0.04$). Receiver operating characteristics (ROC) curve analysis was performed to determine the cut-off value for the NLR. Neutrophil-lymphocyte ratio cut-off value to distinguish endometrial carcinoma among endometrial pathologies was determined 3.55 with the highest Youden index [likelihood ratio (LR) = 2.65] (area under the curve, AUC = 0.587) (Fig. 1). Median platelet to lymphocyte ratio of endometrial cancer, hyperplasia with atypia, hyperplasia without atypia, and patients with normal endometrial findings groups were 137.6 (54.2–476.6), 126.8 (37.5–391.8), 125.2 (55.1–626), and 133.8 (15.5–363.9), respectively. There was no significant

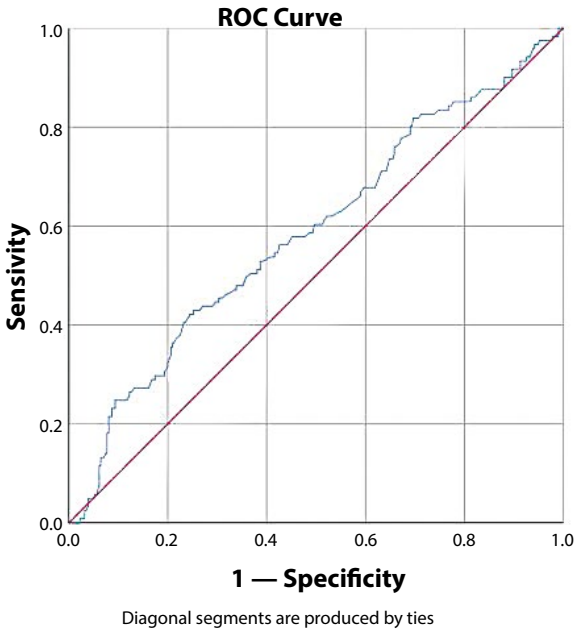

Figure 1. Receiver operating characteristics (ROC) curve analysis of the NLR for endometrial cancer in endometrial pathologies; NLR — neutrophil to lymphocyte ratio

difference between groups in terms of PLR (p = 0.84). Associations between NLR, PLR, and endometrial pathologies were summarized in Table 2. Besides, endometrial pathologies were divided into subgroups by histopathological tumor grade and The International Federation of Gynecology and Obstetrics (FIGO) staging in itself, then compared with non-cancerous pathologies including EH (with or without atypia) and normal endometrial results in terms of NLR and PLR. It was found that grade 1 and grade 3 EC patients had significantly higher NLR compared to patients with non-cancerous endometrial pathologies including EH (with or without atypia), and normal endometrial findings (p = 0.04). On the other hand, there was no significant difference between the EC subgroups by tumor grade and non-cancerous endometrial pathology groups in terms of PLR (p = 0.84) (Tab. 3). In addition, no significant difference was detected between EC subgroups by FIGO staging and non-cancerous endometrial pathology groups in terms of NLR and PLR (p = 0.09; p = 0.91, respectively) (Tab. 4).

Table 5 shows the univariate and multivariate analysis of the factors associated with endometrial cancer. In the multivariate analysis, the ORs of the NLR, and PLR were 0.9 (95%

Table 2. Neutrophil to lymphocyte and platelet to lymphocyte ratios of the patients

	Endometrial cancer (n = 121)	Hyperplasia with atypia (n = 71)	Hyperplasia without atypia (n = 123)	Normal endometrium (n = 116)	p value
Neutrophil-lymphocyte ratio, median (range)	2.4 (0.7–12.2)	2.1 (0.01–18)	2.1 (0.1–148)	2 (0.4–6)	0.04*
Platelet-lymphocyte ratio, median (range)	137.6 (54.2–476.6)	126.8 (37.5–391.8)	125.2 (55.1–626)	133.8 (15.5–363.9)	0.84

Table 3. Neutrophil to lymphocyte and platelet to lymphocyte ratios of the patients (EC patients divided into three groups by tumor grade)

	Grade 1 — EC (n = 36)	Grade 2 — EC (n = 63)	Grade 3 — EC (n = 22)	Hyperplasia with atypia (n = 71)	Hyperplasia without atypia (n = 123)	Normal endometrium (n = 116)	p value
Neutrophil-lymphocyte ratio, median (range)	2.3 (1.2–7.3)	2.2 (0.7–12.2)	2.6 (0.7–6.2)	2.1 (0.01–18)	2.1 (0.1–148)	2 (0.4–6)	0.04*
Platelet-lymphocyte ratio, median (range)	131.4 (63.3–325.0)	132.6 (54.2–476.6)	157.7 (69.6–318.0)	126.8 (37.5–391.8)	125.2 (55.1–626)	133.8 (15.5–363.9)	0.84

EC — endometrial cancer

Table 4. Neutrophil to lymphocyte and platelet to lymphocyte ratios of the patients (EC patients divided into early and advanced stages by FIGO staging)

	Stage I–II (n = 103)	Stage III–IV (n = 18)	Hyperplasia with atypia (n = 71)	Hyperplasia without atypia (n = 123)	Normal endometrium (n = 116)	p value
Neutrophil-lymphocyte ratio, median (range)	2.3 (0.7–12.2)	2.7 (0.8–5.1)	2.1 (0.01–18)	2.1 (0.1–148)	2 (0.4–6)	0.09
Platelet-lymphocyte ratio, median (range)	137.8 (54.2–476.6)	128.3 (55.4–264.6)	126.8 (37.5–391.8)	125.2 (55.1–626)	133.8 (15.5–363.9)	0.91

EC — endometrial cancer; FIGO — The International Federation of Gynecology and Obstetrics

Table 5. Univariate and multivariate analysis of factors associated with endometrial cancer

		Univariate		Multivariate	
		OR (95% CI)	p value	OR (95% CI)	p value
Age [year]		1.1 (1.0–1.1)	< 0.01*	1.0 (1.0–1.1)	< 0.01*
Parity		1.1 (0.9–1.2)	0.11	0.8 (0.6–1.0)	0.06
Diabetes	Absent	1 (reference)	< 0.01*	1 (reference)	< 0.01*
	Present	5.3 (3.1–9.1)		4.4 (2.2–8.5)	
Family history of cancer	Absent	1 (reference)	< 0.01*	1 (reference)	< 0.01*
	Present	9.2 (2.4–31.1)		19.8 (4.3–91.1)	
Menopause	Absent	1 (reference)	< 0.01*	1 (reference)	< 0.01*
	Present	11.1 (6.7–18.4)		5.2 (2.4–11.2)	
NLR		0.9 (0.9–1.0)	0.72	0.9 (0.8–1.0)	0.58
PLR		1.0 (0.9–1.0)	0.77	1.0 (0.9–1.0)	0.23

CI — confidence interval; NLR — neutrophil to lympohocyte ratio; OR — odds ratio; PLR — platelet to lymphocyte ratio

Table 6. Neutrophil to lymphocyte and platelet to lymphocyte ratios of the endometrial cancer patients by grouping according to tumor grade and FIGO stage

		Neutrophil- lymphocyte ratio, median (range)	p value	Platelet-lymphocyte ratio, median (range)	p value
FIGO stage	Stage I–II (n = 103)	2.3 (0.7–12.2)	0.79	137.8 (54.2–476.6)	0.70
	Stage III–IV (n = 18)	2.7 (0.8–5.1)		128.3 (55.4–264.6)	
Tumor grade	Grade 1 (n = 36)	2.3 (1.2–7.3)	0.22	131.4 (63.3–325.0)	0.61
	Grade 2 (n = 63)	2.2 (0.7–12.2)		132.6 (54.2–476.6)	
	Grade 3 (n = 22)	2.6 (0.7–6.2)		157.7 (69.6–318.0)	

CI 0.8–1.0; p = 0.58), and 1.0 (95% CI 0.9–1.0; p = 0.23), respectively. Other clinical factors including age, diabetes, family history of cancer, and menopause were found associated with endometrial cancer. Moreover, no significant association was found between NLR, PLR, and tumor grade, FIGO stages (p = 0.22; p = 0.61; p = 0.79; p = 0.70, respectively) (Tab. 6).

DISCUSSION

In a study that investigated the blood parameters in cancer, it was found that relative lymphocytopenia secondary to the increased neutrophil count can be seen as a response to systemic inflammation. Tumor-associated neutrophils (TANS) affect the extracellular environment through enzymatic interactions that result in endothelial cell migration, increased fibroblast growth factor secretion, and migration of tumor cells. As a result of these, tumor progression and neo-vascularization occur [7, 8]. Certain studies regarding lung and anal cancer also support this finding. The result of these studies is that neutrophilia is a strong factor that predicts the poor prognosis in anal cancer and advanced stage III lung cancer [9, 10]. In another study conducted by Tavares-Murta et al. [11], showed that neutrophilia is a good prognostic factor to predict the metastasis and recurrence in advanced stage cervical carcinoma. Besides, patients who had locally advanced cervical cancer with higher baseline lymphocyte count had better treatment responses to chemoradiotherapy [12]. NLR is accepted as an effective and simple parameter of inflammation [13]. Starting from this point of view, NLR and prognosis association has been investigated in different types of cancer [14–16]. Higher NLR association with prognosis can be explained by these: i) immune-response to the tumor is mainly via lymphocytes; ii) neutrophils are secreting the vast majority of vascular endothelial growth factor (VEGF) to the circulation which enhances the tumor progression [17]. An important study that investigates the NLR differences between endometrial pathologies revealed that NLR was higher in EC patients rather than patients with non-cancerous endometrial pathologies [18]. In another recent study that evaluates the NLR as a discriminative factor for endometrial pathologies showed that EC patients have significantly higher NLR than patients with other endometrial pathologies including endometrial hyperplasia and normal endometrial findings, however, they did not separate the endometrial hyperplasia patients as with atypia and without atypia in their study [13]. In the present study, it was determined that higher NLR

is associated with EC as compatible as the abovementioned studies, however, no difference was found between endometrial hyperplasia with atypia and endometrial hyperplasia without atypia patients in terms of NLR. In a study conducted by Cong et al. [4], ROC curve was generated to calculate a cut-off value for overall-survival (OS) in endometrial cancer patients and it was found that higher NLR was associated with poor OS rates. In the present study, ROC curve analysis was performed to detect a cut-off value to distinguish EC among groups and higher values of NLR were determined associated with cancer. Therefore, it can be said that NLR can be used to discriminate EC from other endometrial pathologies according to the findings of the present study.

Increased platelet count is another inflammation marker that occurred as a response to tumor [19]. Cytokines as a response to inflammation such as IL-1, IL-6 initiate thrombocytosis via megakaryocyte proliferation [20, 21]. Inflammation is associated with increased platelet and decreased lymphocyte levels. Decreased lymphocyte levels were showed colon cancer and pancreatic adenocancer previously. It was also shown that poor prognosis in pancreatic adenocancer is associated with decreased number of tumor-infiltrating lymphocytes [22, 23]. Thus, platelet to lymphocyte ratio becomes another marker for inflammatory processes by the combination of haematologic parameters [24]. Higher PLR was found associated with poor prognosis in non-small cell lung cancer [25]. Besides, PLR was found associated with lymphovascular space invasion (LVSI), lymph node involvement, and distant metastasis in endometrial cancer [26]. In a study conducted by Cakmak et al. [27], PLR was determined as a non-specific inflammatory marker that gives access to predict atypical EH in abnormal uterine bleeding patients, however, they did not enroll the EC patients in their study. Moreover, another crucial study that investigates the importance of platelets to discriminate endometrial pathologies showed that PLR was not significantly different between EC patients and patients with benign endometrial pathologies, however, patients with EH were not enrolled in this study [28]. In another study, PLR was found significantly higher in EC patients in comparison with patients with endometrial hyperplasia or normal endometrial findings, and this study also did not divide the patients of hyperplasia group to with and without atypia groups [29]. In the present study, PLR was determined higher in EC patients among all groups of patients. However, this difference was not found statistically significant. In the present study, there was also a small increase in PLR, which was not statistically significant, in the endometrial hyperplasia group with atypia compared to the endometrial hyperplasia group without atypia. According to the findings of the present study, PLR does not seem to be a good non-specific inflammatory marker in contrast to the NLR in terms of predicting EC or hyperplasia with atypia among endometrial pathologies.

In the previous studies which investigated the prognostic value of NLR and PLR in endometrial cancer patients, it was found that higher NLR and PLR are associated with higher FIGO stages and tumor grades [4, 30, 31]. On the other hand, no significant difference was found between FIGO stages in terms of NLR and PLR in the study conducted by Kurtoglu et al. [28]. In the present study, no significant association was found between NLR, PLR and tumor FIGO stages, tumor grades.

The retrospective design of the present study is the main limitation. However, the strenght of this study is the data homogeneity that comes from single-center experience and being conducted by the same team.

CONCLUSIONS

NLR and PLR are systemic immune response parameters that can be easily evaluated from routine blood tests with no additional cost. NLR was found significantly higher in EC among endometrial pathologies. Thus, NLR potentially might be used in the future to discriminate EC from other endometrial pathologies including endometrial hyperplasia and normal endometrial findings. PLR is not a good predictor to make discrimination among endometrial pathology groups according to present study findings. In addition to other inflammation markers to the NLR and PLR may give access to discriminate one of the pathologies among endometrial cancer, endometrial hyperplasia with atypia, endometrial hyperplasia without atypia, and pathologically normal patients. Further studies are needed to investigate the value of NLR and PLR in endometrial pathologies.

Contributions

OI: manuscript writing, data management, data analysis. RIM: data collection and analysis. OA: project development and administration. AM: data collection and analysis. SK: supervision, review of the manuscript.

Ethical approval

This study was carried out in consensus with our university´s ethics guidelines. The ethics committee approval was obtained for this study.

IRB approval

This study was carried out in consensus with our university's ethics guidelines.

Conflict of interest

The authors declare that they have no conflict of interest.

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