RESEARCH ARTICLE

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Predictive Value of Hematological Inflammatory Markers in Endometrial Neoplasia

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Abstract

Objective: To investigate the predictive role of neutrophil lymphocyte ratio (NLR) and the platelet lymphocyte ratio (PLR) as hematological inflammatory markers in cases of endometrial hyperplasia and cancer. Material and Method: This retrospective study was performed between 2005-2015 with 247 cases of 83 endometrial adenocarcinoma (group 1), 64 of endometrial hyperplasia (group 2) and 100 controls (group 3) who underwent a curettage due to abnormal uterine bleeding and had a normal histopathology in our tertiary clinic. The cases were chosen from patients without chronic diseases, that do not have infection or medication that could affect the systemic inflammatory response. Pre-intervention blood parameters were taken into account. The neutrophil/ lymphocyte and platelet/lymphocyte ratios were and statistical comparisons of the groups were conducted. **Results:** The age distribution of 247 patients was between 26 and 85 years, and the mean age was 48.8 ± 8.92.The median age was 54 in group 1, 46 in group 2 and 45 in group 3. The age was significant between group 1 and the other groups (p=0.001). Some 71% of the cases were premenopausal and 29% were postmenopausal, the latter being significantly more frequent in group 1 (62.7%; p=0.001). Of the cases with endometrial hyperplasia, 42 (65.6%) had simple and 22 (34.4%) have atypical-complex lesions. The median NLRs in groups 1, 2, and 3 were 2.15, 2.10, and 1.92, respectively, with median PLRs of 135.1, 134.0 and 145.6. There was a statistically significant difference between the NLR measurements of the cases from different groups (p=0.048; p<0.05). The NLR value for the endometrial adenocarcinoma group was significantly higher than for the control group (p=0.033; p<0.05). The optimum cut-off value was calculated to be ≥4, at which sensitivity was 20.5%, specificity 99%, positive predictive value (PPV) 94.4% and negative predictive value (NPV) 60%. **Conclusion:** The value of NLR ≥4 has predictive significance in distinguishing endometrial pathologies before intervention in patients with abnormal uterine bleeding. Simple, cheap and easy-to-perform, the NLR can be used as a potential hematological marker for endometrial malignancy.

Keywords: Endometrial cancer- endometrial hyperplasia-neutrophil lymphocyte ratio- platelet lymphocyte ratio

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Introduction

Endometrium cancer is the most common gynecological cancer. According to the records of American International Cancer Institute number of the cases per year is 61.380, the number of the deaths per year is 10.920 (American Cancer Society, 2017). Although different methods are used for diagnosis, there is not any noninvazive diagnosis method. One certain diagnosis method is an invasive method called as endometrial sampling (Kim et al., 2012).

Inflammation and immunogenesis are important for cancer progression and metastasis.3DNA damage by inflamatory mediators and by apoptosis inhibition cause angiogenesis, tumor cell growth, immigration and metastasis (Kim et al., 2009). Blood neuthrophile lymphocyte ratio (NLR) and blood platelets lymphocytes ratio(PLR) are basic indicators of systemic inflamatory response. There are publications about predictive-prognostic values of NLR and PLR in endometrial premalign and malign patologies.5-10 In our study we research for the predictive role of NLR and PLR in endometrial hyperplasia and cancer cases.

Materials and Methods

This retrospective study done between 2005-2015 with total 247 cases: 83 endometrial adenocarsinom (group 1), 64 endometrial hyperplasia (group 2) and 100 anormal uterine bleeding cases that undergone currettage and get normal histopathologies (group 3,control). These 247 cases are chosen from the cases who do not have any disorders, infection or medication that could affect systemic inflamatory response. The blood parameters before any intervention are considered in the study. Peripheral blood

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samples drawn from patients before intervention were analysed in our clinical laboratory. Pre-intervention blood parameters were taken into account because this might affect the blood parameters. From these parameters neutrophile/lymphocyte and platelet/lymphocyte ratios are calculated. For group 1 patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines. We staged endometrial cancer cases early stage (stage 1 and 2) and advanced stage (stage 3 and 4).

For statistical analyses, NCSS(Number Cruncher Statistical System) 2007 andPASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) programmes are used. Descriptive statistical analyses are done. For quantitative data comparison, normal distributed (Hanahan and Weinberg, 2011) or more group comparison are done with One-way ANOVA test and Tukey HSD test is used to ascertain the group that cause the difference. Kruskal Wallis test is used to compare not normally distributed (Hanahan and Weinberg, 2011) or more groups and Mann Whitney U test is used to ascertain the group that cause difference. For the comparison of qualitative data, Pearson Ki Squared test is used. To set the cut off values for the parameters diagnosis-screening tests and ROC curve analysis are used. Univariate ANOVA test was used to determine effective risk factors on NLR. $p<0.05$ is considered as statistically meaningful.

Results

Age distribution of 247 patients was between 26 and 85 years, and mean age was 48.76 ± 8.92. The age distribution of the groups are; 31-85/median 54 for the group 1, 26-69/ median 46 for the group 2 and 30-53/median 45 for the group 3. The age difference between the groups was significantly higher in group 1 than the other groups (p=0.001).71% of the cases were premenopausal and 29% were postmenopausal. Postmenopausal patients were significantly more at group 1 (62.7%; p=0.001). From the cases with endometrial hyperplasia, 42 (65.6%) have simple and 22 (34.4%) have atypical-complex hyperplasia.

There was no statistically significant difference between the groups in hemoglobin values. In control group all the patients have abnormal uterine bleeding. so this factor is not affective for NLR and PLR results.

The groups are compared by calculated NLR and PLR results (Table 1). For PLR, there is not statistically meaningful relation($p>0.05$). On the other hand, the difference of NLR values of the groups is statistically meaningful($p=0.048$). To state the difference Mann Whitney U Test is done and according to the results, NLR value of endometrial adenocarcinoma group was significantly higher than the control group ($p=0.033$; $p<0.05$)

NLR cut off value is calculated for the group 1. The cut off value was found as ≥4. Sensitivity was 20.48%, specificity was 99%, positive predictive value (PPV) was94.4% and negative predictive value (NPV) was 60% at this cut off value (Table 2). Area under the ROC curve (AUC) is found as 59.2% and standard deviation as 4.3% (Figure 1).

To determine the risk factors affecting NLR, we modeled the Univarite ANOVA Regression model by using age and menopause that effect the model.

The model was statistically significant (F = 3,833; p <0,01). Only the group effect was significant in the model (p <0,01). As a result of using Bonferroni correction, The end Ca group (mean ± SE; 4,05 ± 0,34) was significantly higher in terms of NLR measurements from endometrial hyperplasia (mean ± SE; 2,26 ± 0,41) and control (mean ± SE; 2,056 ± 0,64) (p: 0.002, p: 0.021, respectively).

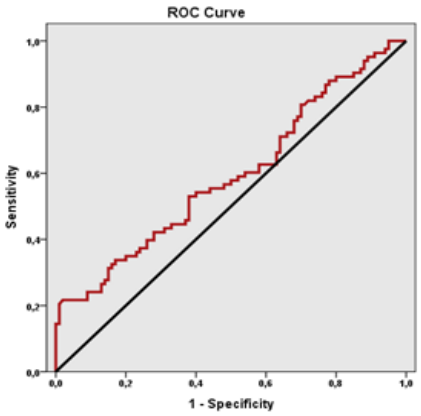

Figure 1. ROC Curve Graph for NLR.

Table 1. NLR and PLR Results by Groups

		Group 1 (n=83)	Group 2 (n=64)	Group 3 (n=100)	p
NLR	Min.-Max.(Median)	0.9-29.73 (2.15)	0.77-5.1 (2.1)	0.11-7.11 (1.92)	0.048*
	Mean±SD	3.78±4.51	2.29±1.07	2.08±0.96	
PLR	Min.-Max.(Median)	29.53-1438.46 (135.1)	23.65-396.67 (134.03)	55.17-249.39 (145.62)	0.728
	Mean±SD	162.90±153.67	146.90±63.47	145.10±41.36	

*Kruskal Wallis test, $p<0.05$

Table 2.Diagnostic screening tests and ROC curve results for NLR

	Diagnostic Scan					ROC Curve		
	Cut off	Sensitivity	Specificity	PPV	NPV	AUC	95% Confidence Interval (CI)	p
NLR	≥4.00	20.48	99	94.4	60	0.592	0.508-0.675	0.033

Table 3. Univariate ANOVA Results of Risk Factors Affecting NLR, Tests of Between-Subjects Effects.

Source	F	p
Corrected Model	3.833	0.001**
Intercept	11.651	0.001**
Age	2.494	0.116
Menopause	0.161	0.689
group	7.455	0.001**
Menopouse group	0.008	0.992

We did not use univarite ANOVA regression model for PLR, there is not statistically meaningful relation for PLR ($p>0.05$).

Between early and advanced stage endometrial cancer cases no statistical differences for NLR and PLR ($p >0.05$).

Discussion

Since endometrium cancer is most common gynecological cancer seen in developed countries; easily used, cheap, reachable diagnoses methods are still a need. Since gold diagnosis method is an invasive method, endometrial biopsi/curettage and tumor indicators are not useful; systemic inflamatory response markers' importance at the diagnosis is still at research.Usefulness is limited since the markers increase at the systemic diseases.

Unfullfilled estrogen that cause inflammation at endometrial tissue is main mechanism for the development of endometrioid type adenocarcinom (Wallace et al., 2010).

At this issue, there are researches show that inflamatory response markers increase at the endometrial malign cases and also researches that show no increasement at the markers.

Kurtoglu et al., (2015) at their study in which they exclude systemic disorders, did not find any meaningful difference at NLR and PLR values of benign endometrial pathology and of endometrial adenocarcinom patients. Median NLR at malign group was 2,11 and median PLRwas 129,1.

Yavuzcan et al., (2014) did not find any meaningful difference at NLR and PLR values of benign endometrial pathology and endometrial cancer cases. Yılmaz et al., (2016) do not find any meaningful difference at NLR values of endometrial hyperplasia, endometrial cancer and normal endometrial biyopsied control patients. However in these two studies, the diseases that could affect systemic inflamatory response were not excluded and the number of the cancer cases was poor.

Acmaz et al., (2014) in their study in which they excluded the diseases and the conditions that could affect systemic inflamatory response, they compare the values of NLR and PLR of endometrial hyperplasia, endometrial cancer and normal endometrial biopsied control patients. They found median NLR as 2,89 at endometrial cancer group and median PLR as 144,9. They underlined that NLR and PLR at cancer group are meaningfully higher when compared with control group. They do not set a cut off value for NLR and PLR. They declare that the difference between the endometrial cancer and other groups could be found by using non spesific inflamatory indicators.

Ural et al., (2015) in their study in which they excluded the comorbid situations, they compare the values of NLR and PLR at endometrial hyperplasia, endometrial cancer and normal endometrial biyopsied control patients. In their study they found median NLR of endometrial cancer group as 3.8 and found it meaningfully higher according to control group, but they do not set a cut off value for NLR. They do not find any meaningful difference at the different groups' PLR values. In this study they found that NLR is a robust inflamatory marker in favor of endometrial patologies.

Cummings et al., (2015) made their research with 605 endometrial cancer patients; from these patients, 468 adenocarsinom cases' median NLR found as 2,48 and median PLR as 143. Cutoff values declared as ≥2.4 for NLR and ≥240 for PLR. In this study they found NLR and PLR as independent prognostic indicators for endometrial cancer. Also, Haruma et al., (2015), in their study with 320 endometrial cancer cases (247 adenocarsinom cases) found pre-treatment median NLR as 2,376 and median PLR as 162,148; but they underline only NLR as predictor for bad prognosis.

Cakmak et al., (2015) in their study in which they seperate the cases as basic and atypic endometrial hyperplasia, they compare the cases with the normal endometrial biopsied patients and show that NLR and PLR could be used as predictors for atypic hyperplasia in the patients.

A new study from China, Ding et al., (2017) found that preoperative and postoperative NLRs were independently associated with inflammatory system response markers and could be combined to evaluate the prognosis of patients with endometrial cancer following surgery. This study showed us also NLR could be an important marker for postoperatif period.

According to a meta-analysis published in 2017, high NLR is associated with adverse survival outcomes.15 NLR is a readily available prognostic marker in the preoperative setting, and its role to guide treatment management and impact on immune-directed and targeted therapies warrants further investigation.

As a result, according to our findings NLR values 4 or more at the cases with anormal uterine bleeding are indicators for malign endometrial patology. Thus NLR is pretreatment reachable, cheap, non invazive, hematological inflamatory predictive indicator.

The limitation was in our study that we did not use ultrasonographic finding so because of uterine myomas and secreted erytropeoitin can effect hematological markers.

In addition, related to this topic more researches with more cases and with exclusion of co-morbid systemic inflamation conditions are in need.

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