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Comparison of Preoperative Hematological Parameters Among Benign, Premalignant, and Malignant Uterine Pathologies

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Abstract

Objective: Based on the influence of uterine inflammation on the development of malignancy, we aimed to determine the difference in the preoperative parameters in benign uterine pathology of haematological parameters analysed and to evaluate the association with premalignant and malignant.

Method: Our study included 343 patients who underwent surgery for benign, premalignant and malignant pathologies of the uterus between January 2007 and August 2014 at Education and Research Hospital. Of the total 343 operated patients, 228 (66.5%) were diagnosed with uterine myoma. Among the 58 patients in the endometrial hyperplasia group, 33 (56.9%) were diagnosed with simple hyperplasia without atypia, 7 (12.1%) with simple atypical hyperplasia, 7 (12.1%) with complex hyperplasia without atypia and 11 (18,9%) with complex atypical hyperplasia. In the endometrial cancer group, which consisted of 57 patients, 52 (91.2%) were diagnosed with endometrioid-type endometrial adenocarcinoma, 3 (5.2%) with carcinosarcoma, 1 (1.7%) with a mixed type (serous papillary + endometrioid) and 1 (1.7%) with endometrial stromal sarcoma. All patients achieved hemograms in the preoperative period.

Results: In our study group, the endometrial carcinoma and hyperplasia neutrophil count (Neu) , neutrophil percentage (Neu%) , haemoglobin (Hb), haematocrit (Hct) and mean corpuscular volume (MCV) were significantly higher than those in the control group. Lymphocyte ratio and red cell distribution width (RDW) terms were significantly lower than those in the control group.

Conclusion: We think that routine haematological parameters such as Neu, Neu%, MCV and RDW which are inexpensive, repeatable and easily accessible from complete blood count panels may be useful in predicting benign and malignant diseases of the endometrium.

Keyword: Lymphocytes, platelets, neutrophils, endometrial neoplasms, thrombocytosis.

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INTRODUCTION

Endometrial hyperplasia is defined as morphological and biological changes in the endometrial gland and stroma due to endogenous or exogenous estrogenic stimulation that is not met with progestogens. Endometrial hyperplasia and endometrial neoplasia are two different biological diseases. The most discriminating feature is the absence or presence of cytological atypia (1). Endometrial hyperplasia is a well-known precancerous lesion that lies on the pathway from normal endometrial tissue to adenocarcinoma.

The relationship between cancer and inflammation was proposed by Virchow in the 19th century. A dense leukocyte ratio in cancerous tissues was observed as the result of a chronic inflammatory process, suggesting that leukocytes may be the cause of tumor growth. Inflammatory mediators formed by cells carry tumor progression to the next process.

Due to their angiogenic, metastatic, and proteolytic activities, platelets have a major role in the background of inflammation. The systematic review demonstrated that pretreatment thrombocytosis is correlated with poor survival outcome and adverse clinicopathological parameters in endometrium cancer and thrombocytosis is a potential prognosis predictor for endometrium cancer (2). Mean platelet volume (MPV) is an important inflammatory marker indicating platelet activation (3).

In recent years, NLR (neutrophil lymphocyte ratio) and PLR (platelet lymphocyte ratio) values, which we can easily see from the complete blood count, have been used as SIR (systemic inflammatory response) markers. SIR changes the distribution of white blood cells by causing neutropenia and lymphocytopenia due to malignancies (4).

In this study, we aimed to evaluate preoperative hematological parameters in premalignant, malignant and benign pathologies of the uterus and to evaluate the relationship between them, based on the effect of inflammation on cancer development

METHODS

In our study, 343 patients who were admitted to the Training and Research Hospital with complaints of abnormal uterine bleeding in the premenopausal period, uterine bleeding in the postmenopausal period, abnormal smear results, postmenopausal follow-up and pelvic pain were examined retrospectively. This study was conducted as a specialty thesis project in 2014, before institutional ethics committee approval was required for retrospective chart

reviews. No identifiable patient information was used. The study adhered to the ethical rules of the Declaration of Helsinki. Informed consent was obtained from the patients.

Inclusion criteria were as follows: After exclusion of systemic diseases, curettage for diagnostic purposes was performed in patients over 35 years of age with abnormal uterine bleeding, patients with postmenopausal bleeding, patients with postmenopausal endometrial thickness greater than 5 mm, patients with atypical glandular cells in their cervical cytology and risk factors under 35 years of age. The patients were assessed in three groups.

Group 1 (n: 57): endometrial carcinoma group, Group 2 (n: 58): endometrial hyperplasia group and Group 3 (n: 228): myoma uteri group. All patients in the myoma uteri group underwent preoperative endometrial sampling (either endometrial biopsy or curettage) to exclude coexisting endometrial hyperplasia or malignancy. Histopathological evaluation confirmed normal endometrial findings in all cases. Therefore, this group was used as the benign control group with histologically verified non-pathologic endometrial tissue.

Endometrial hyperplasia cases were subclassified into simple and complex forms with or without atypia, based on the WHO 1994 classification. However, due to the relatively small sample size of each subgroup, statistical comparisons were performed by combining all hyperplasia cases into a single group for analysis.

The routine hemogram was obtained by taking venous blood from the antecubital region 2 weeks before the preop. The exclusion criteria were as follows: patients with benign curettage results and no pathology detected in gynecological examination and patients with hematological disease, inflammatory disease or liver disease who were treated with medical therapy were excluded from the study. A routine hemogram was obtained by taking venous blood from the antecubital region on average 2 weeks before the operation and the study group was formed.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Kaysville, Utah, USA) program was used for the statistical analysis. The normality of data distribution was assessed using the Shapiro-Wilk test before applying appropriate parametric or non-parametric tests.

During the evaluation of the study data, one-way ANOVA test was used for the comparisons of descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as comparisons of three or more groups with normal distribution and Kruskal-Wallis test was used for the comparisons of three or more groups without normal distribution. Following

significant results from the ANOVA or Kruskal-Wallis tests, Tukey's HSD test or Dunn's test with Bonferroni correction, respectively, were used for post-hoc comparisons between groups. Receiver Operating Characteristic (ROC) curve analysis was performed to assess the diagnostic performance of hematological parameters and the area under the curve (AUC), optimal cut-off values, sensitivity, specificity, positive and negative predictive values were calculated. Statistical significance was accepted as $p < 0.05$.

RESULTS

The mean age of the patients included in our study was 52.02 ± 9 years. A total of 228 (66.5%) of our operated patients were diagnosed with myoma uteri. Thirty-three (9.6%) of them were diagnosed with simple hyperplasia without atypia, 7 (2%) of them with simple atypical hyperplasia, 7 (2%) of them with complex hyperplasia without atypia and 11 (3.2%) of them with complex atypical hyperplasia. Fifty-two (15.2%) patients were diagnosed with endometrioid-type endometrial adenocarcinoma, 3 (0.9%) were diagnosed with carcinosarcoma, 1 (0.3%) was diagnosed with mixed-type (serous papillary + endometrioid type) and 1 (0.3%) was diagnosed with endometrial stromal sarcoma. We compared hematological parameters in the study and control groups (Table 1).

No significant differences in Hb (p=0.169), Hct (p=0.668), NLR (p=0.440), Neu (p=0.855), Neu% (p=0.580), MCV (p=0.716) or RDW (p=0.663) among the endometrial hyperplasia subgroups. In our study, it was statistically higher in the endometrial cancer and hyperplasia groups than in the benign group in terms of neutrophil count and neutrophil percentage (p=0.04 and p=0.02).

Among the evaluated hematologic markers for distinguishing endometrial cancer; Hb (AUC: 0.633, cut-off: 12.94 g/dL), MCV (AUC: 0.630, cut-off: 86 fL), Hct (AUC: 0.616, cut-off: 35%) and Neu% (AUC: 0.607, cut-off: 58.9%) were found to be diagnostically valuable, showing particularly high negative predictive values (88%, 89%, 89%, and 89% respectively), indicating strong utility in ruling out malignancy. In contrast, RDW (AUC: 0.324) demonstrated very poor specificity (1%) and a low positive predictive value (16%), thus lacking clinical diagnostic significance (Table 2, Figure 1).

In our study, the lymphocyte count was not found to be statistically significant compared to that in the control group in endometrial cancer and hyperplasia but the lymphocyte percentage was found to be statistically lower than that in the control group (p=0.02). NLR was not statistically significant in the endometrial cancer and hyperplasia groups compared to the benign group. No difference was found between platelet values and PLR in endometrial

cancer compared with the hyperplasia and benign groups.

Hb and Hct values were found to be statistically significantly lower in the benign group than in the cancer and hyperplasia groups. There was a significant difference between the groups in terms of RDW (p= 0.001). In the study group, RDW was lower than that in the control group. MCV values were found to be statistically significantly higher in the cancer and hyperplasia groups than in the benign group (p=0.01). There was no difference between the groups in terms of the MPV value which is a marker of the SIR.

Table 1. Hematological Parameters in Myoma Uteri, Endometrial Hyperplasia, and Endometrial Cancer

Parameter	Myoma (mean ± SD)	Hyperplasia	Endometrial Cancer	P value
Hb (g/dL)	11.1 ± 1.9	11.3 ± 2.2	12.0 ± 1.7	0.006
Hct (%)	34.8 ± 5.1	35.1 ± 5.7	36.9 ± 4.5	0.018
Lymphocyte (x10³/µL)	2.2 ± 0.8	2.2 ± 1.4	2.1 ± 0.7	0.428
Lymphocyte % (%)	32.1 ± 9.2	31.5 ± 8.7	28.2 ± 9.5	0.021
MCH (pg)	25.4 ± 4.0	25.9 ± 4.4	27.4 ± 3.0	0.006
MCHC (g/dL)	31.9 ± 1.6	32.1 ± 1.7	32.6 ± 1.4	0.025
MCV (fL)	79.1 ± 10.3	80.2 ± 11.1	83.8 ± 6.9	0.010
MPV (fL)	8.8 ± 1.0	8.6 ± 0.7	8.7 ± 1.1	0.150
Neutrophil (x10³/µL)	4.4 ± 2.0	4.4 ± 2.0	5.1 ± 2.5	0.043
Neutrophil % (%)	57.9 ± 9.8	58.5 ± 9.7	62.2 ± 10.9	0.021
NLR	2.0 ± 1.5	2.3 ± 2.6	2.5 ± 1.8	0.116
PCT (%)	0.2 ± 0.09	0.2 ± 0.07	0.2 ± 0.07	0.538
PDW (fL)	14.4 ± 6.4	13.9 ± 5.7	15.7 ± 6.5	0.271
RDW (%)	17.9 ± 4.8	16.5 ± 3.9	15.1 ± 3.2	0.001
PLT (x10³/µL)	306 ± 91.5	303 ± 95.2	308.9 ± 127.1	0.974
PLR	148.6 ± 59.0	147.7 ± 77.9	155.1 ± 62.5	0.761
WBC (x10³/µL)	7.1 ± 2.1	7.5 ± 2.2	7.7 ± 1.7	0.187

Data analyses are given as mean ± SD.
Abbreviations: Hb – Hemoglobin, Hct – Hematocrit, RDW – Red Cell Distribution Width, MCV – Mean Corpuscular Volume, MPV – Mean Platelet Volume, PLT – Platelet Count, WBC – White Blood Cell Count, NLR – Neutrophil-to-Lymphocyte Ratio, PLR – Platelet-to-Lymphocyte Ratio, MCH – Mean Corpuscular Hemoglobin, MCHC – Mean Corpuscular Hemoglobin Concentration, PCT – Plateletcrit, PDW – Platelet Distribution Width.

Table 2. ROC Curve analysis of hematological parameters

Parametre	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV
Hb	0.633	12.94	0.44	0.79	0.29	0.88
Hct	0.616	35.0	0.7	0.5	0.22	0.89
Neu%	0.607	58.9	0.64	0.56	0.22	0.89
MCV	0.63	86.0	0.55	0.67	0.24	0.89
RDW	0.324	11.7	1.0	0.01	0.16	1.0

Abbreviations: Hb–Hemoglobin, Hct–Hematocrit, Neu-Neutrophil, RDW–Red Cell Distribution Width, MCV–Mean Corpuscular Volume, AUC-Area Under the Curve, PPV-Positive Predictive Value, NPV-Negative Predictive Value

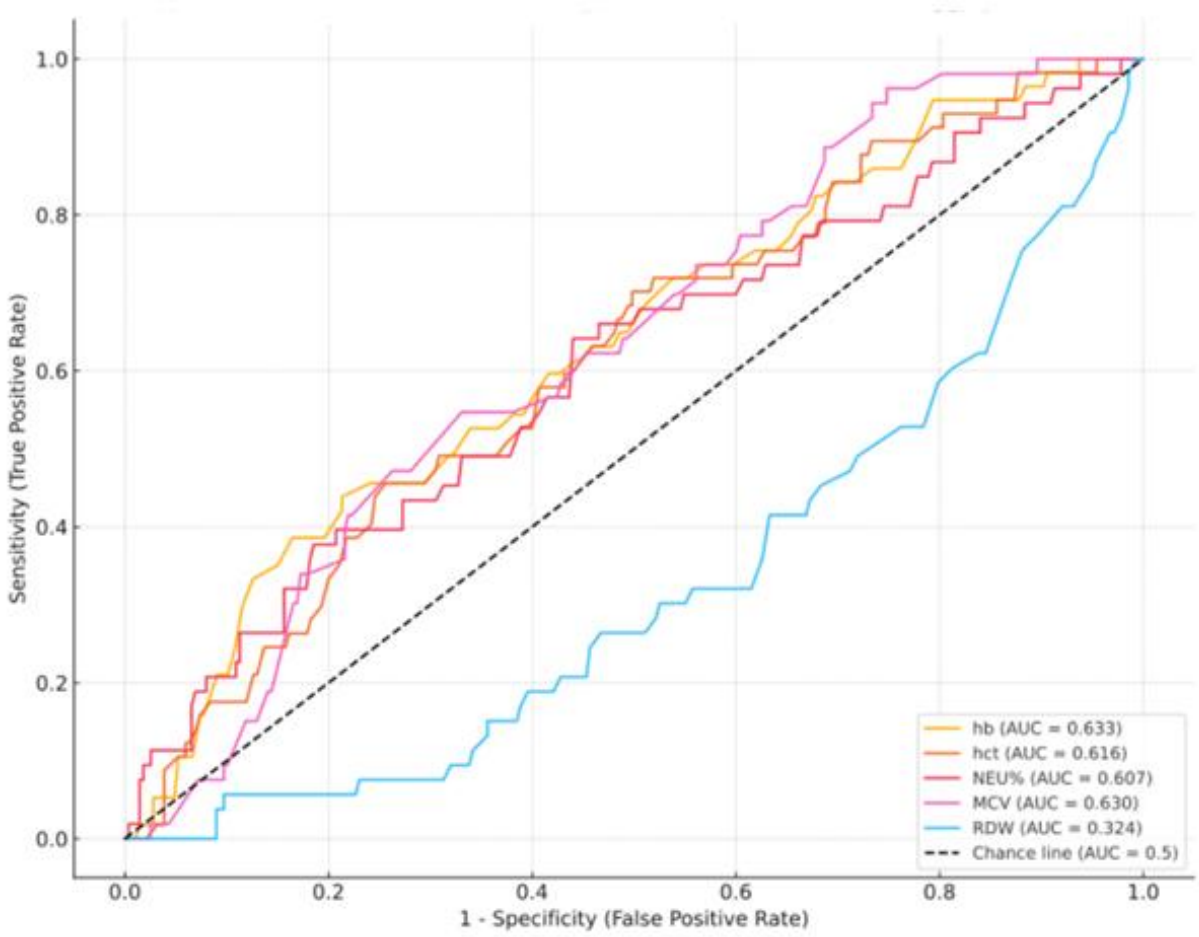

Figure 1. ROC Curves Hematologic Markers in Endometrial Cancer Diagnosis

DISCUSSION

Experimental and clinical information has proven that chronic inflammation plays a role in the development of cancer. Leukocytes (neutrophils, monocytes, macrophages and eosinophils) directly cause the production of reactive oxygen and nitrogen species that damage genes that control cell growth (5). In addition, the proinflammatory environment may play a role in the development of endometrial cancer by directly increasing estrogen production (6). Studies have shown that in endometrial cancer, preoperative abnormal haematological parameters like, anaemia, thrombocytosis and leucocytosis appears to be associated with FIGO advanced-stage and unfavourable outcome (7). In the study of Salem et al., preoperative leukocytosis is correlated with poor tumor FIGO stage, higher cumulative incidence of relapse and poor disease-free survival (DFS) and preoperative leukocytosis may identify high-risk patients who may require more intensified therapy in terms of aggressive debulking and/or perioperative chemotherapy (8).

In the study of Petric et al., lymphocyte count was statistically significantly lower in patients with endometrial cancer in comparison to

patients with premalignant changes (9). In their study, Selen et al., preoperative lymphocyte values were lower in the complex atypical hyperplasia/ endometrial intraepithelial neoplasia (CAH/EIN) from endometrioid grade 1 adenocancer (10).

In our study, the lymphocyte percentage was significantly lower in endometrial cancer and hyperplasia than in the control group and the lymphocyte count was not significantly different. Although the absolute lymphocyte count was not significantly different between groups, the lymphocyte percentage was significantly lower in malignant and premalignant cases. This discrepancy can be explained by elevated total leukocyte and Neu in malignancy-related SIR which reduces the relative proportion of lymphocytes. Therefore, lymphocyte percentage may more sensitively reflect systemic inflammation than absolute count.

Studies have shown that NLR measurement may have an important value in the evaluation of the prognosis of some cancers, such as colon cancer, gastric cancer, lung cancer, renal cell carcinoma and breast cancer, colorectal cancer, pancreatic cancer and soft tissue sarcoma. In their study, Petric et al.showed patients with endometrial cancer higher levels of NLR and PLR in comparison to patients with premalignant changes of uterine mucosa (9). Muangto et al. reported that NLR and PLR were not significantly predictive of malignancy potential in endometrial lesions although NLR was associated with myometrial invasion of uterine mucosa (11). In our study, NLR was not found to be statistically significant in the endometrial cancer and hyperplasia groups compared to the benign group. . Similarly, Fırat et al. also found no statistically significant differences in NLR and PLR values between patients with normal endometrium, atypia and endometrial carcinoma. These findings suggest that the prognostic utility of NLR may vary depending on tumor stage, histological subtype and host immune status (12).

Thrombocytosis is a result of malignant diseases; it is accepted as an independent prognostic factor for ovarian cancer and endometrial cancer. In the study, pre-treatment thrombocytosis is a potential sign of advanced stage ovarian carcinomas and may be predictive of suboptimal tumour debulking during surgery (13). In our study, no difference was found between platelet values in the endometrial cancer, hyperplasia and benign groups.

In the study of Mohamadianamiri et al., concluded that PLR were identified as independent prognostic items associated with the stage and grade of endometrial cancer (14). In our study, no difference was found between the groups in terms of PLR and platelet distrubution width (PDW).

Preoperative anemia significantly correlated with advanced endometrial carcinoma FIGO stage III-IV, ≥50% myometrial invasion, lymph

node metastasis, non-endometrioid histology adnexal involvement, cervical involvement, positive peritoneal cytology, preoperative thrombocytosis and lymphovascular space invasion (15). In our study, the hemoglobine and hematocrit values were found to be significantly lower in the benign group than in the cancer and hyperplasia groups.

Eoh et al. showed that RDW had significantly advanced-stage pelvic lymph node metastasis and recurrence compared to those in the low-RDW group (16).

Interestingly, in our study, RDW was found to be lower in the malignant and hyperplasia groups compared to the benign (myoma) group which contrasts with several previous studies reporting elevated RDW levels in endometrial cancer (17). In our control group, patients with uterine myomas frequently presented with menorrhagia and chronic blood loss which may lead to iron deficiency anemia and consequently elevated RDW. Therefore, the increased RDW observed in the benign group might reflect underlying microcytic anemia rather than an absence of systemic inflammation.

Yayla Abide et al. showed that MCV measurements were found to be significantly higher in endometrial carcinoma and endometrial hyperplasia groups compared to the control group (3). In our study, we found the MCV value to be higher in the study group than in the control group.

In addition, the role of MPV has been extensively investigated in several types of cancer, such as gastric, colon, breast and lung cancer. It has been reported that MPV were not significantly different among endometrial cancer, hyperplasia with atypia/endometrial intraepithelial neoplasia, hyperplasia without atypia and normal controls (17). In our study, no difference was found between the groups in terms of MPV value.

The observed elevation in Neu and Neu % in endometrial cancer patients suggests a potential role of systemic inflammation in tumor biology. In clinical practice, preoperative neutrophil counts, readily available from routine blood tests, could serve as a supportive marker in identifying patients at higher risk of malignancy. Although not specific, elevated neutrophil values might prompt further diagnostic evaluation or raise preoperative suspicion especially when combined with other clinical and radiological findings.This approach is supported by previous research indicating that neutrophilia and high NLR, PLR are associated with poor outcomes and higher tumor aggressiveness in gynecologic malignancies (18). Future prospective studies are needed to validate whether such parameters can be integrated into risk stratification models.

In our study, NLR and PLR values did not show a statistically significant increase in patients with endometrial cancer. This finding contrasts with some previous studies such as Petric et al.,

which reported significantly elevated NLR and PLR levels in malignant cases (9). Several factors may explain this discrepancy, including differences in study design, sample size, patient selection criteria and the timing of hematological parameter measurement. Future larger-scale and prospective studies are needed to better elucidate the diagnostic and prognostic utility of NLR and PLR in endometrial cancer.

Our study has some limitations.Among demographic variables, only age data were consistently available for all patients. Due to the retrospective design and limited documentation, body mass index (BMI) and menopausal status could not be retrieved from hospital records.Another limitation is that we could not determine the potential differences between hyperplasia subgroups due to the low number of cases. Given the limited number of patients in the cancer and hyperplasia groups, our findings should be carefully interpreted.Future studies involving larger, multicenter cohorts are needed to confirm these observations and to better evaluate the diagnostic performance of hematologic parameters in uterine pathologies.

CONCLUSION

In conclusion, we think that routine hematological parameters such as Neu, Neu%, Hb, Hct, RDW and MCV may have diagnostic value in distinguishing benign and malignant uterine pathologies. However, further validation with larger and prospective datasets is essential before clinical application.

Ethics Committee Approval: This study was conducted as a specialty thesis project in 2014, before institutional ethics committee approval was required for retrospective chart reviews. No identifiable patient information was used. The study adhered to the ethical rules of the Declaration of Helsinki. Informed consent was obtained from the patients.

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