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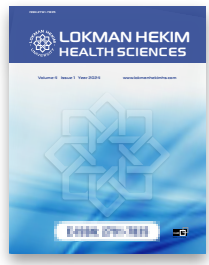

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ORIGINAL ARTICLE

Relationship Between Preoperative Complete Blood Count Parameters and Clinicopathological Features in Endometrioid Type Endometrium Cancer Patients

Endometrioid Tip Endometriyum Kanseri Hastalarında Preoperatif Tam Kan Sayımı Parametreleri ve Klinikopatolojik Özelliklerin İlişkisi

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Abstract

Introduction: Complete blood count parameters are associated with the inflammatory process in the diagnosis and prognosis of several types of cancer; thus, they have been studied as markers. In this study, the preoperative complete blood count parameters in patients with and without endometrioid type endometrial cancer were evaluated and the relationship of these biomarkers with prognostic factors in the cancer group was investigated.

Methods: This study is retrospective in design. All the patients with endometrial cancer were of the endometrioid type. The cancer group involved 94 pathologically confirmed cases, and the control group comprised 96 women diagnosed with dysfunctional uterine bleeding with no signs of organic gynecological pathology. The clinicopathological features and preoperative complete blood count results of all the patients were evaluated.

Results: In comparison with the controls ($p<0.05$), in the cancer group, hemoglobin, leucocyte, and platelet measurements were higher, whereas lymphocytes, monocytes, and mean platelet volume were lower. When subjects with endometrial cancer performed self-evaluation, the monocyte/lymphocyte ratio was higher in cases with lymph node metastasis in comparison with early-stage cases ($p=0.006$). Age was the only consistent factor in predictive of prognostic factors such as myometrial invasion depth, lymph node metastases, advanced stage, and grade.

Discussion and Conclusion: Complete blood count parameters can be simple, readily available, and low-cost markers in endometrial cancer. Moreover, increasing monocyte/lymphocyte ratios may help predict an advanced disease. Nevertheless, to determine the actual predictive potential of these biomarkers, molecular studies that precisely examine the expression of secretory factors (cytokine/interleukin secretion of lymphocytes/macrophages, immunoglobulin secretion of plasma cells) are required.

Keywords: Blood Count; Endometrial Cancer; Grade; Prognose; Stage

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Endometrial cancer is the most prevalent gynecological cancer in developed and Western countries and the sixth most frequent cancer among women worldwide.[1,2] The incidence of obesity and the increased older population contribute to the incidence of this cancer, which is gradually increasing.[3] Endometrium cancer typically causes abnormal uterine bleeding and is restricted to the uterine corpus in more than two-thirds of the cases at diagnosis.[4,5] Several risk factors including tumor histology, (grade 3 endometrioid histology and non-endometrioid histology) deep myometrial invasion, and cervical stromal invasion can predict the spread of the disease outside the uterus and poor prognosis.[6,7] The primary component of its treatment is surgery that includes a comprehensive staging surgery, total abdominal hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymph node dissection, and peritoneal lavage.[8] Nonetheless, in terms of the extent of surgery and selection of patients, the role of lymph node dissection is disputed. Presently, routine lymphadenectomy can be safely disregarded in women with low risk (grade 1–2 histology and superficial myometrial invasion) without negatively impacting the prognosis and with fewer complications (vascular and neural damage, lymphedema, and lymph cysts).[9] In women with moderate risk (superficial grade 1–2 histology with lymphovascular invasion, superficial grade 3 histology, nonendometrioid invasion, and deeply invasive tumor), survival can be enhanced via combined pelvic–paraaortic lymphadenectomy.[10] In a group of patients, systemic chemotherapy and/or radiotherapy are employed as a complementary treatment option. Despite a promising prognosis, some patients with endometrial cancer may endure recurrences, rendering treatment difficult.

The standard preoperative hematological assessment (hemogram or complete blood count) in patients with endometrial cancer who are scheduled to have surgery primarily includes hemoglobin, leucocyte count, and platelet count. As suggested by several studies, these easily available measurements could be diagnostic and prognostic predictors for cancer.[8,11,12]

Tumor suppression or progression is mainly dependent on the interaction between immune cells and cancer cells. The immune cells, especially macrophages are defined as the primary mediators.[13] The potential sources of the macrophages that give an immune response to the tumor and have important roles in the tumor microenvironment are the circulatory monocytes. Leukocytosis is frequently seen in patients with a solid tumor,[14] and it has been proven to be an independent risk factor for death from endometrial cancer.[11] Reportedly, neutrophils play a role in metastases through expressions of some growth factors including vascular endothelial growth factor and specific proteases.[15] Lymphopenia induces cytotoxic cell death and prevents tumor cell proliferation and migration. Thus, it minimizes the immune response to malignancy and may impact its fundamental role in tumor cell modification.[16] Moreover, thrombocytosis has been shown to be related to endometrial cancer, and low hemoglobin levels before treatment can be a predictor of poor prognostic factors such as positive cytology and cervical invasion.[17]

Some studies were performed to determine whether complete blood count parameters can be the markers for the diagnosis and prognosis of several cancer types since they are related to the inflammatory process. Additionally, complete blood count is easily available and inexpensive. In the studies that evaluate complete blood count parameters in endometrial cancer, histological type, which has a significant impact on prognosis, varies, and statistical analyses of the data did not include advanced analyses such as multiple regression analysis. The present study, conducted to fill this gap, aimed to evaluate preoperative hemogram parameters in patients with and without endometrial cancer and to examine the relation between these parameters and prognostic factors in patients with endometrioid endometrial cancer.

Materials and Methods

This study is retrospective in design. Ethical approval was acquired from the Ethical Board of Noninterventional Research at Aydın Adnan Menderes University, Faculty of Medicine (date: 26.07.2013, number: 2013/248). Owing to the study's retrospective design, data were obtained via medical data reviewing. The endometrial cancer group comprised 94 patients diagnosed with endometrioid endometrial cancer and undergoing surgery in the Obstetrics and Gynecology Clinic of Aydın Adnan Menderes University Hospital. Conversely, the control group involved 96 patients undergoing endometrial biopsy due to dysfunctional uterine bleeding, not diagnosed with endometrium cancer and/or hyperplasia, and having a benign condition on pathological examinations (proliferative endometrium, secretory endometrium, and atrophic endometrium).

Patients with endometrial cancer had frozen sections and surgery, and only the ones with endometrioid cancers were included. Prior to surgery, none of the patients in the cancer group received radiotherapy and/or chemotherapy. As part of routine practice in the hospital where the study was performed, endometrial cancer was staged based on the staging system of the

International Federation of Gynecology and Obstetrics.[18] The low risk group did not have lymphadenectomy, but the moderate risk group (grade 1–2 histology with lymphovascular invasion, grade 3 histology, and myometrial invasion depth of >1/2) had combined pelvic–paraaortic lymphadenectomy. Tumor differentiation on pathological examinations was categorized into well-differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3). Those with a malignant disease other than endometrial cancer, acute/chronic inflammatory disease, and hematological/myeloproliferative disease were not included in the study. Data about complete blood count parameters were collected from patient records. Complete blood counts measured before surgery in the endometrial cancer group and 14–21 days before biopsy in the control group were analyzed statistically. All analyses were performed with the same analyzer, Mindray BC 6800 (M68 LH LYSE, China) in the hematology laboratory of the study center. Blood hemoglobin concentrations lower than 12 g/dL indicated anemia, white blood counts higher than $>10\times10^3/\mu L$ indicated leukocytosis,[19] and platelet concentrations higher than $450\times10^3/\mu L$ indicated thrombocytosis.[20]

Statistical Analyses

Data analysis was carried out using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY, USA). Kolmogorov–Smirnov test was employed to determine whether continuous variables were normally distributed, and Levene's test was utilized to determine whether homogeneity of variances was achieved. Descriptive statistics for continuous variables were expressed in mean±standard deviation or median (the first quartile– the third quartile) and descriptive statistics for categorical variables were presented by using the number and percentage of cases. The significance of the differences in the continuous variables with a normal distribution was analyzed using Student's t-test when there were two independent groups and with one-way analysis of variance (ANOVA) when there were more than two independent groups. The significance of the differences in the continuous variables without a normal distribution was analyzed using the Mann–Whitney U test when there were two independent groups and with the Kruskal–Wallis test when there were more than two independent groups. When the results of the analyses with one-way ANOVA were significant, the group(s) that caused the difference was determined using post-hoc Tukey honestly significant difference. When the expected frequency was <5 in at least one-fourth of the cells in 2×2 contingency tables, the categorical variables concerned were evaluated by using Fisher's exact test. When the expected frequency was 5–25, the categorical variables were evaluated using Yate's continuity corrected test and Pearson's Chi-square test otherwise. When the expected frequency was <5 in at least one-fourth of the cells in the RxC contingency tables [at least one of the categorical variables in the columns or the rows had more than two positive results], the categorical variables concerned were analyzed using the likelihood ratio test and with Pearson's Chi-square test otherwise. The effects of all the factors that were likely to be predictive of myometrial invasion, lymph node metastasis, and FIGO stages were examined using multivariate logistic regression analysis, and the effects of all the factors that were likely to be predictive of differentiating grade 1 from grades 2 and 3 were examined using multinominal regression analysis. As a result of univariate analyses, the variables with $p<0.10$ were included in the regression models. The odds ratio, 95% confidence interval, and Wald statistics were calculated for each variable. To determine whether there was a significant correlation between tumor diameter and demographic features and biochemical measures in the endometrial cancer group, Spearman's ranked order correlation analysis was carried out. The factors that were most predictive of a change in tumor diameter were examined using multivariate linear regression analysis. As a result of univariate analyses, the variables found to be significant at $p<0.10$ were included in the regression analysis. The regression coefficient, 95% confidence interval, and t-statistics were calculated for each variable. Since the data regarding tumor diameter did not have a normal distribution, logarithmic conversion was carried out in linear regression analyses.

Results

Table 1 and Figure 1-3 present comparisons of demographic and clinical features and hematological measurements between the groups. Table 2 shows descriptive statistics regarding clinical features of the endometrial cancer group. Table 3 demonstrates demographic and clinical features and biochemical measurements concerning the depth of myometrial invasion in the cancer group.

The cancer group with a myometrial invasion depth of >1/2 had a significantly higher mean age and neutrophil level than the cancer group with a myometrial invasion depth of <1/2 ($p=0.003$ and $p=0.017$, respectively), but the former group had a significantly lower lymphocyte level ($p=0.020$). No significant differences were found in the remaining clinical and demographic features and hematological

Table 1. Demographic and clinical features and hematological measurements of the endometrial cancer and control groups

	Controls (n=96)	Endometrial cancer (n=94)	p
Age (years)	51.0±11.3	59.5±9.4	**<0.001**†
BMI (kg/m^2)	27.4 (25.6–30.9)	30.1 (27.9–33.8)	**<0.001**‡
Gravidity	3 (2–5)	3 (2–4)	0.727‡
Parity	2 (2–4)	2 (2–3)	0.618‡
Hemoglobin (gr/dL)	12.0±1.91	12.6±1.47	**0.024**†
Anemia	37 (38.5%)	28 (29.8%)	0.203¶
MCV (fL)	84.2 (77.4–88.2)	85.0 (79.6–87.4)	0.745‡
Leukocyte(WBC) (10^3/µL)	7155.0 (6242.5–8625.0)	8310.0 (6625.0–10247.5)	**0.004**‡
Leukocytosis	10 (10.4%)	26 (27.7%)	**0.004**¥
Neutrophil (%)	59.6 (54.5–66.0)	62.4 (55.7–68.4)	0.060‡
Lymphocyte (%)	30.5±7.8	28.3±7.8	**0.049**†
Monocyte (%)	6.0 (5.1–7.3)	5.3 (4.5–6.4)	**<0.001**‡
Monocyte/Lymphocyte	0.21 (0.17–0.25)	0.19 (0.15–0.23)	0.125‡
Platelet (10^3/µL)	269.5 (225.0–321.7)	296.5 (260.5–365.5)	**0.003**‡
Thrombocytosis	1 (1.0%)	7 (7.4%)	**0.034**$
Platelet/WBC	37.9 (29.8–44.1)	38.2 (29.2–47.8)	0.645‡
MPV (fL)	10.1 (9.3–10.7)	9.3 (8.6–10.4)	**<0.001**‡
Diabetes mellitus	7 (7.3%)	34 (36.2%)	**<0.001**¥
Hypertension	14 (14.6%)	49 (52.1%)	**<0.001**¶

†: Student's t test; ‡: Mann Whitney U test; ¶: Pearson's Chi-Square test; ¥: Continuity corrected Chi-Square test; $: Fisher's exact test of probability. BMI: Body mass index; WBC: White blood cell; MCV: Mean corpuscular volume; MPV: Mean platelet volume.

measurements between the groups (p>0.05). All the variables found to be significant at p<0.10 in the univariate analyses were included in the logistic regression analysis. Given that there were multiple relations between lymphocytes and monocyte/lymphocyte ratio, two different regression models were established. Model 1 presents the significant effect of age on myometrial invasion independent of other factors (OR=1.080, 95% CI: 1.024–1.140, and p=0.005). In Model 2, as age increased, the likelihood of myometrial invasion of >1/2 significantly increased (OR=1.079, 95% CI: 1.024–1.138, and p=0.005) (Table 4).

The patients in the cancer group with metastases to the lymph nodes (Stage 3) had a significantly higher age, neutrophil level, and monocyte/lymphocyte ratio (Fig. 4) than those without metastases to the lymph nodes (Stages 1 and 2) (p=0.042, p=0.012, and p=0.006, respectively), but the former group had a significantly lower lymphocyte level (p=0.006). The groups did not significantly differ in the other variables examined (p>0.05) (Table 5). All the variables found to be significant at p<0.10 in the univariate analyses were included in the logistic regression analysis. Owing to multiple connections, Model 1 included data regarding original white blood cells, and Model 2 included whether leukocytosis was present. Since the confidence intervals for the odds ratios about the monocyte/lymphocyte ratio were unacceptably large, the monocyte/lymphocyte ratio was not included in the model. Model 1 presented a significant effect of age on metastases to the lymph nodes independent of other variables (OR=1.086, 95% CI: 1.006–1.172, and p=0.035). In Model 2, as age increased, the likelihood of metastases to the lymph nodes independent of other factors increased (OR=1.086, 95% CI: 1.007–1.171, and p=0.033) (Table 6).

The mean age was significantly different between the groups (p<0.001). This difference was due to the significantly higher age of the grade 3 patients than of grades 1 and 2 patients (p<0.001 and p=0.003). The mean hemoglobin level also significantly varied between the groups (p=0.039). The difference was due to the significantly higher mean hemoglobin level of the grade 2 patients than of the grade 1 patients (p=0.032). Additionally, there was a significant difference in the prevalence of thrombocytosis between the groups (p=0.026). The grade 2 patients had a significantly lower prevalence than the grade 1 patients (p=0.034). Other variables examined were not significantly different between the patients (p>0.05) (Table 7). All the variables found to

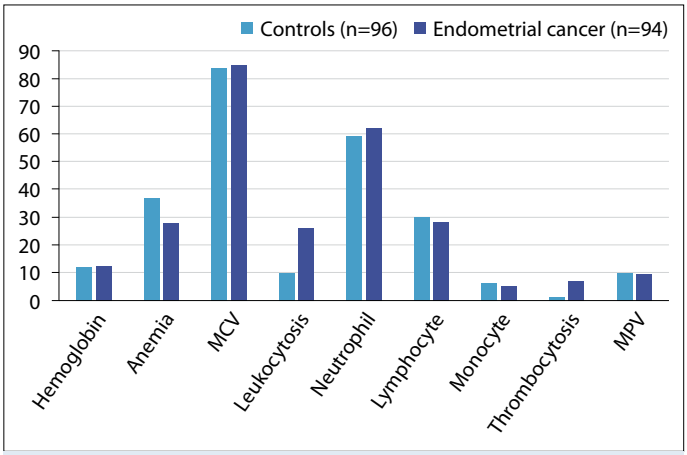

Figure 1. Hematological measurements of the endometrial cancer and control groups.

MCV: Mean corpuscular volume; MPV: Mean platelet volume.

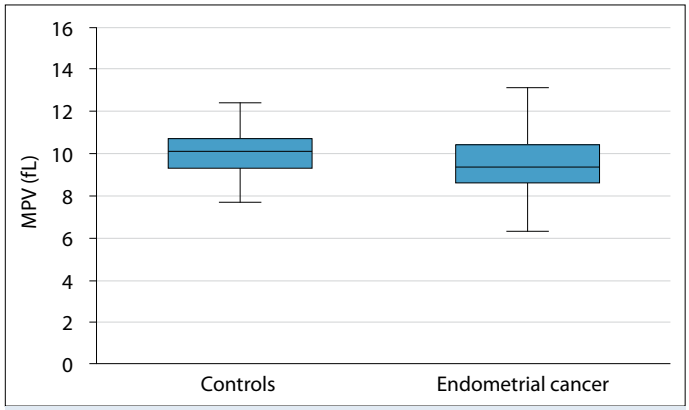

Figure 3. The comparison between controls and endometrial cancer groups in terms of MPV measurements. The horizontal lines in the middle of each box indicate the median, while the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box mark the maximum and minimum MPV levels.

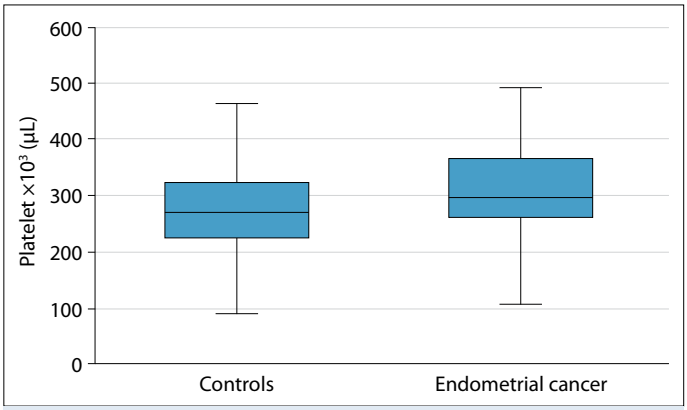

Figure 2. The comparison between controls and endometrial cancer groups in terms of platelet measurements. The horizontal lines in the middle of each box indicate the median, while the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box mark the maximum and minimum platelet levels.

be significant at p<0.10 in the univariate analyses were added to the logistic regression analysis. Thrombocytosis was found to be significant in the univariate analyses, but it was not included in the regression analysis model because none of the grade 3 patients had thrombocytosis. Model 1 included age and hemoglobin, and Model 2 included age and anemia. Model 1 showed that age was a predictor distinguishing grade 1 from grade 3 independent of hemoglobin (OR=1.172, 95% CI: 1.071–1.282, and p<0.001). Model 2 showed that independent of anemia, as age increased, the likelihood of grade 3 significantly increased (OR=1.178, 95% CI: 1.076–1.291, and p<0.001) (Table 8).

Correlations between tumor stage and demographic and clinical features and hematological measurements in the cancer group are presented in Table 9. As leukocyte levels increased, tumor stage significantly increased (r=0.242 and p=0.019). Nonetheless, as lymphocyte levels increased, tumor size significantly decreased (r=–0.223 and p=0.031). As the monocyte/lymphocyte ratio increased, tumor size significantly increased (r=0.214 and p=0.038). Tumor size did not have a significant correlation with the other variables (p>0.05) (Table 9).

Table 10 shows the comparisons of tumor sizes concerning clinical features in the cancer group. There was not a significant change in tumor sizes regarding clinical features (p>0.05). Effects of all the factors likely to be predictive of a change in tumor sizes were investigated using the linear regression analysis. All the variables shown to be significant in the univariate analyses at p<0.10 were included in the logistic regression analyses. In Model 1, independent of neutrophil levels, every 1000-unit increase in leukocytes increased tumor size (B=0.059, 95%CI: 0.008–0.110, and p=0.024). In Model 2, independent of lymphocyte levels, every 1000-unit increase in leukocyte levels significantly increased tumor size (B=0.058, 95% CI: 0.007–0.109, and p=0.027). In Model 3, independent of neutrophils and the ratio of monocytes/lymphocytes, an increment of 1,000 units in leukocytes caused a significant increase in tumor size (B=0.058, 95% CI: 0.006–0.110, and p=0.030). As data on tumor size were not normally distributed, logarithmic conversion was used in the linear regression analysis (Table 11).

Discussion

In this study, preoperative hemogram parameters in patients with endometrial cancer and those without were evaluated, and the relations of these parameters with prognostic factors were investigated. Complete blood

Table 2. Clinical characteristics of the cases within the cancer group

	n=94
Myometrial invasion depth	
<1/2	53 (56.4%)
>1/2	41 (43.6%)
Lymph node metastasis	12 (12.8%)
Grade	
1	26 (27.7%)
2	54 (57.4%)
3	14 (14.9%)
Tumor size (cm)	2.0 (1.7–4.0)
FIGO stage	
1A	53 (56.4%)
1B	22 (23.4%)
2	7 (7.4%)
3C1	7 (7.4%)
3C2	5 (5.4%)

FIGO: International Federation of Gynecology and Obstetrics.

count is an inexpensive test routinely employed during preoperative preparations for anesthesia. The results showed that expectedly, age and body mass index were higher in the cancer group than in the control group. Furthermore, a higher rate in the cancer group had diabetes and hypertension as risk factors for endometrial cancer.

Various studies have been carried out to evaluate complete blood count parameters in cancer cases for a long time and some of the parameters have been reported to be significant in terms of diagnosis and prognosis of cancer.[21–25] In a comparative study by Yayla Abide et al.,[21] the patients with endometrial cancer were found to have lower hemoglobin and hematocrit but a higher mean corpuscular volume (MCV) compared with the control group. Song et al.[22] reported that hemoglobin, leukocyte, and platelet counts were similar in the cancer patients and controls but that the mean platelet volume (MPV) was higher in the cancer patients. Ural et al.[24] revealed that the neutrophil count and neutrophil/lymphocyte ratio were higher in cancer patients than in controls. In the present study, the MCV was similar in cancer and control groups, but the hemoglobin count was higher in the cancer group. This can be attributed to the fact that the control group consisted of patients diagnosed with abnormal uterine bleeding and having an endometrial biopsy. The patients in the control group were younger, and some of them were premenopausal women. Unlike several studies,[21,22–24] the present study showed a significantly

Table 3. Demographic and clinical features and hematological measurements with regard to myometrial invasion depth within the cancer group

	<1/2 (n=53)	>1/2 (n=41)	p
Age (years)	57.0±9.4	62.8±8.4	**0.003**†
BMI (kg/m^2)	31.4 (27.9–34.2)	29.6 (27.9–32.6)	0.366‡
Gravidity	3 (2–4)	3 (2–4)	0.450‡
Parity	3 (2–3)	2 (2–3)	0.359‡
Hemoglobin (gr/dL)	12.5±1.67	12.7±1.17	0.488†
Anemia	18 (34.0%)	10 (24.4%)	0.436¶
MCV (fL)	84.3 (76.7–87.7)	85.2 (81.3–86.9)	0.366‡
Leukocyte (WBC) (10^3/µL)	8520.0 (6780.0–10040.0)	8240.0 (6410.0–10725.0)	0.793‡
Leukocytosis	13 (24.5%)	13 (31.7%)	0.590¶
Neutrophil (%)	60.7 (55.0–67.0)	64.0 (58.1–73.1)	**0.017**‡
Lymphocyte (%)	29.9±6.6	26.2±8.7	**0.020**†
Monocyte (%)	5.3 (4.2–6.4)	5.3 (4.6–6.4)	0.909‡
Monocyte/Lymphocyte	0.18 (0.14–0.22)	0.20 (0.16–0.26)	0.055‡
Platelet (10^3/µL)	298.0 (269.0–366.0)	287.0 (252.0–362.5)	0.573‡
Thrombocytosis	5 (9.4%)	2 (4.9%)	0.463¥
Platelet/WBC	37.7 (29.8–48.5)	38.7 (28.4–47.4)	0.591‡
MPV (fL)	9.3 (8.6–10.5)	9.4 (8.5–10.3)	0.960‡
Diabetes mellitus	18 (34.0%)	16 (39.0%)	0.772¶
Hypertension	30 (56.6%)	19 (46.3%)	0.436¶

†: Student's t test; ‡: Mann Whitney U test; ¶: Continuity corrected Chi-Square test; ¥: Fisher's exact test of probability.

Table 4. Multivariate logistic regression analysis of the combined effects of all possible factors in distinguishing cases with regard to myometrial invasion depth within the cancer group

	Odds ratio	95% Confidence interval	Wald	p
Model 1				
Age	1.080	1.024–1.140	8.061	**0.005**
Lymphocyte	0.902	0.727–1.119	0.878	0.349
Neutrophil	0.972	0.806–1.171	0.092	0.762
Model 2				
Age	1.079	1.024–1.138	7.951	**0.005**
Neutrophil	1.054	0.990–1.122	2.667	0.102
Monocyte/Lymphocyte	2.261	0.006–903.402	0.071	0.790

higher platelet count and MPV in the control group. Moreover, although the leukocyte count and leukocytosis appear to be in the normal range, these parameters were higher, but the lymphocyte and monocyte counts were lower in the cancer group.

Although complete blood count parameters have been reported to be diagnostic markers in the literature, they are more frequently regarded as prognostic factors in cancer cases.[8,17,19,23,25–27] An effective model developed by Luomaranta et al.[8] to predict cancer cases having lymph nodes and distant metastases included leukocytosis and thrombocytosis. Njølstad et al.[19] showed in their study on 557 patients with endometrial cancer that anemia, leukocytosis, and thrombocytosis on preoperative hemogram were associated with an advanced cancer stage and decreased disease-specific survival. Several other studies have shown that the platelet/lymphocyte ratio,[23] the neutrophil/lymphocyte ratio,[23,25] and high monocyte counts[23] can have a relation with distant metastases.[23] In a study that included 166 patients, a high preoperative monocyte count was associated with disease stage, recurrences, and omental involvement, but it was not found to have a relation with tumor grade, myometrial invasion, lymph node positivity, and lymphovascular invasion.[26] In particular, thrombocytosis was found to be related to poor prognostic factors,[17] increased recurrences, and continues to be a poor prognostic factor in multiple regression analyses.[27] In the current study, the median platelet count was higher in patients with lymph node metastases, although it was not significant. Likewise, although the lymphocyte count was lower and the neutrophil count was higher in the patients with myometrial invasion higher than ½ (excluding those with Stage 1A) than those with myometrial invasion lower than ½ (Stage 1A), the only predictive factor to distinguish these two groups was found to be age in the regression analyses. Additionally, although the lymphocyte count was lower and the neutrophil count was higher in the patients with lymph node metastases (Stage 3C) than those without lymph node metastases, age was the only predictor of lymph node metastases in the regression analyses. Unlike the present study, the studies reported thus far did not employ regression analyses.

Leukocytosis can be regarded as a paraneoplastic syndrome described in various gynecological cancers.[28] It was believed that the granulocyte colony-stimulating factor was secreted by the tumor or that the proinflammatory factors released by monocytes in endometrial cancer increased the leukocyte count. Gilani et al. [26] reported that a high preoperative monocyte count had a relation with the disease stage, recurrences, and omental involvement but had no relation with the myometrial invasion depth, tumor grade, lymphovascular invasion, and lymph node involvement. Worley et al.[11] evaluated 1,144 patients in their study and found that preoperative leukocytosis was associated with an advanced disease stage, cervical stromal

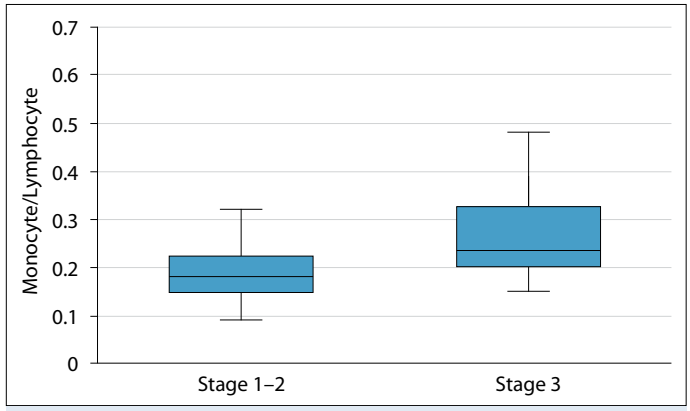

Figure 4. The comparison between Stage 1–2 and Stage 3 groups in terms of Monocyte/Lymphocyte ratios (MLR). The horizontal lines in the middle of each box indicate the median, while the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box mark the maximum and minimum MLR levels.

Table 5. Demographic and clinical features and hematological measurements of the cancer cases with regard to the groups with (stage 3) and without (stage 1–2) lymph node metastasis

	No lymph node metastases (n=82) Stage 1–2	Lymph node metastases (n=12) Stage 3	p
Age (years)	58.8±9.4	64.7±7.9	**0.042**†
BMI (kg/m^2)	30.5 (28.0–34.2)	29.6 (27.4–31.4)	0.193‡
Gravidity	3 (2–4)	3 (1–4)	0.345‡
Parity	2 (2–3)	2 (1–3)	0.251‡
Hemoglobin (gr/dL)	12.6±1.49	12.4±1.36	0.622†
Anemia	25 (30.5%)	3 (25.0%)	>0.999¶
MCV (fL)	85.0 (79.7–87.3)	84.8 (77.7–91.1)	0.777‡
Leukocyte (WBC) (10^3/µL)	7955.0 (6625.0–10020.0)	9955.0 (6692.5–13490.0)	0.082‡
Leukocytosis	20 (24.4%)	6 (50.0%)	0.085¶
Neutrophil (%)	62.1 (55.2–67.3)	72.9 (59.6–78.2)	**0.012**‡
Lymphocyte (%)	29.1±7.4	22.5±8.0	**0.006**†
Monocyte (%)	5.3 (4.3–6.4)	5.6 (4.6–6.4)	0.537‡
Monocyte/Lymphocyte	0.18 (0.14–0.22)	0.23 (0.20–0.32)	**0.006**‡
Platelet (10^3/µL)	296.0 (254.2–362.0)	310.0 (269.2–394.2)	0.359‡
Thrombocytosis	6 (7.3%)	1 (8.3%)	>0.999¶
Platelet/WBC	38.7 (29.3–47.2)	34.5 (27.0–48.9)	0.552‡
MPV (fL)	9.3 (8.6–10.4)	9.5 (8.2–10.5)	0.790‡
Diabetes mellitus	30 (36.6%)	4 (33.3%)	>0.999¶
Hypertension	44 (53.7%)	5 (41.7%)	0.640¥

†: Student's t test; ‡: Mann Whitney U test; ¶: Fisher's exact test of probability; ¥: Continuity corrected Chi-Square test.

Table 6. Combined effects of all possible factors in distinguishing cases with (stage 3) and without (stage 1-2) lymph node metastasis - multivariate logistic regression analysis

	Odds ratio	95% Confidence interval	Wald	p
Model 1				
Age	1.086	1.006–1.172	4.433	**0.035**
Lymphocyte	1.002	0.686–1.464	0.000	0.992
WBC	1.000	1.000–1.000	1.035	0.309
Neutrophil	1.109	0.805–1.529	0.400	0.527
Model 2				
Age	1.086	1.007–1.171	4.532	**0.033**
Lymphocyte	0.992	0.682–1.444	0.002	0.967
Neutrophil	1.112	0.812–1.521	0.439	0.508
WBC	1.448	0.337–6.226	0.247	0.619

involvement, adnexal involvement, and lymphovascular invasion. In a prospective study that involved 557 patients with endometrial cancer, the patients with advanced stages of the disease and lymph node metastases were observed to have a higher leukocyte count.[19] In the present study, the patients with lymph node metastases (Stage 3C) had a higher leukocyte count, although the difference was not significant. This may be because the number of patients with lymph node involvement was lower than those with early stages of the disease. All the patients with a Stage 3 disease (n=12) had a Stage 3C disease, and none had a stage 3A or 3B disease. Furthermore, unlike the studies reported in the literature,[17,19,24–27] the present study only included patients with endometrioid cancer.

Table 7. Demographic and clinical features and hematological measurements of the cases in terms of grade within the cancer group

	Grade 1 (n=26)	Grade 2 (n=54)	Grade 3 (n=14)	p
Age (years)	55.1±12.1[a]	59.4±6.4[b]	68.1±8.2[a,b]	**<0.001**†
BMI (kg/m^2)	31.4 (27.2–34.3)	30.2 (28.1–33.7)	28.7 (27.3–32.0)	0.530‡
Gravidity	3 (2–4)	3 (2–4)	3 (3–5)	0.140‡
Parity	2 (1–3)	2 (2–3)	3 (2–3)	0.597‡
Hemoglobin(gr/dL)	11.9±1.97[c]	12.8±1.24[c]	12.7±0.84	**0.039**†
Anemia	12 (46.2%)	14 (25.9%)	2 (14.3%)	0.070¶
MCV (fL)	82.4 (74.4–86.6)	85.1 (80.3–87.6)	85.6 (83.7–87.5)	0.124‡
Leukocyte (WBC) (10^3/µL)	8105.0 (6465.0–10310.0)	8595.0 (7115.0–10247.5)	7175.0 (5820.0–11040.0)	0.688‡
Leukocytosis	7 (26.9%)	14 (25.9%)	5 (35.7%)	0.763¶
Neutrophil (%)	62.1 (55.3–66.4)	62.5 (56.5–70.6)	62.2 (55.3–69.6)	0.585‡
Lymphocyte (%)	29.9±5.1	27.4±7.9	28.7±10.9	0.393†
Monocyte (%)	5.1 (4.3–6.3)	5.3 (4.2–6.4)	5.4 (4.9–6.0)	0.653‡
Monocyte/Lymphocyte	0.18 (0.14–0.22)	0.18 (0.15–0.24)	0.20 (0.15–0.26)	0.371‡
Platelet (10^3/µL)	319.0 (275.7–400.2)	291.5 (251.5–341.5)	284.5 (260.5–379.2)	0.239‡
Thrombocytosis	5 (19.2%)[c]	2 (3.7%)[c]	0 (0.0%)	**0.026**¥
Platelet/WBC	43.7 (28.9–52.2)	34.3 (29.2–42.6)	42.3 (32.4–48.2)	0.137‡
MPV (fL)	8.8 (8.5–10.3)	9.4 (8.6–10.5)	9.6 (8.4–10.4)	0.411‡
Diabetes mellitus	9 (34.6%)	22 (40.7%)	3 (21.4%)	0.400¶
Hypertension	15 (57.7%)	26 (48.1%)	8 (57.1%)	0.668¶

†: One-Way ANOVA; ‡: Kruskal Wallis test; ¶: Pearson's Chi-Square test; ¥: Likelihood ratio test; a: Statistically significant difference between Grade 1 and Grade 3 (p<0.001); b: Statistically significant difference between Grade 2 and Grade 3 (p=0.003); c: Statistically significant difference between Grade 1 and Grade 2 (p<0.05).

Table 8. Multi-variate logistic regression analysis of the combined effects of all possible factors in distinguishing Grade 1 cases from Grade 2 and Grade 3 cases within the cancer group

	Odds ratio	95% Confidence interval	Wald	p
Model 1				
Grade 2				
Age	1.044	0.980–1.113	1.792	0.181
Hemoglobin	1.358	0.955–1.930	2.902	0.088
Grade 3				
Age	1.172	1.071–1.282	11.911	**<0.001**
Hemoglobin	1.157	0.632–2.119	0.224	0.636
Model 2				
Grade 2				
Age	1.054	0.990–1.122	2.683	0.101
Anemia	0.528	0.186–1.497	1.441	0.230
Grade 3				
Age	1.178	1.076–1.291	12.447	**<0.001**
Anemia	0.327	0.051–2.096	1.391	0.238

Grade 1 is accepted as reference.

Unlike the studies reported in the literature thus far, this study evaluated the relationship between complete blood count parameters and tumor grade and tumor size. The patients with a grade 3 tumor were older than those with grade 1 and 2 tumors. Surprisingly, the patients with grade 2 and 3 tumors had a higher hemoglobin count than those with grade 1 tumors. Because some of the patients with grade 1 tumors were younger and had menopausal symptoms, they might have attributed their irregular bleeding to menopause and presented to the

Table 9. Correlations between tumor size and demographic and clinical characteristics and hematological measurements of the cases within the cancer group

	Correlation coefficient	p†
Age (years)	0.136	0.191
BMI (kg/m^2)	-0.118	0.255
Gravidity	-0.043	0.684
Parity	-0.099	0.343
Hemoglobin	-0.001	0.990
MCV	0.090	0.386
Leukocyte(WBC)	0.242	**0.019**
Neutrophil	0.196	0.059
Lymphocyte	-0.223	**0.031**
Monocyte	0.038	0.713
Monocyte/Lymphocyte	0.214	**0.038**
Platelet count	0.016	0.879
Platelet/WBC	-0.182	0.079
MPV	0.057	0.582

†: Spearman's correlation test.

Table 10. Tumor size with regard to the clinical characteristics of the cases within the cancer group

	Tumor size (cm)	p†
Anemia		0.563
No	2.0 (1.5–4.0)	
Yes	2.0 (2.0–3.8)	
Leukocytosis		0.058
No	2.0 (1.5–3.0)	
Yes	3.1 (1.8–4.6)	
Thrombocytosis		0.717
No	2.0 (1.7–4.0)	
Yes	1.8 (1.5–4.5)	
Diabetes mellitus		0.537
No	2.0 (1.5–3.9)	
Yes	2.1 (1.8–4.0)	
Hypertension		0.186
No	2.5 (1.5–4.0)	
Yes	2.0 (1.7–3.0)	

†: Mann Whitney U test.

hospital late. Despite that, the mean hemoglobin count was 11.9 gr/dL in the patients with grade 1 endometrial cancer. Regression analyses revealed that of all the factors, age was the only predictor in distinguishing grade 1 patients from grade 2 and 3 patients. The tumor diameter correlated positively with the leukocyte count and monocyte/lymphocyte ratio and negatively correlated with the lymphocyte count. Nevertheless, the tumor size did not correlate with clinical features including anemia, leukocytosis, thrombocytosis, and the presence of systemic diseases such as hypertension and diabetes. The regression analysis revealed that the leukocyte count was the only predictor of changes in tumor sizes.

Thus far, several studies on endometrial cancer and preoperative complete blood count[17,19,23–26] have reported that some clinical features (anemia, leukocytosis, and thrombocytosis), counts of white cells such as monocytes, lymphocytes, and neutrophils, and the ratios of these cells to each other have diagnostic and prognostic importance. In the previous studies, regression analyses were not employed. In the present study, when all the factors believed to help distinguish endometrial cancer cases were investigated by using multiple regression analyses, age was the only variable predictive of prognostic factors including myometrial invasion, lymph node positivity, and advanced stage of the disease. Only leukocytosis was found to be a significant marker for tumor size. The results of this study determined age as a significant predictor for various clinicopathological features. Even though the increased susceptibility of older adults to oncogenic mutations is not fully understood, age may cover the duration of environmental and genetic exposures and the accumulation of cancer risks. Hallmarks of aging such as genomic instability and epigenetic alteration are also the hallmarks of cancer. Transformation of normal cells to oncogenic cancer cells necessitates the accumulation of DNA damage and mutations over time aside from DNA repair disorders and cell cycle regulation systems. Age-related changes in the microenvironment of the cell including elevated inflammation and decreased function of the immune system may cause mutations that turn into proliferation of cells and cancer transformation.

The limitations of this study include its retrospective design, inclusion of premenopausal patients, and no evaluation of recurrences and survival. A retrospective nature could have introduced selection bias and limited the ability to establish causality. Another limitation is the lack of follow-up data. Considering that the study center was a tertiary care center, patients who were treated only with surgery, especially in the early stages, continued their treatment in the centers that referred them, not in the study center. Moreover, the control group consisted of women with dysfunctional uterine bleeding. This may not be the most appropriate group for comparison. However, we thought that definitely proven negative pathology for cancer may be more discriminatory. Since biopsy could not be

Table 11. Multivariate linear regression analysis of the combined effects of all possible factors in predicting the change in tumor size within the cancer group

	Regression coefficient	95% confidence interval		t-test	p
		Upper bound	Lower bound		
Model 1					
WBC*	0.059	0.008	0.110	2.300	**0.024**
Neutrophil	0.006	-0.008	0.020	0.873	0.385
Model 2					
WBC*	0.058	0.007	0.109	2.241	**0.027**
Lymphocyte	-0.008	-0.024	0.008	-0.996	0.322
Model 3					
WBC*	0.058	0.006	0.110	2.211	**0.030**
Neutrophil	0.005	-0.012	0.021	0.566	0.573
Monocyte/Lymphocyte	0.287	-1.273	1.847	0.366	0.715
Model 4					
Leukocytosis	0.202	-0.074	0.478	1.451	0.150
Neutrophil	0.010	-0.005	0.024	1.345	0.182
Model 5					
Leukocytosis	0.193	-0.084	0.471	1.386	0.169
Lymphocyte	-0.012	-0.028	0.004	-1.454	0.149
Model 6					
Leukocytosis	0.190	-0.099	0.479	1.305	0.195
Neutrophil	0.008	-0.008	0.025	1.017	0.312
Monocyte/Lymphocyte	0.241	-1.393	1.876	0.293	0.770
Model 7					
Platelet/WBC	-0.006	-0.017	0.004	-1.171	0.245
Neutrophil	0.011	-0.003	0.025	1.620	0.109
Model 8					
Platelet/WBC	-0.006	-0.016	0.005	-1.111	0.270
Lymphocyte	-0.013	-0.029	0.002	-1.727	0.088
Model 9					
Platelet/WBC	-0.006	-0.016	0.005	-1.067	0.289
Neutrophil	0.009	-0.007	0.025	1.093	0.277
Monocyte/Lymphocyte	0.398	-1.199	1.995	0.495	0.622

*: The effect of every 1000-unit increase in the leukocyte count.

carried out on patients with no complaints or symptoms, this group was chosen as the control group. The present study included cancer patients only with endometrioid type endometrial cancer. This may limit the generalizability of the findings. This situation may be a limitation on one side and a superiority on the other part. Depending on the subtype, histopathologic properties, genetic mutations, risk factors, and clinical outcomes including survival vary. Since there are differences in several parameters based on subtype, it may be advantageous to include cases of a single type and the most common type. A relatively large sample size, evaluation of endometrioid cancer cases only, and utilization of regression analysis to investigate all the factors likely to distinguish the cases increase the strength of the study. To investigate the real predictive potential of various biomarkers such as factors secreted by leukocytes (cytokine/interleukin secretion rate of lymphocytes and macrophages, immunoglobulin secretion rate of plasma cells) and platelets and especially genetic expression of secretory factors, further studies are necessary.

Conclusion

Increasing monocyte/lymphocyte ratios may aid in the prediction of an advanced disease. The multiple regression analyses showed that age is the most important predictor of clinicopathological features including myometrial invasion depth, lymph node involvement, disease stage, and tumor grade.

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