

Hematological and biochemical markers in determining the diagnosis and stage prediction of endometrial cancer

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ABSTRACT

Objectives: To establish whether there is a statistically significant difference in hematological and biochemical parameters between the patients with premalignant changes of the uterine mucosa and those with malignant changes. The aim is to establish whether hematological and biochemical parameters may be useful in predicting the stages of endometrial malignancy and in differentiating premalignant and malignant endometrial changes.

Material and methods: A retrospective study included 100 patients (70 with endometrial carcinoma diagnosis and 30 with atypical hyperplasia). We compared hematological and biochemical parameters in both groups.

Results: CRP, granulocytes, platelets, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) are statistically significantly higher in patients with malignant changes. Lymphocyte count is statistically significantly lower in patients with malignant changes. Platelet count is statistically significantly lower in patients with stages I and II in comparison to patients with higher disease stage. NLR and PLR have good discriminatory power for carcinoma presence. Patients with advanced changes have statistically significantly higher CRP values, higher granulocyte and platelet count, as well as higher values of NLR and PLR, and statistically significantly lower values of lymphocytes and MPV in comparison to benign changes.

Conclusions: There is a possibility of using hematological and biochemical parameters in the assessment of endometrial changes as well as in the prediction of stages, in confirmed malignant changes of the endometrium.

Key words: endometrial cancer; hematological parameters; biochemical parameters; stage

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INTRODUCTION

Endometrial carcinoma is the most common gynecological carcinoma. It is the fourth most common carcinoma in women, after breast cancer, lung cancer and colorectal cancer. Endometrial cancer incidence is expected to increase, along with an increase in obesity, especially in developed countries [1]. In the period between 1990 and 2019 endometrial cancer incidence increased worldwide [2]. Currently, 7% of malignancies in women are confined to uterine cancer, and 4% of all death cases are caused by uterine body cancer [3]. Fortunately, the endometrial cancer mortality rate has globally been decreasing. Unfortunately,

in developing countries increasing trends have been observed in both the incidence and mortality rates [2, 4].

There are two different pathways in the carcinogenesis of endometrial cancer: estrogen-dependent and estrogen-independent mechanism [5]. Estrogen-dependent leading to type I (endometrioid type of endometrial cancer) and estrogen independent leading to type II (non-endometrioid type of endometrial cancer). Atypical hyperplasia is considered a precursor lesion for type I endometrial cancer, and it is estimated that 25% of patients with this endometrial change will progress over time to endometrial cancer [6]. ECI (endometrial carcinoma) is an endometrial lesion

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where endometrial surface I gland cells are transformed into malignant cells, often serous endometrial carcinoma (type 2) and the carcinogenesis pathway does not include atypical hyperplasia [7].

The most common manifestation of endometrial cancer is postmenopausal uterine bleeding. Evaluation of abnormal uterine bleeding in postmenopausal women involves clinical examination, transvaginal ultrasonography and explorative curettage [8, 9]. Explorative curettage is the gold standard in establishing the diagnosis, but the method is an invasive one, so the application of additional, less invasive diagnostic procedures, may help in making decisions on performing curettage or not.

A great number of patients have repeated uterine bleeding. In case histopathology findings after uterine mucosa sampling register benign pathology, such as endometrial polyp, hyperplasia without atypia features, inflammatory conditions, the patient will probably undergo explorative curettage once again, or even more. As the procedure is an invasive one, there is a need for a classical diagnostic approach (clinical examination, ultrasonography, curettage) to be complemented with a noninvasive procedure that may reduce the number of unnecessary explorative curettages.

The occurrence of repeated abnormal uterine bleeding requires re-evaluation of already evaluated patients. Abnormal uterine bleeding is a cause of concern, both for the patient and the doctor. Incidence of endometrial cancer in premenopausal women is low (0.33%), and in postmenopausal women it is about 30% [10, 11]. It means that 70% of patients with postmenopausal bleeding will have benign or inflammatory causes of bleeding [11].

All in all, about 90% of patients with endometrial cancer have abnormal uterine bleeding. However, 90% of patients with abnormal bleeding do not have endometrial cancer, and 10% of patients with endometrial cancer have complete absence of abnormal uterine bleeding. Hence, there is a need for defining a new marker in the algorithm of decision making about the procedure related to abnormal uterine bleeding, especially repeated uterine bleeding [12].

Patients with diagnosed endometrial cancer are mostly surgically treated. Those with severe comorbidities may have nonsurgical options [9].

Besides reduction in invasive procedures, additional markers could help in predicting malignancy presence, in patients with atypical hyperplasia in curettage-obtained samples. This is of particular importance in patients who desire to preserve fertility, in whom conservative treatment is planned. Apart from decreasing the frequency of invasive procedures, new markers would help in predicting malignancy presence, in patients with atypical hyperplasia finding, obtained from curettage samples. It is of special importance in patients who desire to preserve

fertility, in whom conservative treatment is planned, as well as uterus maintenance in women who want to have children [13–16].

The aim of the study

The aim of the study was to determine whether there is a statistically significant difference in hematological parameters: erythrocyte count (RBC), leukocyte count (WBC), platelet count (PLT), neutrophil leukocyte count (NEU), lymphocyte count (Ly), monocyte count (Mo), platelet distribution width (PDW); mean platelet volume (MPV); plateletcrit (PCT); neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) between the patients with premalignant and malignant changes of the uterine mucosa. The aim was to determine whether hematological parameters may be useful in predicting the stage of endometrial malignant disease and in differentiating premalignant from malignant endometrial changes.

MATERIAL AND METHODS

In our study we examined parameters of full blood count and C-reactive protein level in patients with endometrial malignancy, type I (endometrioid type) and in patients with atypical hyperplasia. Hematologic parameters were analyzed before planned surgery in patients with endometrial malignancy and in patients with atypical hyperplasia. We monitored complete leukocyte count (WBC), hemoglobin (HGB), PLT, PDW, MPV, and PCT. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio have been analyzed.

Patients with atypical hyperplasia and endometrial cancer were operated on. Classical abdominal hysterectomy with bilateral adnexectomy was performed. Patients with suspected cervical invasion underwent radical hysterectomy. All the patients with endometrial cancer were staged according to International Federation of Gynecology and Obstetrics (FIGO) classification after the analysis of surgically excised specimens.

After staging, we compared hematological and biochemical parameters in patients with early and advanced endometrial cancer. We also compared these parameters in patients with atypical hyperplasia and in patients with advanced endometrial cancer (stages III and IV).

We analyzed hematological parameters in patients operated on precancerous endometrial changes and in patients operated on malignant changes of the uterine mucosa. The study was a retrospective one. It comprised of 100 patients. We used: surgical protocols, preoperative histopathological findings, postoperative histopathological findings, medical histories. Criteria for inclusion in the research were: diagnosis of endometrial carcinoma of the endometrium or diagnosis of atypical endometrial hyperplasia, performed surgical treatment and staging of the disease, available preopera-

tive hematological and biochemical analyzes. The patients underwent surgery in the period 2017–2020.

All of them underwent total abdominal hysterectomy with bilateral adnexectomy. Seventy patients were operated on for diagnosed endometrial cancer (endometrioid type). Control group included 30 patients operated for atypical hyperplasia, having been diagnosed with atypical hyperplasia on surgically excised uterus. Patients were grouped according to their histopathological findings. In case atypical hyperplasia was detected upon explorative curettage and malignancy found on surgically excised uterus, the patient was included in the group with mucosal malignant changes. If it is confirmed that postoperative histopathological finding is identical to preoperative one (atypical hyperplasia), the patient is classified into the control group/patients with premalignant changes.

Hysterectomy tissue samples were processed by standard techniques, stained with hematoxylin and eosin (H&E), and diagnosed at the Center of Pathology and Pathological Anatomy, Clinical Center Nis, Serbia. All the slides were reviewed by three independent gynecologic pathologists (Biljana Djordjevic, Ljubinka Velickovic, Ivana Djordjevic), from the same center according to the current 2020 World Health Organization (WHO) criteria [17]. Any disagreement was resolved by the debate at the three-headed microscope. The 2017 FIGO stage was assessed based on local hysterectomy findings and additional available clinical data.

The age distribution was also analyzed in both groups. Evaluation of the disease stages was performed in the group of patients with endometrial cancer. They were classified into two groups: early endometrial cancer (stages I and II) and advanced endometrial cancer (III and IV). Preoperative hematological parameters were also assessed (BC, WBC, NEU, Ly, Mo, NLR, PLT, PLR), mean platelet volume MPV, platelet distribution width PDW, plateletcrit PCT. Potential statistically significant differences in certain hematological parameters between the experimental and control group were also assessed, as well as the difference in monitored parameters between the patients with early and advanced endometrial cancer, and also the differences between premalignant and malignant changes in advance stages.

Statistical analysis

Sample size was not initially calculated to investigate the impact of the hematological and biochemical parameters and the presence of malignancy. However, to determine whether the sample size chosen was adequate, a post hoc power analysis was conducted. The power analysis demonstrated that the sample size ($n = 100$) had an acceptable level of power (0.96) and was deemed adequate for the analysis. A post hoc power analysis was conducted using the software package, G*Power version 3.1.9.2 (Faul, Universität Kiel, Germany).

The data are shown as arithmetic mean and standard deviation, as absolute and relative numbers. Continuous values were compared by using the t-test or Mann-Whitney test, depending on data distribution. Logistic regression analysis (univariate and multivariate) was performed to estimate an association between hematological and biochemical parameters and the presence of malignancy. The receiver operating characteristic curve (ROC) was used for testing NLR and PLR discriminative power in relation to the presence of malignant changes. The hypothesis was tested with a significance threshold of $p < 0.05$. Statistical data processing was performed by using the R programming package.

RESULTS

The study encompassed 100 women, mean age 51.40 ± 15.92 years (Min 19 years, Max 83 years) categorized into two groups (70 with malignant and 30 with premalignant changes) with malignant and premalignant changes.

The values of creactive protein (CRP), granulocytes, platelets, NLR and PLR are statistically significantly higher in patients with malignant diseases ($p < 0.001$, $p < 0.001$, $p = 0.001$, $p = 0.023$, $p < 0.001$, $p < 0.001$ respectively). Lymphocyte count is statistically significantly lower in patients with malignant changes ($p < 0.001$) (Tab. 1).

Platelets are statistically significantly lower in patients with stages I and II in comparison to patients with higher stages of the disease ($p = 0.011$) (Tab. 2).

Patients with advanced changes are statistically significantly older ($p = 0.003$); they have statistically significantly higher values of CRP ($p < 0.001$), higher granulocyte count ($p < 0.001$), platelet count ($p = 0.001$), NLR ($p < 0.001$) and PLR ($p < 0.001$) and statistically significantly lower values of lymphocytes ($p < 0.001$), MPV ($p = 0.031$) in comparison to benign changes (Tab. 3).

Univariate logistic regression analysis showed significant association between an increase in CRP (OR 1.089, $p = 0.002$), decrease in lymphocytes count (OR 0.694, $p < 0.001$), increased granulocytes (OR 1.283, $p = 0.006$), increased platelet count (OR 1.005, $p = 0.016$) and malignant disease (Tab. 4). A multivariate model shows that an increase in CRP (OR 1.068, $p = 0.047$) is a statistically significant risk factor for malignant changes (Fig. 1).

The analysis of the ROC curve showed that NLR and PLR have good discriminatory power for the presence of cancer (AUC 0.761, or AUC 0.786). As for NLR, the cutoff value is 0.85, with sensitivity of 68%, and specificity of 82%. The PLR cutoff value is 59.31, with sensitivity of 88%, and specificity 66%. Levels of NLR and PLR are statistically significantly higher in patients with malignant changes ($p < 0.001$, $p < 0.001$, $p = 0.001$, $p = 0.023$, $p < 0.001$, $p < 0.001$ respectively) (Tab. 5, Fig. 2).

The ROC curve analysis showed that NLR and PLR do not have statistically significant discriminatory power in relation

Table 1. Examined parameters in patients with endometrial cancer and in patients with atypical hyperplasia

	Patients with endometrial cancer	Patients with atypical hyperplasia	p ¹
Age	54.44 ± 15.47	48.36 ± 15.94	0.056
C-reactive protein	30.46 ± 46.09	5.22 ± 5.77	< 0.001 ²
Erythrocyte count	4.35 ± 0.57	4.38 ± 0.41	0.737
Leukocyte count	8.46 ± 3.23	9.01 ± 3.75	0.699 ²
Lymphocyte count	3.07 ± 2.43	5.77 ± 3.25	< 0.001 ²
Neutrophil count	4.65 ± 3.27	2.84 ± 2.50	0.001 ²
Monocyte count	6.51 ± 41.07	0.50 ± 0.30	0.252 ²
Platelet count	316.26 ± 138.75	258.32 ± 67.21	0.023 ²
Mean platelet volume	9.78 ± 11.56	10.62 ± 12.74	0.062 ²
Plateletcrit	0.38 ± 1.67	0.15 ± 0.14	0.887 ²
Platelet distribution width	16.37 ± 5.87	16.30 ± 4.46	0.468 ²
Neutrophil/ lymphocyte ratio	2.99 ± 3.71	0.74 ± 0.92	< 0.001 ²
Platelet/lymphocyte ratio	175.27 ± 167.55	63.63 ± 47.59	< 0.001 ²

¹t-test; ²Mann-Whitney test

Table 2. Examined parameters in patients with endometrial cancer in relation to the stage of the disease: early/advanced endometrial cancer

	Early endometrial cancer (Stage I and II)	Advanced endometrial cancer (Stage III and IV)	p ¹
Age	50.48 ± 16.60	59.09 ± 12.87	0.071
C-reactive protein	28.08 ± 50.91	33.25 ± 40.66	0.102 ²
Erythrocyte count	4.34 ± 0.52	4.37 ± 0.64	0.953
Leukocyte count	7.77 ± 2.92	9.27 ± 3.45	0.104 ²
Lymphocyte count	2.93 ± 2.24	3.24 ± 2.68	0.977 ²
Neutrophil count	4.13 ± 3.11	5.26 ± 3.24	0.185 ²
Monocyte count	11.54 ± 55.88	0.62 ± 0.30	0.066 ²
Platelet count	266.59 ± 97.50	374.56 ± 158.31	0.011 ²
Mean platelet volume	11.12 ± 15.69	8.20 ± 1.40	0.325 ²
Plateletcrit	0.56 ± 2.27	0.18 ± 0.17	0.115 ²
Platelet distribution width	16.20 ± 7.10	16.57 ± 4.12	0.942 ²
Neutrophil/lymphocyte ratio	2.64 ± 3.07	3.40 ± 4.39	0.326 ²
Platelet/lymphocyte ratio	138.12 ± 126.95	218.87 ± 199.49	0.122 ²

¹t-test; ²Mann-Whitney test

to the stage of cancer (AUC 0.581, $p = 0.326$, or AUC 0.628, $p = 0.122$) (Fig. 3).

Patients with advanced changes are statistically significantly older ($p = 0.003$). They have statistically significantly higher CRP values ($p < 0.001$), higher granulocyte count ($p < 0.001$), platelet count ($p = 0.001$), NLR ($p < 0.001$) and PLR ($p < 0.001$) and statistically significantly lower values of lymphocytes ($p < 0.001$), and MPV ($p = 0.031$) in comparison to benign changes (Tab. 3).

DISCUSSION

After the diagnosis of endometrial malignant tumor has been established, decisions should be made regarding

therapeutic options and the possibility of surgical treatment. Usual preoperative assessment of the patients includes another clinical examination, laboratory testing: complete blood count, biochemical analyses, coagulation factor; diagnostic imaging (mandatory chest radiography, abdominal ultrasound, small pelvic ultrasound).

Full blood count is a mandatory part of the patients' assessment. This analysis proved to be useful and applicable in patients with a malignant disease.

The aim of our study was to determine whether the parameters of the full blood count are different in patients with malignant (endometrial cancer) and premalignant (atypical hyperplasia) endometrial pathology. These parameters may

Table 3. Examined parameters in patients with atypical hyperplasia in relation to advanced stages of the endometrial cancer

	Patients with atypical hyperplasia	Patients with advanced endometrial cancer (stage III and IV)	p ¹
Age	48.36 ± 15.94	59.09 ± 12.87	0.003
C-reactive protein	5.22 ± 5.77	33.25 ± 40.66	< 0.001
Erythrocyte count	4.38 ± 0.41	4.37 ± 0.64	0.919
Leukocyte count	9.01 ± 3.75	9.27 ± 3.45	0.510
Lymphocytes count	5.77 ± 3.25	3.24 ± 2.68	< 0.001
Neutrophil count	2.84 ± 2.50	5.26 ± 3.24	< 0.001
Monocytes count	0.50 ± 0.30	0.62 ± 0.30	0.064
Platelets count	258.32 ± 67.21	374.56 ± 158.31	0.001
Mean Platelet volume	10.62 ± 12.74	8.20 ± 1.40	0.031
Plateletcrit	0.15 ± 0.14	0.18 ± 0.17	0.242
Platelet distribution width	16.30 ± 4.46	16.57 ± 4.12	0.582
Neutrophil/ lymphocyte ratio	0.74 ± 0.92	3.40 ± 4.39	< 0.001
Platelet/lymphocyte ratio	63.63 ± 47.59	218/87 ± 199.49	< 0.001

¹t-test**Table 4. Association of malignancy and hematological and biochemical parameters (logistic regression analysis)**

Parameter	Univariate			Multivariate		
	OR	95% CI	p ¹	OR	95% CI	p ¹
Age	1.025	0.999–1.052	0.058	1.022	0.989–1.056	0.188
C reactive protein	1.089	1.031–1.150	0.002	1.068	1.001–1.140	0.047
Erythrocyte count	0.871	0.393–1.930	0.734			
Leukocyte count	0.955	0.852–1.071	0.430			
Lymphocytes count	0.694	0.576–0.835	< 0.001	0.792	0.614–1.022	0.792
Neutrophil count	1.283	1.073–1.533	0.006			
Monocytes count	1.472	0.571–3.795	0.424			
Platelets count	1.005	1.001–1.010	0.016	1.006	0.999–1.014	0.111
Mean platelet volume	0.994	0.961–1.028	0.730			
Plateletcrit	1.432	0.424–4.841	0.563			
Platelet distribution width	1.003	0.928–1.083	0.947			
Neutrophil/ lymphocyte ratio	2.115	1.410–3.173	< 0.001	1.761	0.499–6.209	0.379
Platelet/lymphocyte ratio	1.015	1.007–1.024	< 0.001	0.995	0.980–1.011	0.567

¹t-test; Hosmer-Lemeshow test p = 0.893; CI — confidence interval; OR — odds ratio

be easily and cost-effectively determined, can be repeated and reanalyzed. Previous studies showed that complete blood count parameters could be useful in detecting activated immune response in the presence of a malignant disease [18]. Immunology and inflammation are certainly important in the presence of malignant diseases.

Platelets are blood cells believed to have, apart from their role in hemostasis, a significant role in immune responses, cancer progression, and metastatic spread of a malignant disease [19]. Interaction of tumor cells and platelets is crucial in enabling cancer metastasis [20]. Platelets are

nowadays believed to be versatile cells affecting a series of events in the development of a malignant disease [21].

The MPV stands for the mean platelet volume. It is a precise measurement performed as a part of a routine blood count test. Large platelets comprise about 0.2–5% of the whole platelet population. MPV is proportional to the platelet count. The increased production of platelets is proportional to this parameter. MPV is proportional to platelet count and is considered a platelet activation marker. It is also believed that younger platelets are often larger. In the presence of a malignant disease inflammatory processes are

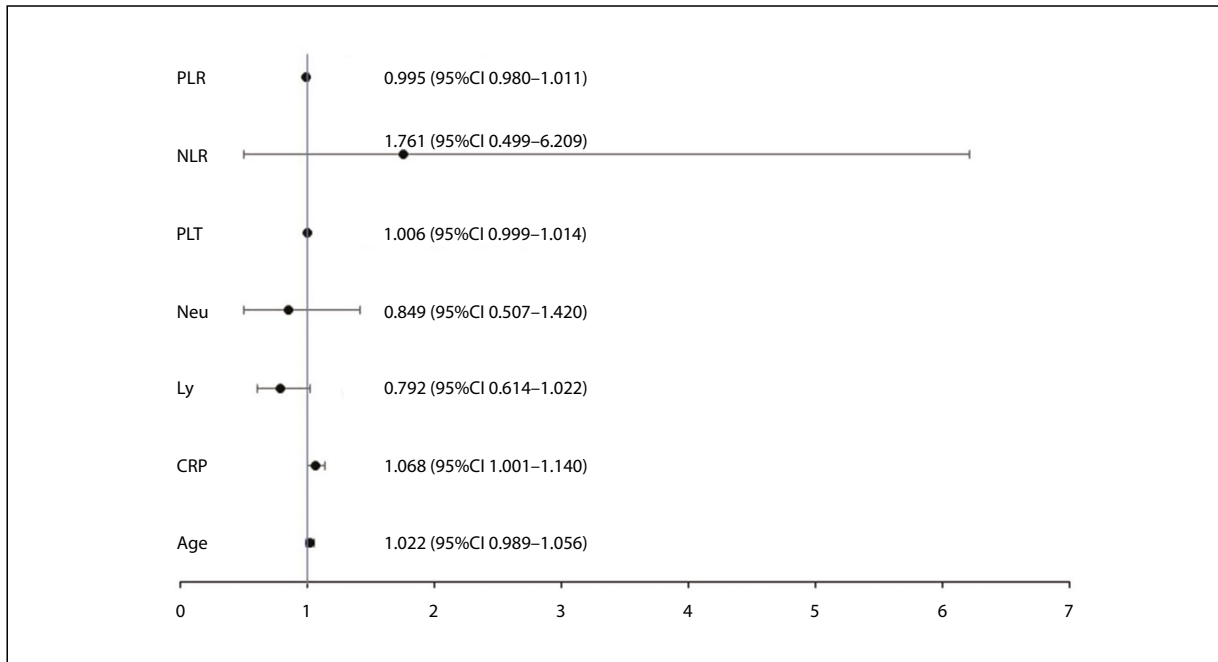


Figure 1. Forest plot of adjusted odds ratio and 95% confidence interval (CI) for the association between hematological and biochemical parameters and malignant changes; PLR — platelet-lymphocyte ratio; NLR — neutrophil-lymphocyte ratio; PLT — platelet count; Neu — neutrophil count; Ly — lymphocyte count; C-reactive protein

Table 5. Parameters of the receiver operating characteristic curve (ROC) curve analysis in relation to the presence/absence of endometrial cancer

Parameter	Cutoff	Sensitivity	Specificity	Area	SE	95% CI	p
NLR	0.85	68%	82%	0.761	0.049	0.665-0.858	< 0.001
PLR	59.31	88%	66%	0.786	0.047	0.695-0.877	< 0.001

NLR — neutrophil-lymphocyte ratio; PLR — platelet-lymphocyte ratio; SE — standard error; CI — confidence interval

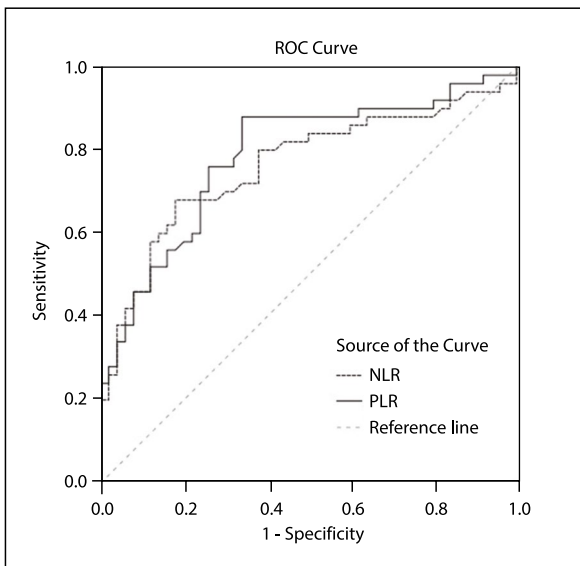


Figure 2. Receiver operating characteristic curve (ROC) curve of neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) as predictors of the presence of malignant changes

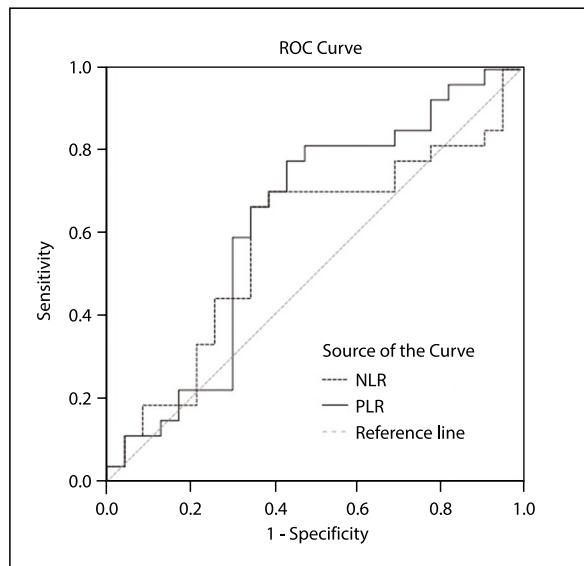


Figure 3. Receiver operating characteristic curve (ROC) of NLR (neutrophil lymphocyte ratio) and PLR (platelet-lymphocyte ratio) for the stage of the disease in malignant changes of the endometrium

always activated, so it is assumed that they may potentially affect platelet activation [22]. Besides MPV, PDW and PCT may be used as platelet activation parameters [22, 23]. These parameters have been monitored in patients with endometrial pathology with confirmation in their increase in patients with a malignant disease and in patients with advanced disease [24, 25]. The authors report MPV cutoff value of 7.54f and below 37.8 for PDW [23]. In our study there was no statistically significant difference in monitored parameters between the patients with endometrial cancer and patients with hyperplasia. Also, we do not find a difference between these parameters between early and advanced endometrial cancer. Besides MPV, platelet distribution width (PDW) may also be monitored. Activated platelets may undergo a transformation, develop pseudopodia, as can be seen in PDW increase. Plateletcrit, PCT, is analogous to hematocrit and is calculated by platelet count and MPV ratio. It does not have clinical importance [19]. Similar to our study, the authors have found no statistically significant difference in the levels of MPV and PDW, except when benign mucosal changes are compared with advanced endometrial cancer [25].

Apart from these parameters, platelet count is very important. It is known nowadays that platelets play a role in hemostasis, as well as in inflammation, immunological responses, and organ regeneration. Now, we are familiar with the fact that a malignant tumor may use these cells to promote its growth and development. A growing tumor stimulates production and activation of the platelets. That stimulation of platelet increase happens at various levels by activation of different mechanisms [26]. Platelet count at the time of diagnosis is an important prognostic factor [26, 27]. Platelet count is statistically significantly higher in the group of patients with mucosal lining change due to a malignancy. Also, platelet count is lower in low-grade tumors in comparison to patients with advanced endometrial cancer. These analyses have been confirmed in our study as well.

Besides platelet count and parameters related to morphology and platelet size, NLR is also important, as well as PLR. NLR is related to histology, stage, myometrial invasion, and lymph node metastases [28]. Neutrophils release cytokines, inhibit apoptosis and promote angiogenesis, while lymphocytes and natural killer (NK) cells inhibit tumor growth and metastases. These features of neutrophils and lymphocytes may explain the poor prognosis in patients with endometrial cancer and high NLR [28]. High NLR and PLR ratio are parameters of lymph node involvement [29], cervical stromal invasion [30], and distant metastases [31, 32]. PLR is also a marker of activated systemic inflammation and its importance has been studied in several types of cancers [28]. The NLR, PLR and PDW are robust inflammatory markers that may be used in the assessment of patients

with endometrial cancer and atypical hyperplasia finding in curettage specimens [33]. In our study, NLR and PLR are statistically significantly higher in patients with malignant changes ($p < 0.001$, $p < 0.001$, $p = 0.001$, $p = 0.023$, $p < 0.001$, $p < 0.001$ respectively). The ROC curve analysis showed that NLR and PLR have good discriminatory power in predicting the presence of a cancer (AUC 0.761, or AUC 0.786). For the NLR, the cutoff value is 0.85, with sensitivity of 68%, and specificity of 82%. For the PLR, the cutoff value is 59.31 with sensitivity of 88%, and specificity of 66%.

The ROC curve analysis showed that NLR and PLR do not have statistically significant discriminatory power in relation to cancer stage (AUC 0.581, $p = 0.326$, or AUC 0.628).

Lymphocyte count is statistically significantly lower in patients with endometrial cancer in comparison to patients with premalignant changes. Lymphocytes are responsible for antitumor response, and neutrophils display activated inflammation in the whole body. This has been confirmed in our study as well (statistically significant neutrophil increase in patients with endometrial cancer).

High values of NLR and PLR are associated with poor prognosis, frequent myometrial invasion, lymph node infiltration, cervical infiltration, poor response to treatment, and poor survival prognosis [32, 34, 35].

Chronic inflammation may be important in endometrial cancer etiopathogenesis. Hematological parameters may be completed with biochemical markers. The levels of C-reactive protein, interleukin 6 and TNF (tumour necrosis factor) are significantly higher in patients with endometrial cancer in comparison to healthy postmenopausal women [36]. Higher levels of C-reactive protein may be predictors of a cancer stage and poor prognosis [37]. In our study, patients with endometrial cancer have significantly higher levels of C-reactive protein in comparison to patients with premalignant lesions of the uterine mucosa.

CONCLUSIONS

Patients with endometrial cancer have significantly higher levels of C-reactive protein, neutrophilic leukocytes, platelets, as well as higher levels of NLR and PLR in comparison to patients with premalignant changes of uterine mucosa. The levels of RBC, WBC, as well as platelet parameters (MPV; PDW; PCT) do not significantly differ in these two groups. Lymphocytes are significantly lower in patients with endometrial cancer in relation to patients with premalignant endometrial lesions. The NLR and PLR have good discriminatory power in detecting the presence of cancer. Patients with advanced changes have statistically significantly higher CRP values, higher granulocyte count, and higher values of NLR and PLR as well, but statistically significantly lower values of lymphocytes and MPV in comparison to benign changes.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

- Felix AS, Yang HP, Bell DW, et al. Epidemiology of Endometrial Carcinoma: Etiologic Importance of Hormonal and Metabolic Influences. *Adv Exp Med Biol.* 2017; 943: 3–46, doi: [10.1007/978-3-319-43139-0_1](https://doi.org/10.1007/978-3-319-43139-0_1), indexed in Pubmed: [27910063](https://pubmed.ncbi.nlm.nih.gov/27910063/).
- Gu B, Shang X, Yan M, et al. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990–2019. *Gynecol Oncol.* 2021; 161(2): 573–580, doi: [10.1016/j.ygyno.2021.01.036](https://doi.org/10.1016/j.ygyno.2021.01.036), indexed in Pubmed: [33551200](https://pubmed.ncbi.nlm.nih.gov/33551200/).
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018; 68(1): 7–30, doi: [10.3322/caac.21442](https://doi.org/10.3322/caac.21442), indexed in Pubmed: [29313949](https://pubmed.ncbi.nlm.nih.gov/29313949/).
- Weiderpass E, Antoine J, Bray FI, et al. Trends in corpus uteri cancer mortality in member states of the European Union. *Eur J Cancer.* 2014; 50(9): 1675–1684, doi: [10.1016/j.ejca.2014.02.020](https://doi.org/10.1016/j.ejca.2014.02.020), indexed in Pubmed: [24656568](https://pubmed.ncbi.nlm.nih.gov/24656568/).
- Djordjević B, Stanojević Z. [Endometrial carcinoma and precursor lesions]. *Srp Arh Celok Lek.* 2007; 135(3–4): 230–234, indexed in Pubmed: [17642468](https://pubmed.ncbi.nlm.nih.gov/17642468/).
- Inoue H, Saegusa M. Is endometrial carcinoma in situ a precursor lesion of endometrial carcinoma? *Kitasato Med J.* 2018; 48: 1–8.
- Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of “untreated” hyperplasia in 170 patients. *Cancer.* 1985; 56(2): 403–412, doi: [10.1002/1097-0142\(19850715\)56:2<403::aid-cncr2820560233>3.0.co;2-x](https://doi.org/10.1002/1097-0142(19850715)56:2<403::aid-cncr2820560233>3.0.co;2-x), indexed in Pubmed: [4005805](https://pubmed.ncbi.nlm.nih.gov/4005805/).
- Scioscia M, Noventa M, Laganà AS. Abnormal uterine bleeding and the risk of endometrial cancer: can subendometrial vascular ultrasound be of help to discriminate cancer from adenomyosis? *Am J Obstet Gynecol.* 2020; 223(4): 605–606, doi: [10.1016/j.ajog.2020.05.049](https://doi.org/10.1016/j.ajog.2020.05.049), indexed in Pubmed: [32497607](https://pubmed.ncbi.nlm.nih.gov/32497607/).
- Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and Management of Endometrial Cancer. *Am Fam Physician.* 2016; 93(6): 468–474, indexed in Pubmed: [26977831](https://pubmed.ncbi.nlm.nih.gov/26977831/).
- Pennant ME, Mehta R, Moody P, et al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. *BJOG.* 2017; 124(3): 404–411, doi: [10.1111/1471-0528.14385](https://doi.org/10.1111/1471-0528.14385), indexed in Pubmed: [27766759](https://pubmed.ncbi.nlm.nih.gov/27766759/).
- Baral R, Pudasaini S. Histopathological pattern of endometrial samples in abnormal uterine bleeding. *Journal of Pathology of Nepal.* 1970; 1(1): 13–16, doi: [10.3126/jpn.v1i1.4443](https://doi.org/10.3126/jpn.v1i1.4443).
- Clarke MA, Long BJ, Del Mar Morillo A, et al. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis. *JAMA Intern Med.* 2018; 178(9): 1210–1222, doi: [10.1001/jamainternmed.2018.2820](https://doi.org/10.1001/jamainternmed.2018.2820), indexed in Pubmed: [30083701](https://pubmed.ncbi.nlm.nih.gov/30083701/).
- Chen M, Jin Y, Li Y, et al. Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. *Int J Gynaecol Obstet.* 2016; 132(1): 34–38, doi: [10.1016/j.ijgo.2015.06.046](https://doi.org/10.1016/j.ijgo.2015.06.046), indexed in Pubmed: [26493012](https://pubmed.ncbi.nlm.nih.gov/26493012/).
- Gressel GM, Parkash V, Pal L. Management options and fertility-preserving therapy for premenopausal endometrial hyperplasia and early-stage endometrial cancer. *Int J Gynaecol Obstet.* 2015; 131(3): 234–239, doi: [10.1016/j.ijgo.2015.06.031](https://doi.org/10.1016/j.ijgo.2015.06.031), indexed in Pubmed: [26384790](https://pubmed.ncbi.nlm.nih.gov/26384790/).
- Rodolakis A, Biliatis I, Morice P, et al. European Society of Gynecological Oncology Task Force for Fertility Preservation: Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients. *Int J Gynecol Cancer.* 2015; 25(7): 1258–1265, doi: [10.1097/IGC.0000000000000493](https://doi.org/10.1097/IGC.0000000000000493), indexed in Pubmed: [26186070](https://pubmed.ncbi.nlm.nih.gov/26186070/).
- Ohyagi-Hara C, Sawada K, Aki I, et al. Efficacies and pregnant outcomes of fertility-sparing treatment with medroxyprogesterone acetate for endometrioid adenocarcinoma and complex atypical hyperplasia: our experience and a review of the literature. *Arch Gynecol Obstet.* 2015; 291(1): 151–157, doi: [10.1007/s00404-014-3417-z](https://doi.org/10.1007/s00404-014-3417-z), indexed in Pubmed: [25118836](https://pubmed.ncbi.nlm.nih.gov/25118836/).
- WHO Classification of Tumours Editorial Board. *Female Genital Tumours: WHO Classification of Tumours, 5th ed.* IARC, Lyon 2020.
- Yayla Abide C, Bostanci Ergen E, Cogendez E, et al. Evaluation of complete blood count parameters to predict endometrial cancer. *J Clin Lab Anal.* 2018; 32(6): e22438, doi: [10.1002/jcla.22438](https://doi.org/10.1002/jcla.22438), indexed in Pubmed: [29604099](https://pubmed.ncbi.nlm.nih.gov/29604099/).
- Karateke A, Kaplanoglu M, Baloglu A. Relations of Platelet Indices with Endometrial Hyperplasia and Endometrial Cancer. *Asian Pac J Cancer Prev.* 2015; 16(12): 4905–4908, doi: [10.7314/apjcp.2015.16.12.4905](https://doi.org/10.7314/apjcp.2015.16.12.4905), indexed in Pubmed: [26163613](https://pubmed.ncbi.nlm.nih.gov/26163613/).
- Schlesinger M. Role of platelets and platelet receptors in cancer metastasis. *J Hematol Oncol.* 2018; 11(1): 125, doi: [10.1186/s13045-018-0669-2](https://doi.org/10.1186/s13045-018-0669-2), indexed in Pubmed: [30305116](https://pubmed.ncbi.nlm.nih.gov/30305116/).
- Huong PT, Nguyen LT, Nguyen XB, et al. The Role of Platelets in the Tumor-Microenvironment and the Drug Resistance of Cancer Cells. *Cancers (Basel).* 2019; 11(2), doi: [10.3390/cancers11020240](https://doi.org/10.3390/cancers11020240), indexed in Pubmed: [30791448](https://pubmed.ncbi.nlm.nih.gov/30791448/).
- Korniluk A, Koper-Lenkiewicz OM, Kamińska J, et al. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. *Mediators Inflamm.* 2019; 2019: 9213074, doi: [10.1155/2019/9213074](https://doi.org/10.1155/2019/9213074), indexed in Pubmed: [31148950](https://pubmed.ncbi.nlm.nih.gov/31148950/).
- Kurtoglu E, Kokcu A, Celik H, et al. Platelet Indices May be Useful in Discrimination of Benign and Malign Endometrial Lesions, and Early and Advanced Stage Endometrial Cancer. *Asian Pac J Cancer Prev.* 2015; 16(13): 5397–5400, doi: [10.7314/apjcp.2015.16.13.5397](https://doi.org/10.7314/apjcp.2015.16.13.5397), indexed in Pubmed: [26225684](https://pubmed.ncbi.nlm.nih.gov/26225684/).
- Song J, Lai X, Zhang Y, et al. Preoperative platelet morphology parameters as prognostic predictors for endometrial malignant carcinoma stage and progesterone receptor. *Medicine (Baltimore).* 2019; 98(47): e17818, doi: [10.1097/MD.00000000000017818](https://doi.org/10.1097/MD.00000000000017818), indexed in Pubmed: [31764773](https://pubmed.ncbi.nlm.nih.gov/31764773/).
- Oge T, Yalcin OT, Ozalp SS, et al. Platelet volume as a parameter for platelet activation in patients with endometrial cancer. *J Obstet Gynaecol Res.* 2015; 41(3): 445–448.
- Lin RJ, Afshar-Kharghan V, Schafer AI. Paraneoplastic thrombocytosis: the secrets of tumor self-promotion. *Blood.* 2014; 124(2): 184–187, doi: [10.1182/blood-2014-03-562538](https://doi.org/10.1182/blood-2014-03-562538), indexed in Pubmed: [24868077](https://pubmed.ncbi.nlm.nih.gov/24868077/).
- Sharma D, Singh G. Thrombocytosis in gynecological cancers. *J Cancer Res Ther.* 2017; 13(2): 193–197, doi: [10.4103/0973-1482.189234](https://doi.org/10.4103/0973-1482.189234), indexed in Pubmed: [28643732](https://pubmed.ncbi.nlm.nih.gov/28643732/).
- Haruma T, Nakamura K, Nishida T, et al. Pre-treatment neutrophil to lymphocyte ratio is a predictor of prognosis in endometrial cancer. *Anticancer Res.* 2015; 35(1): 337–343, indexed in Pubmed: [25550569](https://pubmed.ncbi.nlm.nih.gov/25550569/).
- Suh DH, Kim HS, Chung HH, et al. Pre-operative systemic inflammatory response markers in predicting lymph node metastasis in endometrioid endometrial adenocarcinoma. *Eur J Obstet Gynecol Reprod Biol.* 2012; 162(2): 206–210, doi: [10.1016/j.ejogrb.2012.02.028](https://doi.org/10.1016/j.ejogrb.2012.02.028), indexed in Pubmed: [22445206](https://pubmed.ncbi.nlm.nih.gov/22445206/).
- Wang D, Yang JX, Cao DY, et al. Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. *Onco Targets Ther.* 2013; 6: 211–216, doi: [10.2147/OTT.S41711](https://doi.org/10.2147/OTT.S41711), indexed in Pubmed: [23525143](https://pubmed.ncbi.nlm.nih.gov/23525143/).
- Pergialiotis V, Oikonomou M, Damaskou V, et al. Platelet to lymphocyte and neutrophil to lymphocyte ratio as predictive indices of endometrial carcinoma: Findings from a retrospective series of patients and meta-analysis. *J Gynecol Obstet Hum Reprod.* 2018; 47(10): 511–516, doi: [10.1016/j.jogoh.2018.08.016](https://doi.org/10.1016/j.jogoh.2018.08.016), indexed in Pubmed: [30153505](https://pubmed.ncbi.nlm.nih.gov/30153505/).
- Temur I, Kucukgoz Gulec U, Paydas S, et al. Prognostic value of pre-operative neutrophil/lymphocyte ratio, monocyte count, mean platelet volume, and platelet/lymphocyte ratio in endometrial cancer. *Eur J Obstet Gynecol Reprod Biol.* 2018; 226: 25–29, doi: [10.1016/j.ejogrb.2018.05.028](https://doi.org/10.1016/j.ejogrb.2018.05.028), indexed in Pubmed: [29804024](https://pubmed.ncbi.nlm.nih.gov/29804024/).
- Ural ÜM, Şehitoğlu İ, Tekin YB, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with endometrial hyperplasia and endometrial cancer. *J Obstet Gynaecol Res.* 2015; 41(3): 445–448, doi: [10.1111/jog.12536](https://doi.org/10.1111/jog.12536), indexed in Pubmed: [25363740](https://pubmed.ncbi.nlm.nih.gov/25363740/).
- Dong Y, Cheng Y, Wang J. The Ratio of Neutrophil to Lymphocyte is a Predictor in Endometrial Cancer. *Open Life Sci.* 2019; 14: 110–118, doi: [10.1515/biol-2019-0012](https://doi.org/10.1515/biol-2019-0012), indexed in Pubmed: [33817142](https://pubmed.ncbi.nlm.nih.gov/33817142/).
- Ni L, Tao J, Xu J, et al. Prognostic values of pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in endometrial cancer: a systematic review and meta-analysis. *Arch Gynecol Obstet.* 2020; 301(1): 251–261, doi: [10.1007/s00404-019-05372-w](https://doi.org/10.1007/s00404-019-05372-w), indexed in Pubmed: [31768743](https://pubmed.ncbi.nlm.nih.gov/31768743/).
- Friedenreich CM, Langley AR, Speidel TP, et al. Case-control study of inflammatory markers and the risk of endometrial cancer. *Eur J Cancer Prev.* 2013; 22(4): 374–379, doi: [10.1097/CEJ.0b013e32832835b3813](https://doi.org/10.1097/CEJ.0b013e32832835b3813), indexed in Pubmed: [23702681](https://pubmed.ncbi.nlm.nih.gov/23702681/).
- Terlikowska KM, Dobrzycka B, Terlikowski R, et al. Clinical value of selected markers of angiogenesis, inflammation, insulin resistance and obesity in type 1 endometrial cancer. *BMC Cancer.* 2020; 20(1): 921, doi: [10.1186/s12885-020-07415-x](https://doi.org/10.1186/s12885-020-07415-x), indexed in Pubmed: [32977765](https://pubmed.ncbi.nlm.nih.gov/32977765/).