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POSSIBILITY OF USING BIOCHEMICAL AND HEMATOLOGICAL PARAMETERS IN EVALUATING ADNEXAL MASSES

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Current diagnostic approach to adnexal masses (medical history, clinical examination, transvaginal sonography, tumour markers) does not provide an accurate prediction for potential malignancy. There is a possibility of using hematological and biochemical parameters (platelets count, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet distribution width, level of C-reactive protein) in predicting ovarian malignancy. A retrospective study was conducted. Analysis of aforementioned parameters was performed in patients with histopathologically verified benign/malignant ovarian tumours. CRP levels, total count of granulocytes, and total count of platelets were statistically significantly higher in patients with malignant changes ($p < 0.001$, $p = 0{,}001$, or $p = 0.023$). Total lymphocytes count was statistically significantly lower in patients with malignant changes ($p < 0.001$). Platelet count was statistically significantly higher in patients with stage III ($p = 0.011$). Pl/LY ratio was statistically significantly higher in patients with stage III ($p = 0.043$). CRP was statistically significantly higher in stage III ($p < 0.001$). Lymphocyte count was statistically significantly lower in stage III ($p < 0.001$), and granulocyte count was statistically significantly higher in stage III ($p = 0.001$). Platelet count was statistically significantly higher in stage III ($p = 0.001$). MPV was statistically significantly lower in stage III ($p = 0.031$). Pl/Ly ratio was statistically significantly higher in patients with stage III ($p = 0.044$). Analyzed biochemical and hematological parameters are of limited utility in differentiating benign from malignant ovarian masses. Elevated levels of C-reactive protein, neutrophils and platelets suggest potentially malignant ovarian masses. Analyzed biochemical parameter (high levels of C-reactive protein, reduced lymphocyte count, increased granulocyte count, increased platelet count, increased PLR, as well as lower MPV values) may suggest advanced malignancy.

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Introduction

Adnexal masses represent different changes of gynaecological (functional cysts, inflammatory changes, benign and malignant neoplasma) and nongynaeacological origin. It is not diagnosed easily and diagnostic errors and problems are possible (1-4). Evaluation of adnexal masses involves an accurate anamnesis, careful clinical examination, transvaginal sonography, and determination of tumour markers. Ultrasound diagnostics is non-invasive, cheap and available for adnexal masses evaluation. Transvaginal sonography is the preferred technique (no need for special equipment, area of interest is close to the probe). Ultrasound diagnostics identifies adnexal masses. Masses that are bilateral, large, complex, irregular, and accompanied by ascites are considered suspicious (5). By using ultrasound as a diagnostic tool, patients can be grouped into those in whom surveillance using serial ultrasonography can be applied, and those who require surgery (6). The Gynecologic Imaging Reporting and Data System (GI-RADS) is a reporting system that was created for reporting the findings in adnexal masses based on transvaginal ultrasonography (7). Still, there is a possibility that GI-RADS classification gives a great number of false-positive results, so it is recommended to additionally use tumour markers. Additional measurements to GI-RADS system do not alter clinical approach (6-9).

The success of surgical treatment depends on appropriate preoperative plan. There is a need to define steps in treating indeterminate adnexal changes (10). Monitoring the morphology of tu-

mours, the presence of ascites, and Doppler parameters facilitate approaches in making preoperative plans and the choice of medical center for patients to be treated. Patients with diagnosed adnexal masses indicative of malignancy should be referred to a gyneacological oncologist for optimal patient treatment (11). Surgeries performed by a well-trained surgeon, in a well-equipped center, provide optimal surgical treatment (12-15).

Current diagnostic approach to adnexal masses (history taking, clinical examination, transvaginal sonography, tumour markers) does not provide accurate prediction of potential malignancy, thus potentially affecting the choice and time of treatment, the choice of medical center, specialist doctor and surgical approach (laparotomy/laparoscopy). There is a need to define additional parameters for a more accurate preoperative prediction of potential malignancy. There is a possibility to utilize hematological parameters (platelets count, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet distribution width) that have been used in routine preoperative diagnostics and preoperative preparation. Preoperative determination of these parameters is cheap, available, repeatable, and potentially useful in evaluating adnexal masses (16-20).

Methods of the study

The study is a retrospective one. Patients operated at out Clinic for diagnosed adnexal masses were analyzed. The study enrolled 100 surgically treated patients. They were all operated for ovarian tumours, and all of them were operated at our Clinic according to current oncologic principles (full staging). Standard hematological and biochemical parameters were controlled preoperatively. After the surgery, according to histopathological reports on removed adnexal masses, we formed a group of patients with benign ovarian tumours and a group of patients with malignant ovarian tumours. Patients with detected inflammatory changes (tubo-ovarian abscesses), metastatic ovarian changes, as well as patients with incomplete staging were excluded from the study.

Patients' age, histopathological type of tumour, and stage of the disease were analyzed in patients with malignant ovarian disease. Preoperative hematological parameters, total count of erythrocytes/ml, total count of leukocytes/ml, total count of neutrophils/ml, lymphocyte count/ml, monocyte count/ml, platelet count/ml, neutrophils/platelets count ratio, neutrophils/lymphocyte count ratio, platelet distribution width, platelet volume, and the level of C-reactive protein were analyzed in both groups.

Biochemical and hematological parameters were compared in patients with adnexal masses: a group with histopathologically verified benign ovarian tumours, and a group with verified malignant ovarian neoplasm.

The analyzed parameters were compared in relation to histopathological type of malignant ovarian tumour. We also observed the possibility of statistical difference in monitored biochemical parameters between the groups with early and advanced ovarian cancer, as well as between benign ovarian tumours and values of monitored parameters in patients with advanced ovary cancer (stage III).

Statistical data processing

The data are presented in the form of arithmetic mean ± standard deviation. If data distribution was normal, t-test and ANOVA were used. If not, Mann-Whitney test and Kruskal-Wallis test were used. Hypothesis was tested with significance threshold of $p < 0.05$: Statistical data analysis was performed by software package SPSS 16.0.

Results

The study enrolled 100 patients, mean age 51.40 ± 15.92 years (Min 19, Max 83 years). Patients with malignant adnexal changes were statistically significantly older in comparison to patients with benign changes ($p = 0.037$). CRP values, total count of granulocytes and total count of platelets were statistically significantly higher in patients with malignant changes ($p < 0.001$, $p = 0.001$, or $p = 0.023$). Total count of lymphocytes was statistically significantly lower in patients with malignant changes ($p < 0.001$). Other analyzed parameters showed no statistically significant difference in total count of erythrocytes and monocytes. Also, there was no statistically significant difference in the parameters related to platelet characteristics (MPV, PCT, PDW), neither regarding neutrophil/lymphocyte count ratio nor platelet/lymphocyte count (Table 1).

In the group with malignant tumours, 25 patients (50.0%) had serous carcinoma, 14 patients (28.0%) mucinous carcinoma, and 11 patients (22.0%) had other types of carcinoma. It has been noted that there was no statistically significant difference in relation to histopahological type of cancer (Table 2).

There were 20 patients (40.0%) in the group with malignant disease stage I, 7 patients (14.0%) in the stage II group and 23 patients (46.0%) in the stage III group. Platelet count was statistically significantly higher in patients with stage III ($p = 0.011$). Pl/LY ratio was statistically significantly higher in patients with stage III ($p = 0.043$) (Table 3).

Patients with stage III disease were statistically significantly older ($p = 0.003$). CRP was statistically significantly higher in stage III ($p < 0.001$). Lymphocyte count was statistically significantly lower in stage III ($p < 0.001$), and granulocyte count was statistically significantly higher in stage III ($p = 0.001$). Platelet count was statistically significantly higher in stage III ($p = 0.001$). MPV was statistically significantly lower in stage III ($p = 0.031$). Pl/Ly ratio was statistically significantly higher in patients with stage III disease ($p = 0.044$) (Table 4).

Table 1. Biochemical and hemoatological parameters in analyzed population in comparison to the type of change (benign/malignant)

	Total	Malignant	Benign	p
Age	51.40 ± 15.92	54.44 ± 15.47	48.36 ± 15,94	0.037[1]
CRP	17.84 ± 35.05	30.46 ± 46.09	5.22 ± 5.78	< 0.001[2]
ER	4.37 ± 0.50	4.35 ± 0.57	4.38 ± 0.41	0.737[1]
LE	8.74 ± 3.49	8.46 ± 3.23	9.01 ± 3.75	0.699[2]
LY	4.42 ± 3.16	3.07 ± 2.43	5.77 ± 3.26	< 0.001[2]
GR	3.75 ± 3.04	4.65 ± 3.26	2.84 ± 2.50	0.001[2]
MO	3.51 ± 29.06	6.51 ± 41.07	0.50 ± 0.30	0.252[2]
TR	287.29 ± 112.30	316.26 ± 138.75	258.32 ± 67.21	0.023[2]
MPV	10.20 ± 12.11	9.78 ± 11.56	10.62 ± 12.74	0.062[2]
PCT	0.26 ± 1.18	0.38 ± 1.67	0.15 ± 0.14	0.887[2]
PDW	16.33 ± 5.17	16.37 ± 5.87	16.30 ± 4.46	0.468[2]
Ne/Ly	3.54 ± 3.12	4.11 ± 4.05	2.96 ± 1.59	0.339[2]
Tr/ly	155.05 ± 125.69	178.30 ± 157.95	131.80 ± 76.58	0.394[2]

1- t test, 2- Mann-Whitney test

Table 2. Biochemical parameters in relation to histopathological type of malignant tumours

	Serous	Mucinous	Other	p[1]
Age	58.36 ± 14.61	52.57 ± 14.72	47.91 ± 16.99	0.138
CRP	30.32 ± 40.34	41.81 ± 65.10	16.33 ± 24.33	0.449[2]
ER	4.33 ± 0.60	4.27 ± 0.53	4.50 ± 0.57	0.588
LE	8.44 ± 3.35	9.18 ± 2.43	7.61 ± 3.89	0.238[2]
LY	2.89 ± 2.25	3.31 ± 2.22	3.17 ± 3.20	0.802[2]
GR	4.98 ± 3.17	5.03 ± 2.96	3.43 ± 3.86	0.081[2]
MO	0.55 ± 0.29	1.19 ± 2.43	26.84 ± 87.61	0.551[2]
TR	357.36 ± 163.05	289.42 ± 84.72	256.99 ± 109.98	0.235[2]
MPV	8.30 ± 1.29	7.99 ± 1.34	15.40 ± 24.58	0.186[2]
PCT	0.16 ± 0.17	0.14 ± 0.22	1.20 ± 3.55	0.715[2]
PDW	16.15 ± 4.53	14.23 ± 6.31	19.89 ± 7.00	0.215[2]
Ne/Ly	3.81 ± 3.98	4.06 ± 2.52	4.88 ± 5.76	0.697[2]
Pl/ly	221.08 ± 193.50	131.57 ± 114.34	140.54 ± 78.70	0.189[2]

1- ANOVA, 2- Kruskal-Wallis test

Table 3. Biochemical parameters in relation to the stage of the disease

	Stage I+II	Stage III	p[1]
Age	5048 ± 16.60	59.09 ± 12.87	0.071
CRP	28.08 ± 50.91	33.25 ± 40.66	0.102
ER	4.34 ± 0.52	4.37 ± 0.64	0.953
LE	7.77 ± 2.92	9.28 ± 3.45	0.104
LY	2.93 ± 2.24	3.24 ± 2.69	0.97
GR	4.13 ± 3.11	5.27 ± 3.42	0.185
MO	11.54 ± 55.88	0.62 ± 0.31	0.066
TR	266.59 ± 97.50	374.56 ± 158.30	0.011
MPV	11.12 ± 15.70	8.20 ± 1.40	0.325
PCT	0.56 ± 2.27	0.18 ± 0.17	0.115
PDW	16.20 ± 7.10	16.57 ± 4.12	0.942
Ne/Ly	4.23 ± 4.06	3.97 ± 4.13	0.899
Pl/Ly	141.59 ± 129.62	221.39 ± 179.22	0.043

1-Mann-Whitney test

Table 4. Comparison of biochemical parameters between patients with ovarian carcinoma stage III and patients with benign ovarian tumours

	Ovarian carcinoma stage III	Benign tumours	P
Age	59.09 ± 12.87	48.36 ± 15.94	0.003[1]
CRP	33.25 ± 40.66	5.22 ± 5.78	< 0.001[2]
ER	4.37 ± 0.64	4.38 ± 0.41	0.906[1]
LE	9.28 ± 3.45	9.01 ± 3.75	0.510[2]
LY	3.24 ± 2.69	5.77 ± 3.26	< 0.001[2]
GR	5.26 ± 3.42	2.84 ± 2.50	0.001[2]
MO	0.62 ± 0.30	0.50 ± 0.30	0.064[2]
TR	374.56 ± 158.30	258.32 ± 67.21	0.001[2]
MPV	8.20 ± 1.40	10.62 ± 12.74	0.031[2]
PCT	0.18 ± 0.17	0.15 ± 0.14	0.242[2]
PDW	16.57 ± 4.12	16.30 ± 4.46	0.582[2]
Ne/Ly	3.97 ± 4.13	2.96 ± 1.59	0.288[2]
Tr/ly	221.39 ± 179.22	131.80 ± 76.58	0.044[2]

1- t test, 2- Mann-Whitney test

Discussion

Inflammation and inflammatory response play a pivotal role in the development and progression of malignant diseases. Biochemical and hematological inflammatory markers may be incorporated into prognostic score for various carcinoma types. Patients with malignant ovarian tumours had statistically significantly higher values of C-reactive protein and higher levels of total granulocytes, as observed in our study. High levels of C-reactive protein and leukocytosis are markers of systemic inflammatory response. Many studies suggest that high neutrophil-to-leukocyte ratio (N/LR) is associated with poor survival rate in patients with malignant diseases (20). It seems that an increase of NLR is greater in patients with metastatic disease and longer inflammatory response (21). We have not observed statistically significant difference in NLR between the group with malignant and the group with benign ovarian changes. We also have not registered statistically significant difference in this parameter by comparing groups of patients with an early and advance disease stage III (21). Our study showed that patients with advanced disease had significantly higher count of granulocytes in comparison to those with benign ovarian changes. Neutrophils have a role in immune response, they inhibit the immune system by suppressing cytolytic activity of lymphocytes (22). The presence of tumour-infiltrating lymphocytes is suggestive of better response to treatment (23). Patients in our study have statistically significantly lower total lymphocyte count. A change in neutrophil to lymphocyte ratio may be more useful in tailoring therapy for patients with advanced malignant disease, rather than being an early disease marker (21). There is evidence that neutrophil-to-leukocyte ratio is an available marker of systemic inflammation, but, it has also been reported that this ratio may be useful in predicting operable disease and in forming pretreatment and preoperative strategy (24).

Research has shown that inflammation plays a key role in cancer pathogenesis. It affects tumour microenvironment, cell proliferation signaling, factors that impact programmed cell death, proangiogenesis, capability for invasion and metastasis (25). Inflammation may be evident in some cases at early stages of neoplastic progression. It is believed that inflammatory cells can release agents that may accelerate genetic changes (25).

Besides aforementioned parameters, a complete blood count also includes platelet count and platelet indices. We followed platelet count (Tr, Plt), mean platelet volume (MPV), plateletcrit (Pct) and platelet distribution width (PDW). PDW - Platelet distribution width represents a variation of platelet size distribution index (distribution curves for platelet distribution width). This platelet index is calculated from the distribution curve of the platelet volume and represents the width of the curve. Platelet distribution width (PDW) is a regular parameter in blood routine examination which reflects variation of platelet size distribution with a range from 8.3% to 56.6% (26). Morphological changes of platelets are always present when they are activated during inflammatory response. Plateletcrit (Pct) is a platelet index representing platelet volume as a percentage, or the relation between a total volume of full blood sample and the total number of platelets. Diagnostic value of this index remains to be seen (26).

Our study showed that patients with malignant ovarian tumours had statistically significantly higher platelet levels, but there was no statistically significant difference in PLR in comparison to the patients with benign changes. Some authors report that, despite limited sensitivity and specificity, PLR and NLR may be used as predictive factors for survival (19, 27). We have not found a statistically significant difference in platelet count and platelet parameters in benign/malignant changes (20).

Expressed inflammation, thrombocytosis, and platelet hyperreactivity are often associated with malignancies. In our patients with advanced stages, thrombocytosis, higher PLR and low MPV were registered. Some of these parameters are associated with advanced stages of the disease, inoperability and poor outcome, so these parameters are more useful in predicting advanced stage disease than as early disease markers (18).

Conclusion

The analyzed biochemical parameters are of limited value in differentiating benign from malignant ovarian masses. Elevated levels of C-reactive protein, neutrophils and platelets are indicative of potentially malignant ovarian mass.

The analyzed biochemical parameters (high levels of C-reactive protein, low lymphocyte count, higher granulocyte count, higher platelet count, elevated PLR and lower levels of MPV) may be suggestive of advanced malignant disease, thus potentially changing therapeutic approach.

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MOGUĆNOST KORIŠĆENJA BIOHEMIJSKIH I HEMATOLOŠKIH PARAMETARA U PROCENI ADNEKSALNIH MASA

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Sadašnji dijagnostički pristup adneksalnim masama (anamneza, klinički pregled, transvaginalna sonografija, tumorski markeri) ne omogućava preciznu predikciju mogućeg maligniteta. Postoji mogućnost korišćenja hematoloških i biohemijskih parametara (broj trombocita, odnos neutrofila i limfocita, odnos trombocita i neutrofila, trombocitna širina, nivo C reaktivnog proteina) u predikciji ovarijalnog maligniteta.

Sprovedeno je retrospektivno istraživanje. Analiza pomenutih parametara kod bolesnica sa histopatološki verifikovanim benignim/malignim ovarijalnim tumorima.

Vrednosti CRP-a, ukupan broj granulocita i ukupan broj trombocita statistički su značajno veće kod bolesnica sa malignim promenama ($p < 0,001$, $p = 0,001$; odnosno $p = 0,023$). Ukupan broj limfocita statistički je značajno manji kod bolesnica sa malignim promenama ($p < 0,001$). Broj trombocita statistički je značajno veći kod bolesnica sa stadijumom III tumora ($p = 0,011$). Odnos Tr/LY statistički je značajno veći kod bolesnica sa stadijumom III tumora ($p = 0,043$). CRP je statistički značajno viši kod bolesnica III stadijuma tumora ($p < 0,001$). Broj limfocita statistički je značajno niži kod bolesnica III stadijuma tumora ($p < 0,001$), a broj granulocita je statistički značajno veći kod bolesnica sa III stadijumom tumora ($p = 0,001$). Broj trombocita statistički je značajno veći kod bolesnica sa III stadijumom tumora ($p = 0,001$). MPV je statistički značajno manji kod bolesnica sa III stadijumom tumora ($p = 0,031$). Tr/Ly odnos statistički je značajno veći kod bolesnica na III stadijumom tumora ($p = 0,044$).

Ispitivani biohemijski i hematološki parametri su od ograničene vrednosti u diferencijaciji benignih od malignih ovarijalnih masa. Povišeni nivoi C reaktivnog proteina, neutrofila i trombocita ukazuju na, verovatno, malignu ovarijalnu masu. Ispitivani biohemijski parametri (visoki nivoi C reaktivnog proteina, nizak broj limfocita, viši broj granulocita, viši niovoi trombocita, povišeni odnos PLR-a, kao i niži nivoi MPV-a) mogu ukazati na uznapredovalu malignu bolest.

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Ključne reči: *karcinom jajnika, biohemijski, hematoloski parametri*