ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 28(4): 686-692, 2023
DOI: 10.5505/ejm.2023.87533

Can Preoperative Complete Blood Count Parameters and Tumor Markers Predict The Differential Diagnosis of Mucinous Ovarian Tumors?

Elcin Telli[1*], Tufan Oge[2], Omer Tarık Yalcin[2]

[1]Asistant Professor, Division of Gynecologic Oncology Surgery, Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkiye
[2]Professor, Division of Gynecologic Oncology Surgery, Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkiye

ABSTRACT

Mucinous ovarian tumors are typically large masses that cause preoperative and intraoperative evaluation challenges due to their size. Our study aims to assess the effectiveness of routinely studied preoperative complete blood count parameters and tumor markers in differentiating between benign, borderline, and malignant mucinous ovarian tumors.

Patients who had surgery for a suspected adnexal mass and were diagnosed with a mucinous ovarian tumor between January 2019 and June 2023 were included in this study. The surgeries were performed at a gynecological oncology unit in a tertiary referral center. Cases that met the study criteria were categorized into three groups: benign, borderline, and malignant, based on their pathology results. We evaluated various parameters from the complete blood count (hemoglobin, hematocrit, leukocytes, neutrophils, lymphocytes, platelets, mean platelet volume), ratios of these parameters to each other (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio), tumor markers (Ca 125, Ca 19.9, CEA), and proportions of tumor markers to each other (Ca125/Ca19.9, Ca19.9/CEA).

The serum levels of Ca125, Ca19.9, CEA, and the Ca125/Ca19.9 ratio were significantly different between the groups ($p<0.05$). When using the cut-off values of Ca125>39 U/ml, Ca19.9>24.5 U/ml, CEA>4.9 ng/dl, and Ca125/Ca19.9 ratio ≤0.97, these markers showed sensitivities of 64.7%, 82.4%, 52.9%, and 64.7% respectively in distinguishing between benign and malignant mucinous ovarian tumors.

Ca19.9 was the most sensitive marker in distinguishing between benign and malignant mucinous tumors, as well as borderline and malignant mucinous tumors.

Keywords: mucinous, NLR, ovary, PLR, tumor marker

Introduction

Primary mucinous tumors of the ovary make up 15% of all primary ovarian tumors. They are classified as cystadenomas (benign), mucinous borderline tumors (borderline), and mucinous adenocarcinomas (malignant). Most mucinous cystadenomas are multicystic and unilateral. They can occur at any age and often grow to be very large. Mucinous borderline tumors are typically found in young patients. The average size of intestinal-type borderline tumors, which constitute 85-95% of all borderline mucinous tumors, is 17 cm. About 90% of these tumors are found on one side only, 75% have multiple cysts, and they can be difficult to distinguish from cystadenomas or cystadenocarcinomas based on appearance alone. Borderline mucinous tumors of the endocervical type, which are less common, are found on both sides in about 40% of cases. Most of these tumors have a single mass and can grow as large as 36 cm. In rare cases, invasive carcinoma can be missed in certain areas due to the cysts' large size, even if more sections are examined during the frozen examination of borderline tumors. (1,2).

Primary mucinous carcinomas of the ovary are rare, excluding metastatic tumors. The average age of occurrence is between 39-50, and they can reach a size of up to 40 cm. While all mucinous tumor subtypes can show solid areas on imaging due to fibrous stroma, carcinomas have a higher rate of solid regions. Most carcinomas are unilateral and multicystic, with only about 4% being pure solid. Eighty percent of mucinous

***Corresponding Author:** Elcin Telli, Asistant Professor, Division of Gynecologic Oncology Surgery, Department of Obstetrics and Gynecology, Eskisehir Osmangazi University School of Medicine, Eskisehir, Turkiye
E-mail: drelcinuzmez@hotmail.com, Phone: 0 (505) 442 23 95
ORCID ID: Elcin Telli: 0000-0002-3228-8809, **Tufan Oge:** 0000-0002-1951-9713, **Omer Tarık Yalcin:** 0000-0001-5626-1881
Received: 26.08.2023, **Accepted:** 07.09.2023

ovarian carcinomas are detected in stage IA (1,2). It is difficult to differentiate between mucinous ovarian tumors due to their similar appearance on ultrasound, the fact that all subtypes can grow to enormous sizes, the presence of solid areas even in benign tumors, and the possibility of missing invasive carcinoma even with oversampling during intraoperative frozen examination due to their large size (2).

The tumor-associated inflammation theory is a current area of research in tumorigenesis. Parameters such as preoperative inflammatory cell counts, NLR (neutrophil/lymphocyte ratio), and PLR (platelet /lymphocyte ratio) are direct biomarkers of the body's inflammatory response. They have been associated with the diagnosis, differential diagnosis, and prognosis of many cancers, including ovarian cancer. There is also information in the literature suggesting that tumor markers increase in borderline and malignant ovarian tumors. However, data on Ca19.9 and mucinous tumors are limited (2-7).

In our study, we aimed to determine whether the routinely required complete blood count parameters, tumor markers, and their proportions can be used to predict the differential diagnosis of mucinous ovarian tumors.

Materials and Methods

Patients who underwent laparotomy with a preliminary diagnosis of a suspicious adnexal mass and were later confirmed to have a pure mucinous ovarian tumor were retrospectively evaluated. The study was conducted between January 2019 and June 2023 at a gynecology oncology unit in a university hospital. Data collection began after receiving approval from the ethics committee (local ethics committee date: June 20 th, 2023, number:44). All patients were included in the study, except for those with missing data, hematological disease, intraoperative torsion, concomitant abscess or infectious process, rheumatological or heart disease, concomitant endometriosis, other organ malignancies, metastatic mucinous tumors, and pregnant women. Additionally, transfused patients, patients using anticoagulant/antiaggregant drugs, and patients who received chemotherapy before laparotomy were excluded. During the operation, all patients underwent abdominal exploration, and samples of pelvic cytological fluid were taken.

Adnexal masses were removed by cystectomy or salpingo-oophorectomy, depending on the patient's age and fertility request. The removed masses were sent for frozen examination. Based on the results, additional surgical staging steps were performed for malignant and borderline tumors, taking into account the patient's age, menopause status, and fertility request. In benign cases, the operation was concluded. Blood samples of patients belonging to one week before the process were retrospectively reviewed. After excluding patients who did not meet the study criteria, a total of 74 patients were divided into three groups based on the pathology results: benign (mucinous cystadenoma), borderline (borderline mucinous tumor), and malignant (mucinous adenocarcinoma). The groups were compared in terms of demographic characteristics such as age, number of pregnancies (gravida), number of births (parity), menopause status, comorbidities, location of the mass (right, left, bilateral), preoperative ultrasound appearance of the mass (unilocular cystic, multilocular cystic, solid), and tumor size.

Additionally, preoperative complete blood count parameters (hemoglobin, hematocrit, leukocyte count, neutrophil count, lymphocyte count, platelet count, and mean platelet volume), ratios of blood parameters (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio), and serum tumor markers (cancer antigen 125 (Ca 125), cancer antigen 19.9 (Ca19.9), and carcinoembryonic antigen (CEA)) and their ratios (Ca125/Ca19.9, Ca19.9/CEA) were compared between the groups. Receiver operating characteristic (ROC) analysis was conducted to evaluate the parameters that showed statistical significance in the comparison. Cut-off values were determined, and these parameters' sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the differential diagnosis of mucinous ovarian tumors.

In this study, we used the Shapiro-Wilk test to assess the normality of continuous variables. We conducted ANOVA and Tukey's Multiple Comparison tests for normally distributed variables and expressed the results as mean ± standard deviation (SD). For variables that were not normally distributed, we used the Kruskal-Wallis test and Dunn's multiple comparison tests and reported the results as the median (interquartile range). We used the Chi-square test for categorical variables and presented the results as frequency and percentage. We considered a statistical significance when the level of $P<0.05$. To identify significant variables for the differential diagnosis in benign, borderline, and malignant

groups, we performed a Receiver Operating Characteristic (ROC) analysis. We used IBM SPSS Statistics 23.0 (SPSS Inc., Chicago, Illinois) and MedCalc 15.2 (Ostend, Belgium) for the statistical analyses.

Results

We evaluated 74 patients in our study and grouped them based on their pathological results. The groups consisted of 33 patients with benign results, 24 with borderline results, and 17 with malignant results. Table 1 provides the demographic characteristics of the patients, complete blood count parameters, NLR, and PLR results. We found that the patients in the benign and borderline groups were younger than those with malignant outcomes ($p=0.004$, $p=0.01$, respectively). There was no significant difference between the groups regarding patient comorbidities ($p>0.05$). Among the benign patients, 40% were postmenopausal, while 16.7% of the borderline group and 64.7% of the malignant patients were postmenopausal ($p=0.008$).

In the ultrasonographic evaluation of the masses, we found no significant difference in size and side ($p=0.094$, $p=0.18$, respectively). However, we observed that 48.5% of the benign masses were located on the right side, 62.5% of the borderline masses were found on the left side, and more than half of the malignant masses were located on the right ovary. The rate of bilaterality in primary mucinous ovarian malignancies was found to be 5.9%. Regarding ultrasonographic appearance, most benign cases (37.1%) had an unilocular appearance, while most borderline cases (83.3%) had a multicystic appearance. On the other hand, 64.7% of malignant cases had a multicystic and solid appearance ($p<0.001$).

Table 2 displays tumor markers and their ratios to each other and comparisons between groups. Posthoc analysis was conducted for Ca125, Ca19.9, CEA, and Ca125/Ca19.9 ratios, which yielded statistically significant p values. The analysis results are also presented in Table 2.

Cut-off values were determined for Ca125, Ca19.9, CEA, and Ca125/Ca19.9 ratio, with a p-value of <0.05, among the parameters we investigated for their effectiveness. The variables' sensitivity, specificity, positive predictive value, and negative predictive value were determined based on these values and are shown in Table 3.

Discussion

Most mucinous tumors are benign. The majority of borderline subtypes are confined to the ovary, and only about 3% of cases are in an advanced stage. The prognosis for these cases is promising. The 5-year survival rate for borderline ovarian tumors is 98%, and 96% for ten years. Most mucinous carcinomas that appear to be in advanced stages are usually metastatic from the other parts of the body, with the most common sites of metastasis being the gastrointestinal tract, colon, appendix, and pancreas. Around 80% of primary ovarian mucinous adenocarcinomas are detected in Stage IA, and the 5-year survival rate for these patients is approximately 95% (2,3).

Our study found that platelet, NLR, and PLR values, previously considered helpful in diagnosing epithelial ovarian cancers, were ineffective in distinguishing between mucinous benign, borderline, and malignant tumors. However, we did find that the ratio of Ca 125, Ca19.9, CEA, and Ca125/Ca19.9 is effective in distinguishing between benign and malignant mucinous ovarian tumors when the cut-off values of >39 U/ml, >24.5 U/ml, >4.9 ng/dl, and ≤0.97 are used respectively.

Ultrasonography is an effective imaging method for evaluating adnexal masses' anatomical location and composition. Mucinous ovarian tumors are typically large masses and may require evaluation through abdominal ultrasonography. These tumors are often multilocular, giant masses with varying levels of complexity, featuring honeycomb-like structures and small cystic components (8).

The analysis of frozen sections of borderline ovarian tumors shows a correlation between 62.8% and 87.0% with the final pathology. Differentiating between borderline malignant mucinous tumors is more complicated than serous counterparts, especially during frozen evaluation, due to changes in differentiation and large size. Removing the mass or performing a salpingo-oophorectomy is sufficient for benign mucinous tumors. If fertility is desired and a borderline tumor is diagnosed, pelvic and peritoneal washes, peritoneal biopsies, and omentectomy should be added to the staging process. In postmenopausal patients, hysterectomy and bilateral salpingo-oophorectomy are performed. While only 4% of serous ovarian cancers are detected in stage I, this rate is 83% for mucinous carcinomas. Misdiagnosing borderline tumors during surgery can lead to unnecessary procedures and staging if

Table 1: The Mean Values of The Variables For Each Group and The P-Values After Conducting Comparisons

Variables	Benign (1)	Borderline (2)	Malign (3)	P-value	Posthoc p-value
Age(years)*	45,79±13,8	46,17±11,96	59,94±18,11	0.003	1&3 0.004 2&3 0.01 1&2 0.9
Gravida (s) †	2(3)	2(1.75)	3(3.5)	0.489	
Parity (s) †	2(2)	2(1.75)	2(2)	0.450	
Size (cm)*	14,64±7,31	17,46±6,81	19,38±8,77	0.094	
Hemoglobin (g/dl)*	12,80±1,65	12,1±1,96	12,48±1,48	0.331	
Hematocrit (%) †	39.6(4.25)	37.25(8,3)	38.3(4,6)	0.151	
Leukocyte (µL) †	7860(4490)	7870(3047,5)	8130(4435)	0.984	
Lymphocyte (µL) †	2160(1070)	1980(610)	1900(1020)	0.240	
Neutrophil (µL) †	4790(3705)	5110(3197,5)	5550(3445)	0.750	
Platelet (µL) †	273000(122500)	277500(95500)	277000(111500)	0.961	
Mpv (fl) †	10(1,7)	9,4(1.85)	9,5(2,05)	0.303	
NLR†	2.42(1.52)	2.66(2,71)	2,48(2.77)	0.570	
PLR†	143.16(70.6229)	149.7(90,5486)	140.3226(145.3607)	0.520	

*mean± standard deviation, †medyan (IOR)

Table 2: Values, Comparisons, and Posthoc Analyses of Tumor Markers According To Groups

Variables	Benign (1)	Borderline (2)	Malign (3)	P-value	Posthoc p- value
Ca125 (U/ml) †	20.3(25.7)	26.65 (36.04)	47.9(106,85)	0.018	1&3 0.015 2&3 0.489 1&2 0.422
Ca19.9 (U/ml) †	13.2(15.52)	13,87(17.29)	54.91(375.02)	<0.001	1&3 0.001 2&3 0.01 1&2 1
CEA (ng/ml) †	2(1,25)	2.01(1.93)	5(21.59)	0.007	1&3 0.011 2&3 0.019 1&2 1
Ca125/Ca19.9†	1.56(2.88)	2,11 (4.33)	0,95(1.37)	0.023	1&3 0.033 2&3 0.05 1&2 1
Ca19.9/CEA (U/ng) †	7.3385(9.12)	8.28(15.93)	5,86(48.29)	0.746	

†medyan (IOR)

the case is benign or the need for additional surgical staging, especially in young patients who desire fertility if the case is malignant (9-12).

Thrombocytosis is often found in reactive conditions like acute infection, tissue damage, chronic inflammation, and surgery. However, it can also be seen in tumor formation and cancer development. A study showed that thrombocytosis increases the risk of ovarian cancer by 7.11 times in patients with undiagnosed malignancy (13,14). Neutrophils are believed to be the primary source of vascular endothelial growth factor (VEGF), important in tumor-associated blood vessel formation. Neutrophils also regulate the production of inflammatory cytokines and create a suitable environment for tumor growth. Lymphocytes also play a crucial role in the immune response to cancer (15-19). The levels of NLR and PLR are elevated in malignant ovarian tumors and systemic diseases like heart disease, rheumatologic disease, and infections (3). NLR and PLR are highly sensitive in distinguishing between ovarian tumors and detecting early-stage ovarian cancer (4,20). Most studies have focused on comparing NLR and PLR in benign and malignant tumors, with limited research on borderline tumors (21-23).

Table 3: The cut-off Value, Sensitivity, Specificity, Positive Predictive Percentage, and Negative Predictive Percentage of The Variables

Variables	Cut off	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	NPV (%)
CA 125 (benign&malign)	>39 U/ml	64.7	81.8	0.742	64.7	81.8
CA19.9 (benign&malign)	>24.5U/ml	82.4	84.9	0.860	73.7	90.3
CA19.9 (borderline&malign)	>24.03 U/ml	82.4	79.2	0.737	73.7	86.4
CEA (benign&malign)	>4.9 ng/dl	52.94	90.91	0.860	75	78.9
CEA (borderline&malign)	>4ng/dl	58.8	91.7	0.748	83.3	75.9
CA125/CA19.9 (benign &malign)	≤0.97	64.7	72.7	0.727	55	80

Abbreviations: AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value

Polat et al. found that the NLR (3.1 ± 2.9), (2.6 ± 1.5), (3.9 ± 3.8), and PLR (142.1 ± 55.7), (148.1 ± 59.4), (191.9 ± 115.1) values were present in benign, borderline, and malignant ovarian tumors, respectively, in their studies. They observed that the NLR and PLR values were similar for benign and borderline tumors, suggesting that borderline tumors do not cause a systemic inflammatory response. The optimal cut-off values for identifying ovarian malignancy were determined to be 2.47 (p = 0.02) for NLR and 144.3 for PLR (p = 0.05) (22). Our study found the NLR to be 2.48 and the PLR to be 140 for malignant cases. Still, no significant difference was found between the groups in the differential diagnosis of benign and borderline mucinous tumors. Psomiadou et al. reported that the NLR values for benign, borderline, and malignant tumors were 2.3 ± 1.2, 4.0 ± 2.7, and 3.6 ± 2.7, respectively. They also determined the PLR values for the benign (134.6 ± 50.5), borderline (180.7 ± 88.0), and malignant (210.6 ± 98.6) groups. The values for borderline and malignant ovarian tumors were similar but higher than those for benign tumors. This difference was explained by another study that mentioned the limited number of borderline cases (9 cases) (4, 23). Seçkin et al. found that to avoid missing the diagnosis of ovarian cancer in patients diagnosed with borderline ovarian tumor during intraoperative frozen evaluation; the NLR cut-off value should be 2.18. In this situation, the sensitivity, specificity, PPV, and NPV were reported as 78.02%, 64.45%, 49.58%, and 73.36%, respectively (21). Yun et al. conducted a study where they found that the NLR cut-off value for distinguishing between benign or borderline and malignant ovarian tumors was 2.36, and the PLR cut-off value was 150.02. They also reported that the odds ratio (OR) for malignant ovarian tumors was 3.796 (95% CI; 2.667–5.403) when the NLR was 2.4 or higher. Additionally, they found that the OR for malignant ovarian tumors was 2.857 when the PLR was 150 or higher (4). These findings are consistent with previous studies in the literature regarding NLR and PLR values. However, our study observed a similar NLR value compared to the literature but a lower PLR value (21-23). This situation contradicts the thrombocytosis theory in tumorigenesis. A higher number of benign cases compared to the borderline and malignant groups, a low number of malignant cases, ethnic differences, and differences in the comparison between the three groups may explain why our results differ from the published literature in terms of NLR and PLR.

Ca125 was first reported in 1983 as a biomarker for ovarian cancer. It is also found in other types of cancer, such as pancreatic, bladder, and lung cancer. Additionally, it can be elevated in non-cancerous conditions like endometriosis and pelvic inflammatory diseases. Ca125 is a glycoprotein in 80% of epithelial ovarian cancers. The concentration of Ca125 is associated with the stage, recurrence, and survival of epithelial ovarian cancers. While it is commonly used for serous epithelial ovarian cancers, it has also been found to increase in mucinous ovarian cancers. However, in some cases (20%), the Ca125 value remains below the reference range despite malignancy. Its sensitivity and specificity are reportedly low in preoperative evaluation (24-26). Some studies have shown that Ca125 does not increase in

mucinous neoplasms (7). Another study found that when combined with NLR and PLR, Ca125 did not effectively differentiate between borderline and malignant epithelial ovarian tumors (sensitivity and specificity are nearly 70%) (24). In our study, we found that a Ca125 level greater than 39 U/ml had a sensitivity of 64.7%, specificity of 81.8%, positive predictive value of 64.7%, and negative predictive value of 81.8% in distinguishing between benign and malignant mucinous tumors.

CA19.9 is a Lewis A antigen primarily expressed by mucinous tumors. It is expected to increase in the presence of borderline and malignant mucinous tumors. However, there is a lack of publications on using CA19.9 in diagnosing ovarian mucinous tumors (7). According to a study by Seçkin et al., CA19.9 is the most effective marker in distinguishing between mucinous borderline and malignant ovarian tumors, with a sensitivity of 81.39%. The study also found that the NLR was the second most sensitive marker. Based on these findings, the researchers concluded that CA19.9 (>50.5U/ml), CA125 (>41.2U/ml), and NLR (>2.18) values could be helpful parameters with high sensitivity and specificity in predicting mucinous ovarian cancer in cases of intraoperative borderline mucinous tumors (21). In our study, we found that CA19.9 can be used to differentiate between benign-malignant and borderline-malignant mucinous ovarian tumors with a high sensitivity of 82.4% when using cut-off values of >24.5 U/ml and 24.03>U/ml, respectively. Another study by Cho et al. found that an increased level of CA19.9 in women with normal CA125 levels increases the risk of detecting borderline and malignant mucinous ovarian tumors by 6.3 times compared to women with normal CA19.9 levels. In conclusion, they emphasized that CA19.9 is a valuable marker for differentiating mucinous malignancy in cases where CA125 levels do not increase (7).

In conclusion, Ca125, frequently measured in clinical practice, and Ca 19.9 are absolute markers that should be used for the differential diagnosis of mucinous tumors or giant masses. In the future, multicenter studies with large patient numbers should be planned to determine the predictive role of NLR and PLR. When the Ca 125 tumor marker value is greater than 39 U/ml, it can be used as a marker with low sensitivity and high specificity in the differential diagnosis of benign and malignant mucinous ovarian tumors. In our study, CA19.9 was the tumor marker with the highest sensitivity in the differential diagnosis of benign/borderline and malignant mucinous tumors.

Acknowledgements: We would like to thank Professor Fezan Mutlu for her assistance with the statistical data analysis.

References

1. Mills AM, Shanes ED. Mucinous Ovarian Tumors. Surg Pathol Clin 2019;12(2)b:565-585 (in English).
2. Hart WR. Mucinous tumors of the ovary: a review. Int J Gynecol Pathol 2005;24(1):4-25 (in English).
3. Hess V, A'Hern R, Nasiri N, et al. Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. J Clin Oncol 2004;22(6):1040–1044 (in English).
4. Yun TH, Jeong YY, Lee SJ, Choi YS, Ryu JM. Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios in Preoperative Differential Diagnosis of Benign, Borderline, and Malignant Ovarian Tumors. J Clin Med 2022;11(5):1355 (in English).
5. Canney PA, Moore M, Wilkinson PM, James RD. Ovarian cancer antigen CA125: a prospective clinical assessment of its role as a tumour marker. Br J Cancer 1984 ;50(6):765-9 (in English).
6. Wu YY, Qin YY, Qin JQ, Zhang X, Lin FQ. Diagnostic value of derived neutrophil-to-lymphocyte ratio in patients with ovarian cancer. J Clin Lab Anal 2019;33: e22833 (in English).
7. Cho HY, Kyung MS. Serum CA19-9 as a predictor of malignancy in primary ovarian mucinous tumors: a matched case-control study. Med Sci Monit 2014; 20:1334-9 (in English).
8. Marko J, Marko KI, Pachigolla SL, Crothers BA, Mattu R, Wolfman DJ. Mucinous Neoplasms of the Ovary: Radiologic-Pathologic Correlation. Radiographics 2019;39(4):982-997 (in English).
9. Seidman JD, Horkayne-Szakaly I, Haiba M, Boice CR, Kurman RJ, Ronnett BM. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. Int J Gynecol Pathol 2004;23(1):41–44 (in English).
10. Berek JS, Hacker NF. Berek & Hacker's gynecologic oncology (6th ed). Philadelphia, Pa: Lippincott Williams & Wilkins, 2015.
11. Gol M, Baloglu A, Yigit S, Dogan M, Aydin C, Yensel U. Accuracy of frozen section diagnosis in ovarian tumors: Is there a change in the course of time? Int J Gynecol Cancer 2003;13(5):593-7 (in English).
12. Ganesan R, Brown LJ, Kehoe S, McCluggage WG, El-Bahrawy MA. The role of frozen sections in gynaecological oncology: survey of practice in the United Kingdom. Eur J Obstet Gynecol Reprod Biol 2013;166(2):204-8 (in English).

13. Spigel SC, Mooney LR. Extreme thrombocytosis associated with malignancy. Cancer 1977;39(1):339-41 (in English).
14. Giannakeas, V.; Narod, S.A. Incidence of Cancer Among Adults with Thrombocytosis in Ontario, Canada. JAMA Netw. Open 2021, 4, e2120633 (in English).
15. Thavaramara T, Phaloprakarn C, Tangjitgamol S, Manusirivithaya S: Role of neutrophil to lymphocyte ratio as a prognostic indicator for epithelial ovarian cancer. J Med Assoc Thai 2011; 94:871-877 (in English).
16. Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol 2011; 13:499-503 (in English).
17. Kim HS, Choi HY, Lee M, et al. Systemic inflammatory response markers and CA-125 levels in ovarian clear cell carcinoma: A two center cohort study. Cancer Res Treat 2016; 48:250-258 (in English).
18. Grivennikov SI, Greten FR, Karin M: Immunity, inflammation, and cancer. Cell 2010; 140:883-899 (in English).
19. Markl B, Wieberneit J, Kretsinger H, et al. Number of intratumoral t lymphocytes is associated with lymph node size, lymph node harvest, and outcome in Node Negative colon cancer. Am J Clin Pathol 2016; 145:826-836 (in English).
20. Yildirim MA, Seckin KD, Togrul C, Baser E, Karsli MF, Gungor T, Gulerman HC. Roles of neutrophil/lymphocyte and platelet/lymphocyte ratios in the early diagnosis of malignant ovarian masses. Asian Pac J Cancer Prev. 2014;15(16):6881-5 (in English).
21. Seckin KD, Karslı MF, Yucel B, et al.The utility of tumor markers and neutrophil lymphocyte ratio in patients with an intraoperative diagnosis of mucinous borderline ovarian tumor. Eur J Obstet Gynecol Reprod Biol 2016; 196:60-3 (in English).
22. Polat M, Senol T, Ozkaya E, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratios increase in ovarian tumors in the presence of frank stromal invasion. Clin Transl Oncol 2016;18(5):457-63 (in English).
23. Psomiadou V, Prodromidou A, Galati E, et al. The role of inflammation biomarkers in differential diagnosis of pelvic tumours of ovarian origin: a single-centre observational study. Contemp Oncol (Pozn) 2021;25(1):7-11 (in English).
24. Huang K, Xu S, Wang J, Ge L, Xu J, Jia X. Combined use of CA125, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio for the diagnosis of borderline and malignant epithelial ovarian tumors. J Ovarian Res 2023;16(1):37 (in English).
25. Bast Jr. R. C., Klug T. L., St John E., et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *The New England Journal of Medicine* 1983;309(15):883–887 (in English).
26. Cramer D. W., O'Rourke D. J., Vitonis A. F., et al. CA125 immune complexes in ovarian cancer patients with low CA125 concentrations. *Clinical Chemistry* 2010;56(12):1889–1892 (in English).