The European Research Journal 2024;10(1):37-44 Original Article

DOI: https://doi.org/10.18621/eurj.1308975 *Obstetrics and Gynecology*

Comparison of platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios with epithelial ovarian cancer stages

Halil İbrahim Tıraş[1], Yakup Dülgeroğlu[2], Çetin Aydın[3]

[1]Department of Obstetrics and Gynecology, Kulu State Hospital, Konya, Turkey; [2]Department of Medical Biochemistry, Yenisehir State Hospital, Bursa, Turkey; [3]Department of Obstetrics and Gynecology, Izmir Katip Celebi University, Faculty of Medicine, Izmir, Turkey

ABSTRACT

Objectives: Epithelial ovarian cancer (EOC) is the most common histologic type among ovarian cancers. It is usually diagnosed at an advanced stage and the prognosis worsens. The aim of our study was to investigate the predictive value of serum platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), which are systemic inflammatory response markers in EOC stages.

Methods: In this study, 140 patients diagnosed with primary EOC in İzmir Katip Çelebi University Atatürk Training and Research Hospital Gynecology and Obstetrics Clinic between 01.01.2012-01.07.2019 were included. The cases were staged using the FIGO 2014 Ovarian Cancer Staging system. Whether the PLR and NLR values were different between the stages were analyzed with appropriate statistical analysis methods.

Results: A total of 140 patients, 54 were in the early stage (Stage I: 47; Stage II: 7) and 86 were in the advanced stage (Stage III: 73; Stage IV: 13). The PLR and NLR values differed between the four stages (P=0.003 and P=0.032, respectively). The PLR value was different between the early and advanced stages (P=0.033), the AUC value was 0.607, the optimum cut-off was 220, the sensitivity was 47%, and the specificity was 81% in the early and advanced stage discrimination. Accordingly, the Odds ratio of PLR for advanced EOC was 3.82 (95% CI: 1.70-8.57, P=0.0011).

Conclusions: The NLR and PLR values were found to have a prognostic value in the discrimination of EOC stages. It has been determined that PLR value may play a predictive role in advanced EOC before surgery.

Keywords: Epithelial ovarian cancer, stage, prognosis, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

Ovarian cancer consists of different histological subtypes with different risk factors, cells of origin, clinical features, and treatments. Of these histological subtypes, epithelial ovarian cancer (EOC) accounts for approximately 90% and is classified as serous, endometrioid, clear cell, and mucinous carcinomas. Germ cell tumors and sex cord-stromal tumors, which constitute approximately 10% of ovarian cancers, are defined as non-epithelial ovarian cancers [1].

The prognosis of ovarian cancer can be poor, despite advances in surgery and chemotherapy. Although ovarian cancer ranks 8th among female cancers, it re-

Corresponding author: Halil İbrahim Tıraş, MD.
Phone: +90 332 641 61 00. E-mail: ibrahim.iz@outlook.com

How to cite this article: Tıraş Hİ, Dülgeroğlu Y, Aydın Ç. Comparison of platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios with epithelial ovarian cancer stages. Eur Res J. 2024;10(1):37-44. doi: 10.18621/eurj.1308975

Received: June 6, 2023
Accepted: September 10, 2023
Published Online: September 19, 2023

mains the leading cause of death from gynecological cancer and the fifth leading cause of cancer-related death in women. The incidence of new ovarian cancer cases ranges from 9 to 15 per 100,000 women per year, and the death rate averages 5.4 to 11.6 deaths per 100,000 women [2]. According to the Global Cancer Observatory data, 313,959 women were diagnosed with ovarian cancer in 2020. 1.6% of new cancer cases in the world and 1.7% in Turkiye are ovarian cancer [3]. Since the early stages of the disease are usually asymptomatic, approximately 75% of cases are diagnosed in the advanced stages (III and IV). The 5-year survival rate in EOC is directly related to the stage of the disease at the time of initial diagnosis. While the 5-year average survival rate for all EOCs diagnosed at stage 4 is around 20% for all races, this rate rises to 89% in those diagnosed at stage I [4].

Recently, there has been great interest in the role of cancer-associated inflammation in the burden and prognosis of the disease. Inflammation is known to be associated with different stages of tumor development, including initiation, elevation, malignant transformation, invasion, and metastasis. The association between poor prognosis and elevation of white blood cells, platelets, or their ratios can be explained by an inflammatory process elicited by cancer cells [5]. Therefore, systemic inflammatory response (SIR) markers such as hypoalbuminemia, hyperfibrinogenemia, C-reactive protein (CRP), cancer antigen-125 (CA-125), absolute white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were investigated as prognostic factors in cancer patients [6-8].

Prognostic factors in ovarian cancer include age at diagnosis, The International Federation of Gynecology and Obstetrics (FIGO) tumor stage, histological type, tumor grade, and presence of residual disease after the first surgery [1]. All of these known variables, except age, are only suitable for post-operative evaluation. For this reason, there is no defined screening program for ovarian cancers and there is no biomarker currently used.

The aim of our study is to investigate the prognostic relationship between preoperative NLR and PLR rates and EOC stages, which are easy, inexpensive, and can be used in practice.

METHODS

Clinical Data

Patients who were operated for suspected ovarian cancer and/or adnexal mass in Izmir Katip Celebi University Atatürk Training and Research Hospital, Department of Gynecology and Obstetrics between 01.01.2012 and 01.07.2019, were scanned through the medical records and 223 cases were identified. Among these cases, 83 cases who were diagnosed as benign or borderline ovarian tumors, non-epithelial malignant ovarian tumors, recurrent ovarian malignancies and epithelial ovarian carcinomas in pathological microscopic examination but who had preoperative blood transfusion were excluded from the study. 140 patients diagnosed with primary EOC in the final pathology were included in the study.

Preoperatively studied complete blood count results of 140 EOC cases included in the study were obtained from the medical records. Preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated at all stages. The cases were staged using FIGO 2014 Ovarian Cancer Staging System [9].

This study was approved by Izmir Katip Çelebi University Non-invasive Clinical Research Ethics Committee (Date: 26.09.2019, Decision no. 434).

Statistical Analysis

The data were evaluated in the statistical package program IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA). The dependent variables of the study were the NLR and PLR; the independent variables were determined as the groups obtained by the FIGO 2014 Ovarian Cancer Staging System. Descriptive statistics were given as median ± standard deviation (SD), percent (%). The normal distribution of the data of numerical variables was evaluated with the Shapiro-Wilk normality test. Comparisons of two groups including continuous variables were evaluated with the Mann-Whitney U test according to the results of the normality test. Comparisons of more than two groups were evaluated by Kruskal-Wallis analysis according to the normality test result. In case of difference in Kruskal-Wallis analysis, Dunn-Bonferroni multiple comparison test was used as a post-hoc test.

Table 1. Comparison results of platelet-to-lymphocyte ratio by epithelial ovarian cancer stages

	n	Median±SD	P value (Kruskal-Wallis)		Median±SD	P value (Mann-Whitney U)
Stage I	47	156.67±75.93	0.003	Early stages (I+II)	160.68±83.54	0.033
Stage II	7	177.71±118.42				
Stage III	73	190.04±151.9		Advanced stages (III+IV)	207.15±156.28	
Stage IV	13	303.16±155.13				

SD = standard deviation

ROC analysis was used to calculate the AUC value. The optimum cut-off was calculated with the Youden index. A value of P<0.05 was considered statistically significant.

RESULTS

According to FIGO 2014 Ovarian Cancer Staging System of 140 patients diagnosed with histopathologically EOC, 54 were in the early stage (Stage I: 47; Stage II: 7) and 86 were in the advanced stage (Stage III: 73; Stage IV: 13). Descriptive statistical data of the PLR and NLR values of the stages are shown in Tables 1 and 2.

In the normality analysis, it was observed that the data were not normally distributed (P>0.05). As a result of analysis of variance, a statistically significant difference was found between the PLR and NLR values of the four stages (P=0.003 and P=0.032, respectively) (Tables 1 and 2).

When the PLR values of the four stages were compared, there was a statistically significant difference between stage I and stage IV (P=0.001) and between stage III and stage IV (P=0.03). No difference was found between the other stages (P>0.05). When the NLR values of the four stages were compared, a significant difference was found only between stage III and stage IV (P=0.031). There was no statistically significant difference between the other stages (P>0.05).

When the patients were grouped as early stage (stage I+stage II) and advanced stage (stage III+stage IV), while the PLR value was different between the two groups (Fig. 1), there was no difference in NLR value (P=0.033 and P=0.831, respectively) (Tables 1 and 2).

In correlation analysis, it was observed that PLR values were correlated with stages at a low level (r = 0.263, P=0.002). NLR values were not correlated with stages (r = 0.108, P=0.205).

The prognostic efficacy of PLR and NLR values in the discrimination of stages were evaluated. The AUC value was 0.607, the optimum cut-off was 220, the sensitivity was 47%, and the specificity was 81%

Table 2. Comparison results of neutrophil-to-lymphocyte ratio by epithelial ovarian cancer stages

	n	Median±SD	P value (Kruskal-Wallis)		Median±SD	P value (Mann-Whitney U)
Stage I	47	2.66±2.14	**0.032**	Early stages (I+II)	2.69±2.32	0.831
Stage II	7	3.26±3.37				
Stage III	73	2.76±2.95		Advanced stages (III+IV)	3.03±2.84	
Stage IV	13	4.61±1.90				

SD = standard deviation.

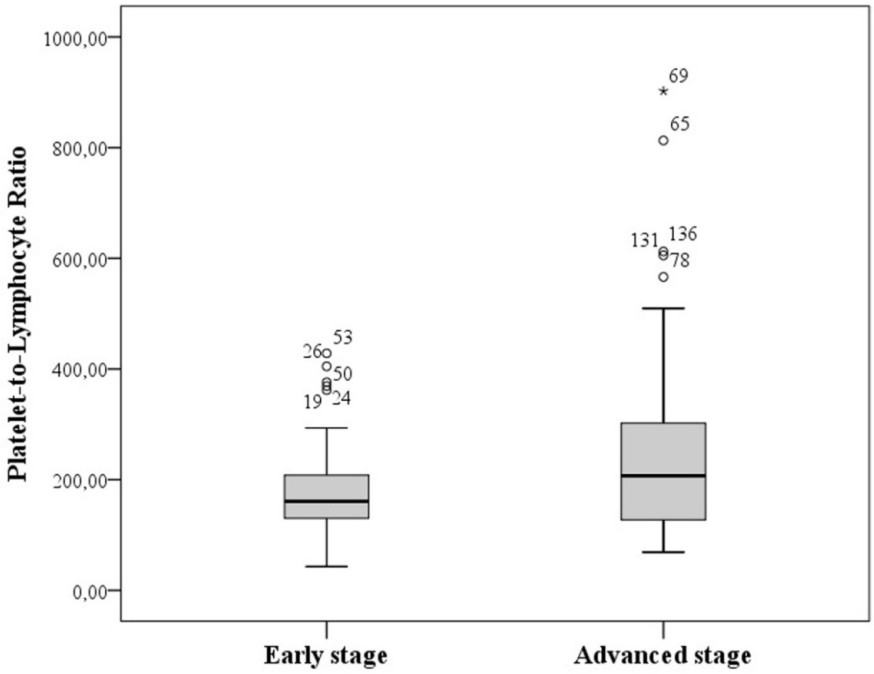

Fig. 1. **Box plot of platelet-to-lymphocyte ratio in early and advanced epithelial ovarian cancer.**

in the discrimination between early stage (stage I+II) and advanced (stage III+IV) for PLR values. When the cut-off was 220 for the PLR value, the Odds ratio for advanced EOC was calculated as 3.82 (95% CI: 1.70-8.57, P=0.0011) (Table 3). The ROC curve for the discrimination of PLR value between early and advanced epithelial ovarian cancer is shown in Fig. 2.

The AUC of PLR was 0.845 (P<0.001) in the discrimination of stage IV from stage I and 0.737 (P=0.007) in the discrimination of stage IV from stage III. The AUC of NLR was 0.730 (P=0.009) in the discrimination of stage IV from stage III. There was no statistically significant difference in PLR and NLR values in the discrimination of the other stages (Table 4). The optimum cut-off value of PLR was calculated as 210 in the discrimination of stage IV from stage I. In this case, the sensitivity of the PLR value was 85% and the specificity was 81%. The optimum cut-off value of the PLR was calculated as 207 in the discrimination of stage IV from stage III. Accordingly, the

Table 3. **Prognostic value of PLR in the discrimination of early and advanced stages of epithelial ovarian cancer**

Stages		PLR<220 (n)	PLR≥220 (n)	AUC (early vs advanced stages)	Odds ratio
Early	FIGO I	40	7	0.607 **(P=0.033)** Sensitivity 47% Specificity 81%	3.82 **(P=0.0011)**
	FIGO II	4	3		
Advanced	FIGO III	42	31		
	FIGO IV	4	9		

AUC= area under the curve, PLR= platelet-to-lymphocyte ratio, FIGO= The International Federation of Gynecology and Obstetrics

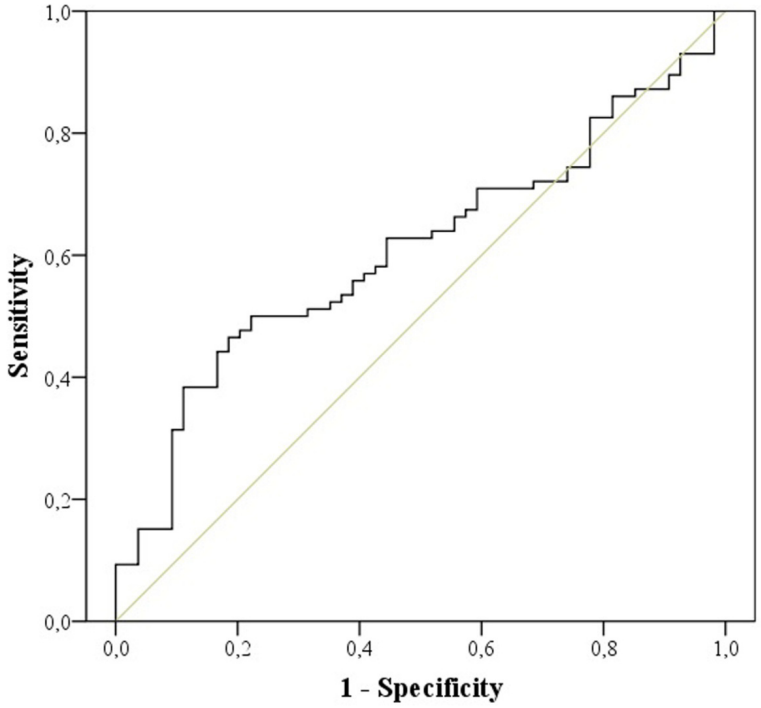

Fig. 2. ROC curve of platelet-to-lymphocyte ratio in the discriminating early and advanced epithelial ovarian cancer.

sensitivity of the PLR value was 85% and the specificity was 56%. The optimum cut-off value of the NLR was calculated as 3.06 in the discrimination stage IV from stage III. In this case, the sensitivity of the NLR value was determined as 85% and the specificity as 59% (Table 4).

DISCUSSION

The role of cancer-associated inflammation theory in oncogenesis and tumor growth has been a major area of study in recent years. Inflammatory cell counts and the ratios derived from these cell counts, such as PLR and NLR, have been investigated for diagnostic, prognostic and treatment follow-up in many cancer types. The biggest advantage of these inflammatory cell numbers and ratios is that they can be easily obtained in complete blood count data and do not require any additional health expenditure. Various studies have shown that these inflammatory parameters, together with CA-125, can contribute to the management of the disease in ovarian cancers [10].

EOC accounts for approximately 90% of ovarian

Table 4. Efficacy of PLR and NLR in discriminating epithelial ovarian cancer stages

FIGO Stages	PLR				NLR			
	Cut-off	AUC	Sen	Spe	Cut-off	AUC	Sen	Spe
I vs IV	210	0.845 **(P<0.001)**	85%	81%	NS	NS	NS	NS
III vs IV	207	0.737 **(P=0.007)**	85%	56%	3.06	0.730 **(P=0.009)**	85%	59%

AUC= area under the curve, PLR= platelet-to-rymphocyte ratio, NLR= neutrophil-to-lymphocyte ratio, Sen=Sensitivity, Spe= Specificity, FIGO= The International Federation of Gynecology and Obstetrics, NS= not significant.

Note: There was no statistically significant difference in PLR and NLR values in the discrimination of the other stages (P>0.05).

cancers in all age and ethnic groups. The fact that patients with EOC are asymptomatic for a long time and therefore are often diagnosed at an advanced stage has intensified studies to determine the diagnostic and prognostic values of inflammatory cell ratios derived from complete blood count parameters such as NLR and PLR [4, 11].

In our study, the effectiveness of NLR and PLR ratios in the evaluation of the stages of patients with EOC was investigated. It was determined that the PLR value increased especially in stage IV compared to other stages. We thought that the lack of a significant difference between stage II and other stages in terms of PLR value may be due to the small number of patients in this group. NLR value was different only between stage III and stage IV. In addition, it was determined that the PLR value was correlated with the stages (stages I-IV), while the NLR value was not. Moreover, while PLR value differs between early stage and advanced stage EOC, there is no difference in NLR value. In summary, it was observed that the PLR value increased as the stage increased. We think that the PLR value may be important in terms of giving an idea about the stage of the disease at the initial diagnosis stage.

In studies in the literature on the subject, it is reported that PLR and NLR values increase as the stage increases, similar to our findings. In a study by Kökçü *et al*. [12], which included 100 patients with epithelial ovarian cancer, it was shown that NLR and PLR levels were increased in advanced stage compared to early stage. In the study, the prognostic value of PLR was found to be better than blood parameters such as platelet and NLR ratio [12]. In a study by Zhang *et al*. [13] in which 190 patients with ovarian cancer were included, it was revealed that while the mean PLR values were 182.6 in stage I, it increased to 234.50 in stage IV, and this increase was statistically significant ($p = 0.032$). In the recently published study by Huang *et al*. [14], it was shown that the value of PLR and NLR did not differ between histological grade, age of the patient or type of ovarian cancer, but increased in advanced ovarian cancer compared to early-stage ovarian cancer. Thus, it has been reported that high PLR and NLR values at the time of diagnosis can be interpreted in favor of probable advanced stage ovarian cancer. Although there are studies in the literature that PLR values increase as the stage increases, which is largely consistent with our findings, there are findings in some studies that the PLR value does not change between stages. In the study of Wang *et al*. [15], it was reported that while there was no increase in PLR values, NLR values increased in advanced EOC compared to the early stage.

In the literature, studies have been conducted to differentiate ovarian cancer from the healthy group, generally for the effectiveness of PLR and NLR in the diagnosis of epithelial ovarian cancer. Considering the results of these studies, the AUC value of PLR in differentiating ovarian cancer from the healthy group varies between 0.621 and 0.684, while the AUC value of NLR varies between 0.604 and 0.737 [16-18]. We were able to find only one study evaluating the efficacy of PLR and NLR in staging ovarian cancers. In this study, using the Multivariate Logistic Regression Analysis method, it was reported that PLR is an independent risk factor associated with the distinction between early and advanced stages in EOC. However, such a result could not be reached for the NLR ratio. In the same study, when the cut-off was determined as 200 for PLR, the odds ratio was calculated as 1.0105 [16]. In our study, the prognostic value of PLR and NLR ratios was investigated in the discrimination of early and advanced stages by ROC analysis. Accordingly, the AUC value of PLR values in the discrimination between early and advanced stages in EOC were found to be 0.607, sensitivity 47%, and specificity 81% (cut-off: 220). In our study, the odds ratio for PLR was found to be 3.82. In the light of these findings, we think that PLR values can be considered in estimating the stage of epithelial ovarian cancer at the initial diagnosis stage.

There are also studies to reveal the prognostic value of PLR and NLR ratios for survival prediction. In a meta-analysis evaluating the results of a total of 3467 patients and 13 studies, it was reported that an increase in NLR had a poor prognostic effect (hazard ratios 1.70 and 1.77, respectively) on overall survival (OS) and progression-free survival (PFS). In the same study, it was stated that the increase in PLR had a slightly higher risk of poor prognosis for OS and PFS (hazard ratio 2.05 and 1.85, respectively) [19]. In our study, an analysis for survival prediction was not performed. However, the stage of EOC at diagnosis is one of the most important factors on survival. In this respect, according to the results of our study, the fact that

the PLR value has a prognostic value in the prediction of early and advanced stages is also compatible with studies on survival prediction.

Limitations

Our study has some limitations. The first is that the number of patients in some stages is low. Especially there were few patients in the stage II. This may have affected the power of statistical analyzes regarding the stage II. Not including a healthy group in our study can be considered as a limitation in terms of investigating the diagnostic value of the ratio of PLR and NLR. However, in this study, only a result was revealed for the use of these values for prognostic purposes in the differentiation of stages at the initial diagnosis stage.

CONCLUSION

According to the data of our study, NLR and PLR values were found to have a statistically prognostic value in the discrimination of EOC stages. It has been determined that NLR value is not effective in distinguishing early and advanced EOC, and PLR value may play a predictive role for advanced EOC before surgery. However, there is a need for more comprehensive studies in this area.

Authors' Contribution

Study Conception: ÇA, HİT; Study Design: ÇA, HİT; Supervision: ÇA, YD; Funding: HİT; Materials: HİT; Data Collection and/or Processing: HİT; Statistical Analysis and/or Data Interpretation: HİT, YD; Literature Review: HİT, YD; Manuscript Preparation: HİT, YD and Critical Review: YD.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

1. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. Nat Rev Dis Primers. 2016;2:16061. doi: 10.1038/nrdp.2016.61.
2. Mathis J, Jellouli MA, Sabiani L, Fest J, Blache G, Mathevet P. Ovarian cancer screening in the general population. Horm Mol Biol Clin Investig. 2019;41(3). doi: 10.1515/hmbci-2019-0038.
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660.
4. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018;68(4):284-296. doi: 10.3322/caac.21456.
5. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-899. doi: 10.1016/j.cell.2010.01.025.
6. Liu Y, Chen S, Zheng C, Ding M, et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. BMC Cancer. 2017;17(1):285. doi: 10.1186/s12885-017-3220-x.
7. Chen L, Wang X, Shu J, Xu S, Wu Q, Yu Y. Diagnostic value of serum D-dimer, CA125, and neutrophil-to-lymphocyte ratio in differentiating ovarian cancer and endometriosis. Int J Gynaecol Obstet. 2019;147(2):212-218. doi: 10.1002/ijgo.12949.
8. Li L, Tian J, Zhang L, et al. Utility of Preoperative Inflammatory Markers to Distinguish Epithelial Ovarian Cancer from Benign Ovarian Masses. J Cancer. 2021;12(9):2687-2693. doi: 10.7150/jca.51642.
9. Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014;124(1):1-5. doi: 10.1016/j.ijgo.2013.10.001.
10. Prodromidou A, Andreakos P, Kazakos C, Vlachos DE, Perrea D, Pergialiotis V. The diagnostic efficacy of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in ovarian cancer. Inflamm Res. 2017;66(6):467-475. doi: 10.1007/s00011-017-1026-6.
11. Ashrafganjoei T, Mohamadianamiri M, Farzaneh F, Hosseini MS, Arab M. Investigating preoperative hematologic markers for prediction of ovarian cancer surgical outcome. Asian Pac J Cancer Prev. 2016;17(3):1445-1448. doi: 10.7314/apjcp.2016.17.3.1445.
12. Kokcu A, Kurtoglu E, Celik H, Tosun M, Malatyalıoglu E, Ozdemir AZ. May the platelet to lymphocyte ratio be a prognostic factor for epithelial ovarian cancer? Asian Pac J Cancer Prev. 2014;15(22):9781-9784. doi: 10.7314/apjcp.2014.15.22.9781.
13. Zhang WW, Liu KJ, Hu GL, Liang WJ. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. Tumour Biol. 2015;36(11):8831-8837. doi: 10.1007/s13277-015-3533-9.
14. 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. doi: 10.1186/s13048-023-01106-4.
15. Wang Y, Liu P, Xu Y, et al. Preoperative neutrophil-to-lymphocyte ratio predicts response to first-line platinum-based chemotherapy and prognosis in serous ovarian cancer. Cancer Chemother

Pharmacol. 2015;75(2):255-262. doi: 10.1007/s00280-014-2622-6.
16. 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):457-463. doi: 10.1007/s12094-015-1387-7.
17. Yildirim MA, Seckin KD, Togrul C, et al. Roles of neutrophil/lymphocyte and platelet/lymphocyte ratios in the early diagnosis of malignant ovarian masses. Asian Pac J Cancer Prev. 2014;15(16):6881-6885. doi: 10.7314/apjcp.2014.15.16.6881.
18. Bakacak M, Serin S, Ercan Ö, et al. Utility of preoperative neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios to distinguish malignant from benign ovarian masses. J Turk Ger Gynecol Assoc. 2016;17(1):21-25. doi: 10.5152/jtgga.2015.0152.
19. Zhao Z, Zhao X, Lu J, Xue J, Liu P, Mao H. Prognostic roles of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in ovarian cancer: a meta-analysis of retrospective studies. Arch Gynecol Obstet. 2018;297(4):849-857. doi: 10.1007/s00404-018-4678-8.