Clinics in Oncology

Research Article
Published: 19 Jan, 2023

The Use of Neutrophils-to-Lymphocytes and Platelets-to-Lymphocytes Ratios as a Prognostic Factor before and after Treatment of Epithelial Ovarian Cancer & Comparison with Clinical and Pathological Features

*Zahav MH[1], Shahar IB[1,2], Zidan MD[3], Safadi M[4], Shnayder J[4] and Zidan J[1,4]**

[1]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

[2]Department of Obstructive and Gynecology, Ziv Medical Center, Safed, Israel

[3]Women's Health Wing, The Galilee Medical Center, Naharya, Israel

[4]Division of Oncology, Ziv Medical Center, Safed, Israel

Abstract

Aims: The prognostic value of NLR (Neutrophils-to-Lymphocytes Ratio) and PLR (Platelets-to-Lymphocytes Ratio) in ovarian cancer is contradictory. The aim of this study was to assess the correlation between NLR and PLR with different characteristics of ovarian cancer.

Materials and Methods: This is a retrospective study. A total of 61 cases with ovarian cancer were summarized. Demographic, clinical, pathological data, blood counts, CA125 were taken from the patients' files. Values of NLR, PLR and CA125 were assessed prior to treatment and 1, 3, 6 months after beginning of treatment.

Results: Nine cases were excluded due to exclusion criteria while 52 pts were evaluable. The average age was 62 years. Most pts (76%) was stage III and IV at diagnosis. After 3 years follow up survival was 40% in pts with NLR<5.0 compared to 20% with NLR>5.0 (p=0.032), and 38% in PLR<250 *vs.* 19% in PLR>250 (p=0.007). CA125 levels were predicting factor in all stages of the disease. No relation was found between NLR, PLR, CA125 levels and disease features and ethnicity.

Conclusion: High rate of NLR and PLR in pts with ovarian cancer before and following treatment are negative prognostic factors. It is applicable in every medical center. No correlation was found between NLR and PLR with menopausal status, type of operation, age, chemotherapy and ethnicity. This study is the first to test NLR and PLR during and after treatment. The study is continued to reach higher number of patients and more significant results.

Keywords: Ovarian cancer; Neutrophils; Platelets to lymphocytes ratio

OPEN ACCESS

Correspondence:
Jamal Zidan, Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Zip 13100, Israel, Tel: +972-4-6828550; Fax: +972-4-6828621; E-mail: Jamalz@ziv.gov.il

Received Date: *26 Dec 2022*
Accepted Date: *14 Jan 2023*
Published Date: *19 Jan 2023*

Citation:
Zahav MH, Shahar IB, Zidan MD, Safadi M, Shnayder J, Zidan J. The Use of Neutrophils-to-Lymphocytes and Platelets-to-Lymphocytes Ratios as a Prognostic Factor before and after Treatment of Epithelial Ovarian Cancer & Comparison with Clinical and Pathological Features. Clin Oncol. 2023; 8: 1980.

ISSN: 2474-1663

Introduction

Ovarian Cancer (OC) is the most aggressive tumor among gynecological malignancies worldwide [1]. It is the second common tumor in this group after uterus cancer [1]. OC is the first cause of mortality in gynecological tumors [2]. OC is more common in women aged 50 years and higher although it may be diagnosed at younger age [3]. Epithelial carcinoma represents 90% of ovarian tumors [1]. Despite the increased development of imaging in medicine most women with ovarian cancer are diagnosed at advanced or metastatic stage (stage III and IV) [1,2]. Stage of disease is still the leading prognostic factor in ovarian cancer [4].

Surgical operation is the main therapy for early and advanced stage (stage I, II and III) OC. Surgery is followed mostly by adjuvant chemotherapy. Chemotherapy is given also as neoadjuvant treatment and for metastatic disease. Taxanes and platinum compounds remain the gold standard combination used in women with OC. Last year bevacizumab; an antiangiogenic therapy is added to advanced and metastatic disease with improvement in survival rates [5,6]. Recently immunotherapy (check point inhibitors) and PARP (Poly(ADP-Ribose) Polymerase) inhibitors are also incorporated in the treatment of metastatic OC [7].

Stage is the cornerstone for treatment choice and follow-up in women with ovarian cancer.

Other prognostic factors in this disease are pathological cell differentiation of the tumor, high CA125, CA19-9, MSI (Mismatch Stability Insufficiency), PDL1 (Programed Death Ligand 1). Yet we have no biomarkers to define the subgroups of patients who can benefit of chemotherapy nor antiangiogenic treatment. The need for further prognostic factors in OC is important and advisable. In the last years NLR (Neutrophil-to-Lymphocyte Ratio) and PLR (Platelet-to Lymphocyte Ratio) were reported to be easily available and promising biomarkers in OC and in other malignancies [8-10]. The cutoff value of the NLR is inconsistent and can be different in different malignancies. Yin et al. in their meta-analysis of 2,919 women with OC they reported cutoff range of 2 to 3.5 (average 2.5) [11]. Higher NLR is a negative prognostic factor. Patients with high NLR had higher mortality. The same was PLR [9,11]. Most publications have evaluated NLR and PLR before surgery or before chemotherapy and not during treatment nor in the follow up [9,11]. The effect of these markers on the prognosis of OC is still controversial [8-11].

The biological basis of NLR as a poor prognostic factor is based on the systemic inflammatory response from cancer cells promotes the infiltration of neutrophils, which benefits cancer progression *via* secreting Interleukin-6 (IL-6), Interleukin-2 (IL-2), Interleukin-10 (IL-10), Vascular Endothelial Growth Factor (VEGF) and Tumor Necrosis Factor a (TNF-a). VEGF is a proangiogenic factor contributes to cancer angiogenesis and tumor growth. Increased IL-10 and TNF-a decrease both lymphocyte count decrease and lymphocyte dysfunction [11-13]. High PLR also is a poor prognostic factor in OC [8,11].

Relying on the conflicting data on the NLR and PLR as a prognostic factor in OC and, on NLR cutoff values and on the use of NLR and PLR not only once before surgery or chemotherapy we conducted this retrospective study to detect the NLR and PLR as a prognostic factor before, during and after treatment and its effect on survival. The second aim of this study was to compare NLR and PLR with all clinical and pathological characteristics of OC in our patient's population.

Methods

In this retrospective study a total of 61 cases of ovarian cancer were examined. All pts were treated in the Oncology Institute at Ziv Medical Center from 2005 until 2017. Demographic, clinical, and pathological data, blood counts, before, during and after treatment were taken from the patients' records at the Oncology Institute in Ziv Medical Center at Northern Israel. Missing data of blood tests were taken from the records of the hematological laboratory at our medical center. Nine out of 61 cases were excluded from the study due to: Other non-epithelial tumors, lack of laboratory data, or parallel tumors. The remaining 52 cases with epithelial OC were evaluable for this study.

The date of diagnosis was defined as the date of initial surgery or biopsy. Optimal cytoreduction was considered as <1 cm of remaining tumors after surgery. Disease stage was done according to the International Federation of Gynecology (FIGO) 2009 criteria. RECIST criteria was used to determine tumor response in imaging (CT, MRI, PET-CT, US). Patients underwent physical examinations routinely. Blood test for complete blood count, liver and kidney function tests, and CA125 were done before surgery, before and during chemotherapy and in follow up of pats.

The values of NLR were computed by the absolute number of neutrophils divided by the absolute lymphocytes count. PLR values were calculated by dividing the number of platelets by the number of lymphocytes in the same blood count. Values of NLR, PLR were assessed prior to surgery or chemotherapy, and 1, 3, 6 months thereafter.

Inclusion criteria

Included women diagnosed with pathologically improved epithelial ovarian cancer, age above 18 years or older and had received first line chemotherapy with taxane + platinum combination with or without bevacizumab.

Exclusion criteria

Included patients with non-epithelial ovarian cancers, less than 3 months follow up since diagnosis, age less than 18, pregnancy at the time of diagnosis and women with second malignancy.

Blood counts before chemotherapy were evaluated then blood counts done 1, 3, 6 months from the beginning of chemotherapy were evaluated for NLR and PLR retrospectively. Results were compared with all features of the disease.

Results

We identified 52 patients evaluable for this study. Mean age of pts at diagnosis was 62.0 ± 13.2 years (range 25-84). All pts had epithelial ovarian cancer. Characteristics of patients, clinical and pathological features are presented in (Table 1). Most women; 39 (75%) pts were Jewish and 13 (25%) were Arab. The majority of pts (79%) were postmenopausal, 17% were premenopausal and 4% were perimenopause. At the time of diagnosis 6 (12%) women were at stage I disease, 6 (12%) stage II, 21 (40%) stage III and 19 (36%) were stage IV disease (Table 1). Optimal debulking surgery was done in 63%, 10% had non-optimal debulking and 27% were not operated because of advanced disease (Table 2).

Chemotherapy with paclitaxel or docetaxel and carboplatin or cisplatin was given both as adjuvant or neoadjuvant treatment of the primary tumor in 90% of patients while 8% of pts were treated with other drugs. Only 12 patients (23%) received bevacizumab combined with chemotherapy (Table 2). CA125 was also summarized in all patients at time of NLR and PLR evaluation.

Mean NLR level was 6.52 ± 6.30 before treatment decreased to 6.43 ± 5.07, 5.56 ± 5.42 and 5.34 ± 5.72 at 1, 3 and 6 months after beginning chemotherapy (p:0.206) (Table 3). Mean PLR was 300.7 ± 233.0 before treatment decreased to 241.4 ± 201.0, 238.4 ± 201.0 and 167.3 ± 109.7 at 1, 3, 6 months from beginning of chemotherapy

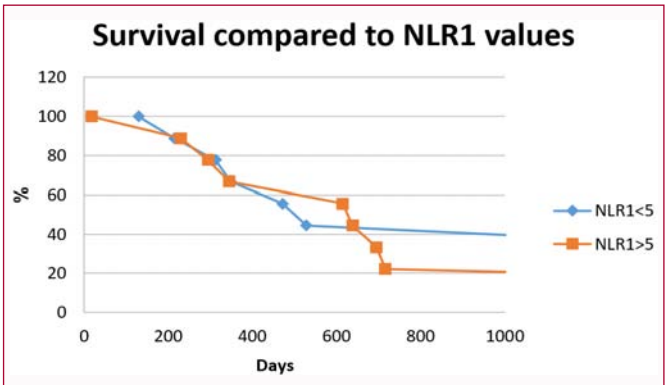

Figure 1: NLR after 1 month of treatment and survival (p=0.032). NLR: Neutrophils-to-Lymphocytes Ratio

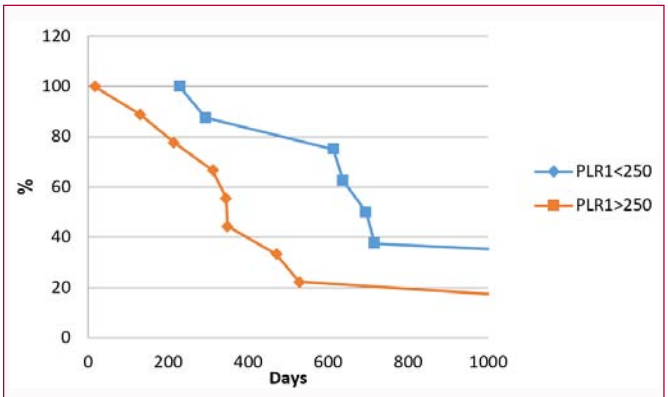

Figure 2: PLR after 1 month of treatment and survival (p=0.007).
PLR: Platelets-to-Lymphocytes Ratio

Table 1: Clinical and pathological characteristics of 52 women with ovarian cancer.

Variable	n	%
Age (year, mean ± SD)	62.0 ± 13.2	
Ethnicity		
Jew	39	75
Other	13	25
Menopausal status		
Post	41	79
Pre	9	17
Peri	2	4
Stage		
I	6	12
II	6	12
III	21	40
IV	19	36
Pathology		
Epithelial cancer	52	100

(p:0.007) (Table 3). CA125 was also summarized in all pts at time of NLR and PLR evaluation. Same decrease rate was detected in CA125 levels after starting chemotherapy: Mean value 751.5 ± 1205.2 before and 554.9 ± 1591.7, 226.4 ± 821.6 and 109.9 ± 314.0 at 1, 3, 6 months of treatment (p<0.001).

At a median follow up of 2 years 25 (48%) pts died with disease, 11 (21%) pts alive with disease and 16 (31%) alive with no evidence of disease (Table 4). When NLR mean value of 5.0 was calculated as cut off in this study a significant difference was found at 3 years in survival between pts with NLR<5.0 (40%) *vs.* NLR>5.0 (20%) one month after treatment (p=0.032), (Figure 1). NLR>5.0 after 3 months, although not significant (p=0.206) but still a negative prognostic factor. Lower levels of PLR were also a positive factor for survival. Patients with mean PLR<250 had a higher survival than those with >250 before and 3 and 6 months after beginning chemotherapy (p=0.007), (Figure 2). CA-125 levels were best as predicting factor in all stages of the disease and in all period of time before and during treatment (p<0.001), (Table 3).

In all stages high NLR, PLR and CA125 values before treatment and 1, 3 months of starting treatment were negative prognostic factors for survival. The main levels of NLR, PLR, and CA125 were

Table 2: Details of treatment of patients.

Variable	no	%
Type of surgery		
Optimal debulking	33	63
Debulking	5	10
No surgery	14	27
Type of chemotherapy		
Taxene + platines	47	90
No taxenes	5	10
Other drugs	4	8
Bevacizumab treatment		
Yes	12	23
No	40	77
Patients status		
Alive without disease	16	31
Alive with disease	11	21
Dead with disease	25	48

also followed at 6 months of starting treatment. High mean levels of PLR and CA125 were still a negative prognostic factor compared to low levels at all timings of calculation. High NLR levels at 6 months has no effect on survival. No relation was found between NLR, PLR, and CA125 levels with menopausal status, type of operation, chemotherapy (paclitaxel or docetaxel nor cisplatin versus carboplatin), bevacizumab, age and ethnicity. Higher response rates (complete response, partial and minimal response) were observed in patients with lower than higher NLR, PLR and CA125. Because number of pts is limited in each stage and combination of treatment differ no statistical difference could be detected. High NLR and PLR were negative prognostic factors in all stages.

Discussion

Biomarkers are widely used and many research is ongoing for new markers in different tumors. Despite the big development in diagnosis and treatment in oncology CA125 and CA19-9 are the only blood tests used as prognostic and detective markers in OC [14,15]. The prognostic effect of systemic inflammatory response in ovarian cancer is controversial.

In the last decade more publications are available on NLR and PLR to be significant prognostic and detective factor in more malignant diseases including ovarian cancer, gastric, lung, breast cancers and other tumors [16-19]. The mechanism of the association between high NLR/PLR and poor prognosis in various malignancies remains unclear [20]. However, the prognostic significance of NLR and PLR in ovarian cancer was contradictory in different publications [21-23]. Asher et al. found no significant difference in overall survival in pts with NLR<4.0 compared to >4.0 (HR: Hazard Ratio 0.87) [24]. Thavaramara et al. reported similar results. They found no relation between NLR ratio <2.6 *vs.* >2.6 on disease free or overall survival in women with OC [16]. In the recent study a significant correlation was found in 3-year overall survival in favor of pts with NLR <5.0 compared to >5.0 (p=0.032) (Figure 1). PLR was also effective prognostic factor for survival in this study. Overall survival at 3 years was higher when PLR was <250 than >250 (p=0.007), (Figure 2). Similar results on the significant prognostic value of NLR and PLR were reported in more publications. Chen et al. in their met-analysis

Table 3: NLR, PLR, CA125 and albumin values in different time points.

	0	1	3	6	p
NLR	6.52 ± 6.30	6.43 ± 5.07	5.56 ± 5.42	5.34 ± 5.72	0.206
PLR	300.7 ± 233.0	241.4 ± 201.0	238.8 ± 141.3	167.3 ± 109.7	0.007
CA125	751.5 ± 1205.2	554.9 ± 1591.7	226.4 ± 821.6	109.9 ± 314.0	<0.001

NLR: Neutrophils to Lymphocytes Ratio; PLR: Platelets to Lymphocytes Ratio; CA125: Cancer Antigen 125

Table 4: Latest status of patients.

Variable	no	%
Alive without disease	16	31
Alive with disease	11	21
Dead with disease	25	48

on 2,892 OC patients published in 2017 they demonstrated that high NLR predicted worse PFS and OS in patients with ovarian cancer, especially significantly associated with shorter PFS when cutoff <3.3 in pre-operation, and obviously related to worse overall survival [25]. As in our study, Yin et al. in their summary of their meta-analysis from 2019 found pts with low NLR and PLR ratios to have higher survival than those with high values. They concluded that NLR and PLR can potentially serve as prognostic biomarkers in OC patients [11]. Similar conclusions were reported also in other studies [26-29].

According to all these studies and others the cutoff value of NLR and PLR is inconsistent, which reduces its clinical applicability. It could be affected by the pts baselines and therapeutic approaches [11,25]. Besides the time of estimation for NLR and PLR in the different publications is nonhomogeneous, being done from blood samples taken before operation in some studies, after operation, at the beginning of chemotherapy or after in other studies [11,25]. In this study we evaluated NLR and PLR rates one week before treatment, 1, 3, 6 months thereafter for testing when it is the most relevant time of blood counts for calculation of biomarkers. We found a significant difference in mean values of NLR and PLR with time since starting treatment (Table 3). Mean NLR changed from 6.52 ± 6.30 to 6.43 ± 5.07 even after 1 months continuing to decrease (p=0.206). PLR changed from 300.7 ± 233.0 to 241.4 ± 201.0 after 1 month and continued to change (p=0.007). This may clarify in part some bias between different studies and may affect the real value of cut off even in the same study.

NLR, PLR, and CA125 levels were not affected by menopausal status, type of operation, type of chemotherapy, bevacizumab, age and ethnicity. High CA-125 levels remained a strong negative prognostic factor for treatment outcomes. Our data is from a single medical center and patients were operated by the same surgical staff. The limitations of this study including retrospective data, and relatively small number of patients.

Conclusion

Elevated NLR and PLR in pts with ovarian cancer before and following treatment are poor prognostic factors for response and survival. No correlation was found between NLR and PLR and menopausal status, type of operation, age, chemotherapy and ethnicity. This study is the first to test NLR and PLR during and at the end of treatment. These tests are inexpensive and easy to access in any small or large hospital and in any reach or poor country. We continue this study to reach higher number of patients and more significant results.

Acknowledgment

The authors would like to thank all the physicians, nurses and secretaries who have assisted in treating patients and collecting data for this study. Many thanks and much love to our Jewish and Arab patients and their families for their peaceful coexistence and cooperation despite Middle East conflict.

References

1. Matz M, Coleman MP, Sant M, Chirlaque MD, Visser O; the CONCORD Working Group, et al. The histology of ovarian cancer: Worldwide distribution and implications for international survival comparisons (CONCORD-2). Gynecol Oncol. 2017;144:405-13.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7-30.
3. Lalrinpuii E, Bhageerathy PS, Sebastian A, Jeyaseelan L, Thomas V, Thomas A, et al. Ovarian cancer in young women. Indian J Surg Oncol. 2017;8(4):540-47.
4. Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N; ESMO Guidelines Working Group, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl 6):vi24-32.
5. Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365:2484-96.
6. Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011;365:2473-83.
7. Tew WP, Lacchetti C, Ellis A, Maxian K, Banerjee S, Bookman M. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-93.
8. Badora-Rybicka A, Nowara EB, Starzyczny-Słota D. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio before chemotherapy as potential prognostic factors in patients with newly diagnosed epithelial ovarian cancer. ESMO Open. 2016;1:e000039.
9. Aizawa M, Gotohda N, Takahashi S, Konishi M, Kinoshita T. Predictive value of baseline neutrophil/lymphocyte ratio for T4 disease in wall-penetrating gastric cancer. World J Surg. 2011;35:2717-22.
10. Tomita M, Shimizu T, Ayabe T, Yonei A, Onitsuka T. Preoperative neutrophil to lymphocyte ratio as a prognostic predictor after curative resection for non-small cell lung cancer. Anticancer Res. 2011;31:2995-8.
11. Yin X, Wub L, Yang H, Yang HB. Prognostic significance of Neutrophil–Lymphocyte Ratio (NLR) in patients with ovarian cancer A systematic review and meta-analysis. Medicine. 2019;98(45):1-6.
12. Lin Q, Ding SJ, Zhu TH, Li TT, Huang XF, Zhang XM. Role and clinical significance of coagulation and inflammatory factors in moderate and severe ovarian endometriosis. Zhonghua Fu Chan Ke Za Zhi. 2018;53:167-71.
13. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539-45.
14. Guo J, Yu J, Song X, Mi H. Serum CA125, CA199, and CEA combined detection for epithelial ovarian cancer diagnosis: A meta-analysis. Open Med (Warsaw, Poland). 2017;12:131-7.

15. Zhang W, Wang L, Xin Z. Combination of serum CA19-9 and CA125 levels and contrast-enhanced ultrasound parametric data facilitates to differentiate ovarian serous carcinoma from ovarian malignant epithelial cancer. Medicine. 2018;97:e0358.

16. 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;94:871-7.

17. Wang H, Ding Y, Li N, Wu L, Gao Y, Xiao C, et al. Prognostic value of neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, and combined neutrophil–lymphocyte ratio and platelet–lymphocyte ratio in stage IV advanced gastric cancer. Front Oncol. 2020;10:841-6.

18. Kemal Y, Yucel I, Ekiz K, Demirag G, Yilmaz B, Teker F, et al. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev. 2014;15:2651-4.

19. Liu X, Qu JK, Zhang J, Yan Y, Zhao XX, Wang JZ, et al. Prognostic role of pretreatment neutrophil to lymphocyte ratio in breast cancer patients: A meta-analysis. Medicine. 2017;96:e8101.

20. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;144 (5):646-74.

21. Miao Y, Yan Q, Li S, Li B, Feng Y. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are predictive of chemotherapeutic response and prognosis in epithelial ovarian cancer patients treated with platinum-based chemotherapy. Cancer Biomark. 2016;17(1):33-40.

22. 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. Tumor Biol. 2015;36(11):8831-7.

23. Medina FJ, Mun˜oz-Casares FC, Arjona-Sa´nchez A, Casado-Adam A, Go´mez-Luque I, Garcilazo Arismendi DJ, et al. Postoperative time course and utility of inflammatory markers in patients with ovarian peritoneal carcinomatosis treated with neoadjuvant chemotherapy, cytoreductive surgery, and HIPEC. Ann Surg Oncol. 2015;22:1332-40.

24. Asher V, Lee J, Innamaa A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. Clin Transl Oncol. 2011;13(7):499-503.

25. Chen S, Zhang L, Yan G, Cheng S, Fathy AH, Yan N, et al. Neutrophil-to-lymphocyte ratio is a potential prognostic biomarker in patients with ovarian cancer: A meta-analysis. Biomed Res Int. 2017;2017: 7943467.

26. Wang Y, Liu P, Xu Y, Zhang W, Tong L, Guo Z, 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;75:255-62.

27. Kokcu A, Kurtoglu E, Celik H, Tosun M, Malatyalıoglu E, Ozdemi AZ. May the platelet to lymphocyte ratio be a prognostic factor for epithelial ovarian cancer? Asian Pac J Cancer Prev. 2014;15(22):9781-4.

28. Bakacak M, Serin S, Ercan O, Köstü B, Bostancı MS, Bakacak Z, 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;17:21-5.

29. Williams KA, Labidi-Galy SI, Kathryn L, Vitonis AF, Welch WR, Goodman A, et al. Prognostic significance and predictors of the neutrophil-to lymphocyte ratio in ovarian cancer. Gynecol Oncol. 2014;132(3):542-50.