Int. J Med. Pharm. Res. (P-ISSN: 2958-3675 | E-ISSN: 2958-3683)
Available on: https://ijmpr.in/

International Journal
of Medical and Pharmaceutical Research

ORGINAL ARTICLE **OPEN ACCESS**

Neutrophil-Lymphocyte Ratio as a Predictor of Outcome in Advanced High Grade Serous Adenocarcinoma of Ovary- A Retrospective Analysis of 100 Cases

Dr.Megha Nandwani[1], Dr.Sharda Patra[2]*, Dr.Debabrata Barmon[3], Dr. Roma Jethani[4]

[1]Academic Senior Resident at Chittaranjan National Cancer Institute, Kolkata, Ex-Fellow, Department of Gynecologic Oncology at Dr. B Borooah Cancer Institute, Guwahati, Assam, India
[2]Director Professor at Lady Hardinge Medical College, New Delhi, Ex-Fellow at the Department of Gynecologic Oncology at Dr. B Borooah Cancer Institute, Guwahati, Assam, India
[3]Head of the Department and Professor of Department of Gynecologic Oncology, Dr. B. Borooah Cancer Institute, Guwahati, Assam, India
[4]Assistant Professor at Tata Medical Center, Varanasi, Ex-Fellow at the Department of Gynecologic Oncology at Dr. B. Borooah Cancer Institute, Guwahati, Assam, India

OPEN ACCESS

***Corresponding Author**
Dr.ShardaPatra

Director Professor at Lady Hardinge Medical College, New Delhi, Ex-Fellow at the Department of Gynaecologic Oncology at Dr.B.Borooah Cancer Institute, Guwahati, Assam, India

Received: 15-11-2024
Accepted: 25-12-2024
Available online: 30-12-2024

A B S T R A C T

Introduction: A measurement of neutrophil to lymphocyte ratio (NLR) and of platelet to lymphocyte ratio (PLR) has been found to be one of the markers of tumour burden for patients with carcinoma ovary. It has been noted that higher the NLR and PLR values, lower is the overall and recurrent free survival. Thus, we undertook the present study to analyse the role of NLR and PLR as a predictor of outcome in advanced high grade serous adenocarcinoma of ovary. ***Materials and Methods:*** A retrospective study was conducted from January 2018 to December 2019 at a tertiary level regional cancer institute of Northeast India including women with high grade epithelial ovarian cancer. A total of 100 cases were analysed and neutrophil is to lymphocyte ratio (NLR) and platelet is to lymphocyte ratio (PLR) was calculated for all patients; pre and post treatment. For comparison of NLR and PLR values pre and post treatment, chi square test was used and p value of less than 0.05 was considered significant. Kaplan-Meier curves were used for comparison of recurrence to survival percentage at 1,3 and 5 years based on pre NACT NLR and PLR and pre-recurrence NLR values. ***Results:*** At initial presentation, the NLR and PLR values were calculated for all 100 patients and it was seen that NLR was less than 8 in 35% cases, 8 to 11 in 15%and more than 11 in 50% of the study population.All patients received 3 to 4 cycles of neo-adjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). Post IDS, NLR was less than or equal to 1 in 61% and more than 1 in 39% cases. The PLR was found to be less than or equal to 5 in 53% and more than 5 in 47% cases. All patients had recurrence within 24 months of completion of treatment.It was seen that when NLR values (post NACT) was more than 11, early recurrence was seen in 61% cases and 35% cases showed late recurrence. This comparison was significant (p value: 0.004).***Conclusion:***The NLR has been proposed to be significant prognosis predictors for ovarian cancers. Yet, the cutoff value of the NLR is inconsistent instudies, which reduces its clinical applicability. In the present study the chosenmedian cut off value of pre NACTNLR > 11(HR:2) and PLR> 59 (HR:1.5) and a pre recurrence NLR> 9 (HR:2.6) had a significant impact on the post recurrence survival. A pre recurrence NLR> 9 was also a poor predictor of survival.

Keywords: Neutrophil lymphocyte ratio, platelet lymphocyte ratio, high grade serous carcinoma ovary, Interval debulking surgery, neo-adjuvant chemotherapy.

INTRODUCTION

An increasing body of evidence shows that systemic inflammation is closely associated with cancer initiation, progression and metastasis, and thus, inflammatory markers, including the neutrophil-lymphocyte ratio (NLR) and

platelet lymphocyte ratio (PLR), have been studied and found to be related to cancer mortality and employed as useful prognostic indicators in many solid tumours. The neutrophil–lymphocyte ratio (NLR), which has been considered as a member of the marker of the systemic inflammation response, is valuable for predicting the prognosis of various cancers [1, 2]. It is now well established that tumours are associated with massive inflammatory response with predominance of neutrophil and a simultaneous fall in the lymphocytes denoting a low level of local immunity causing a proliferation of cancer cell, invasiveness and metastasis. A measurement of neutrophil to lymphocyte ratio (NLR) and of platelet to lymphocyte ratio (PLR) has been found to be one of the markers of tumour burden and its association with prognosis.

Several previous meta-analyses on NLR in patients with ovarian cancers have identified that elevated NLR was significantly correlated with the inferior overall survival (OS), progression-free survival (PFS), and recurrence-free survival (RFS) for patients with ovarian cancer [3-6].

Thus, we undertook the present study to analyse the role of neutrophil is to lymphocyte ratio and platelet is to lymphocyte ratio as a predictor of outcome in advanced high grade serous adenocarcinoma of ovary.

MATERIALS AND METHODS

A retrospective study was conducted from January 2018 to December 2019 at a tertiary level regional cancer institute of Northeast India including women with high grade epithelial ovarian cancer. Women with other histo-pathologies, with primary peritoneal carcinomatosis, with missing data and treated outside were excluded from the study. All cases under went 3 to 4 cycles of NACT (neo-adjuvant chemotherapy) followed by IDS (interval debulking surgery).

A total of 100 cases were analysed and neutrophil is to lymphocyte ratio (NLR) and platelet is to lymphocyte ratio (PLR) was calculated for all patients; pre and post treatment.

NLR and PLR were calculated from complete blood cell count using the absolute neutrophil count divided by the absolute lymphocyte count and the absolute platelet countdividedbytheabsolutelymphocytecount respectively.

In the present study, the inflammatory burden based on NLR & PLR was analysed and these two factors were evaluated for risk of recurrence. Comparison of recurrence to survival percentage at 1, 3 and 5 years was studied based on pre NACT NLR and PLR and pre-recurrence NLR values.

Statistical Analysis

For comparison of NLR and PLR values pre and post treatment, chi square test was used and p value of less than 0.05 was considered significant. Kaplan-Meier curves were used for comparison of recurrence to survival percentage at 1,3 and 5 years based on pre NACT NLR and PLR and pre-recurrence NLR values. SPSS software, version 24 was used for all the calculations.

RESULTS

100 cases of high grade epithelial ovarian carcinoma were analysed. All cases belonged to advanced carcinoma ovary and hence were given neo-adjuvant chemotherapy (NACT) first. After completion of 3 to 4 cycles of NACT, all patients underwent interval debulking surgery (IDS). This was followed by adjuvant chemotherapy.

*Distribution of cases according to baseline NLR and PLR values (Table 1):*At initial presentation, the NLR and PLR values were calculated for all 100 patients and it was seen that NLR of less than 8 was present in 35% cases, from 8 to 11 in 15% cases and more than 11 in 50% of the study population. The mean NLR of the study population was 14.6 and the median value was 11. PLR was also calculated and it was seen that a PLR of less than 30 was seen in 8% cases, 30 to 60 in 40% cases and more than 60 in 52% cases. The mean PLR value was 72.7 with a median of 59.

Table 1:Distribution of cases according tobaseline NLR and PLR values (Pre NACT, N=100)

Variables	Number	Percentage
Neutrophil-Lymphocyte ratio (NLR)		
<8	35	35
8-11	15	15
>11	50	50
Mean±SD, Range	14.6±10.2,3.3-70	
Median	11	
Platelet-Lymphocyte Ratio (PLR)		
<30	8	8
30-60	40	40
>60	52	52
Mean±SD, Range	72.7±48.5,4-285	
Median	59	

Distribution of cases based on post NACT response (Table 2): The mean NLR post NACT was 1.3 with a median of 1.4 and the mean PLR post NACT was 5.8 with a median of 11.

Table 2: Distribution of cases based on the post NACT Biochemical response

Biochemical Variables (Post NACT)	Mean±SD (IU/ML) Range	Median
Neutrophil-Lymphocyte Ratio (NLR)	1.3±0.4(1-3)	1.4
Platelet-Lymphocyte Ratio (PLR)	5.8±2.8(3-22)	11

Distribution of cases based on post IDS values (Table 3): Post interval debulking surgery, it was seen that NLR was less than or equal to 1 in 61% cases and more than 1 in 39% of the study population. The PLR was found to be less than or equal to 5 in 53% cases and more than 5 in 47% cases.

Table 3: Distribution of cases on the Biochemical characteristics (Post IDS) (N=100)

Biochemical Variables (post IDS)	N	Percentage
Neutrophil-lymphocyte ratio		
<=1	61	61
>1	39	39
Post IDSPLR		
<=5.0	53	53
>5.0	47	47

This shows considerable decrease in NLR and PLR values post NACT and IDS.

All patients in our study had recurrence within 24 months of completion of treatment. Early recurrence was considered when the disease reappeared within 10 months of completion of treatment and late recurrence when it was more than 10 months. The pre and post treatment NLR and PLR values were compared with early and late recurrence (Table 4). It was seen that when NLR values (post NACT) was more than 11, early recurrence was seen in 61% cases as compared to 35% cases showing late recurrence. This comparison was significant (p value: 0.004). The PLR value was also compared post NACT but the difference in early versus late recurrence with a 59 cut off was not significant. The NLR and PLR values post IDS were compared with early versus late recurrence and were not found to be significant.

Table 4: Comparison of pre and post treatment NLR and PLR in women with Early and late recurrence

Time to Recurrence based on Cutoff					
Hematological parameters (Median)		**<10 Months (N=51) N(%)**	**>10 Months (N=49) N(%)**	**Chi Square**	**P value**
Pre NACT	NLR				
	<=11	20(39)	32(65)	8.213	0.004
	>11	31(61)	17(35)		
	PLR				
	<=59	23(45)	29(59)	2.829	0.093
	>59	28(55)	20(41)		
Post IDS	NLR				
	<=1	34(66.7)	26(53)	2.584	0.108
	>1	17(33.3)	23(47)		
	PLR				
	<=5.0	24(47)	28(57)	0.527	0.468
	>5.0	27(53)	21(43)		

The recurrence to survival percentage at 1, 3 and 5 years was compared for our study population based on pre NACT NLR, PLR and pre recurrence NLR values using the Kaplan Meier analysis (Table 5). It was seen that patients with pre NACT NLR of more than 11, pre NACT PLR of more than 59 and pre recurrence NLR of more than 9 had lesser median survival as compared to the population who had lesser values and this was statistically significant (Fig 1, 2 & 3).

Table 5:Comparison of Recurrence to survival percentage at 1year, 3 year and 5 years based on Pre NACT NLR, PLR and Pre recurrence NLR by Kaplan Meier analysis

Pre NACTNLR (based on Median as cutoff)	**Recurrence to Survival (%)**			**Median (Months)**	**95%CI**		**P value**
	1 Year	**3 Year**	**5 Year**		**Lower**	**Upper**	
<=11	86	45	46	21.0	14.25	27.75	0.003
>11	46	41	8	11.0	5.62	16.39	
Pre NACTPLR							
<=59	67	35	35	20.0	16.25	23.75	0.001
>59	47	27	20	11.0	4.82	17.18	
Pre recurrence NLR							
<=9	76	44	38	24	19.153	28.847	<0.0001
>9	36	14	14	11	8.661	13.339	

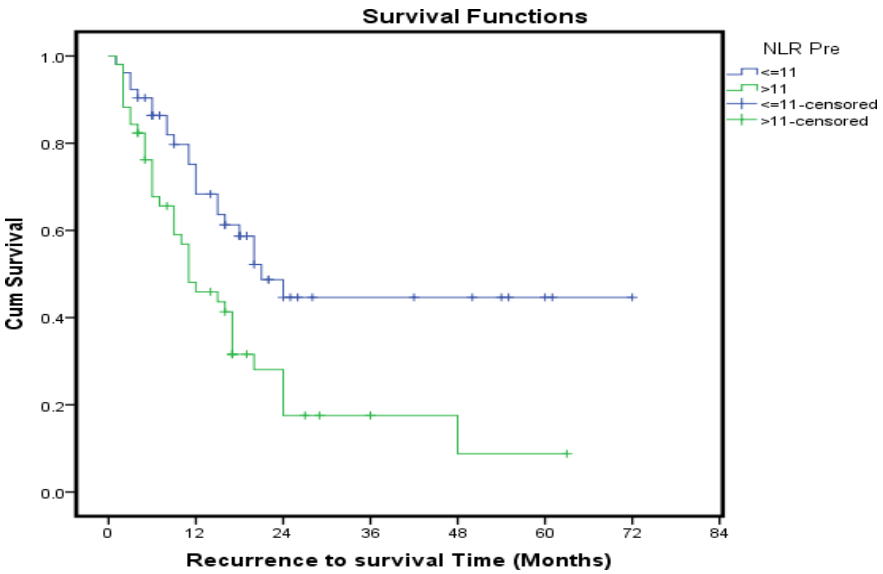

Fig 1: Kaplan-Meier Survival analysis: Recurrence to Survival time in pre NACTNLR>11

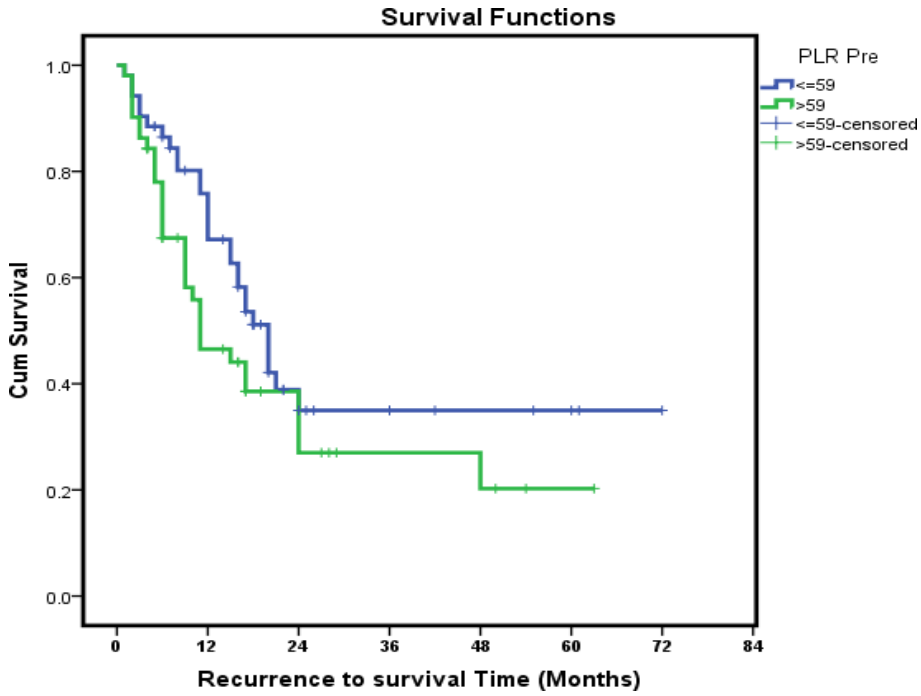

Fig 2: Kaplan-Meier Survival analysis: Recurrence to Survival time pre NACTPLR>59

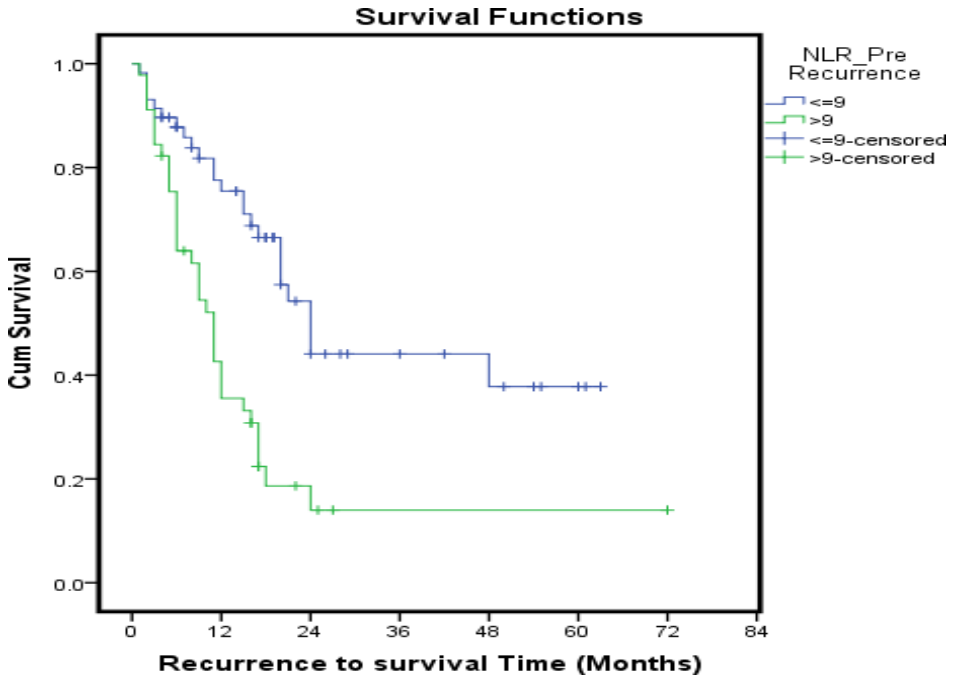

Fig 3: Kaplan-Meier Survival analysis: Recurrence to Survival time at recurrence NLR>9

DISCUSSION

It is now well established that tumours are associated with a massive inflammatory response with predominance of neutrophil and a simultaneous fall in the lymphocytes denoting a low or no local immunity causing a proliferation of cancer cell, invasiveness and metastasis. A measurement of neutrophil to lymphocyte ratio (NLR) and of platelet to lymphocyte ratio (PLR) has been found to be one of the markers of tumour burden and its association with prognosis.

The present study retrospectively calculatedthe NLR and PLR from the haematological parameters and observed a median cut off value of NLR & PLR as 11 & 59 respectively (Mean values of NLR was 14.6±10.2, which ranged from 3.3-70 and mean Platelet-Lymphocyte Ratio (PLR) of 72.7±48.5 ranging from 4-285 (Table 1). For ovarian cancer, data on NLR is more limited.

Cho *et al.*, 2006 [7] compared the NLR amongst women with malignant and benign ovarian tumour with those of normalhealthy women, the NLR were 6, 2.57 and 1.98 respectively. They concluded that thesensitivity and specificity of an abnormal NLRin detecting ovarian cancer is 66% and82%.A high NLR is associated with advanced stage III & IV. Similarly, William *et al.*, 2014 [8] reported a significant correlation between a high pre-treatment NLR (5.7) with advanced stage (III & IV), as cites (6.5) and high-grade serous histology.

Different studies have shown an elevated NLR at diagnosis. Nevertheless, the cut-off used for defining "elevated NLR" was different in each study asa result of differences in the chosen methodologies. While some studies chose the cut-off based on receiver operating characteristic curve analysis, which ranged from 2.60–5.03 [9, 10]. In addition, these studies included patients with all stages of ovariancarcinoma.Very few studies on NACT and its response by NLR and PLR have been reported. Their results are in accordance with the present study.

The study by Eitan R, *et al.*, 2019 [11], the median cutoff NLR was 7.5 ranging from 6-21.5, Similarly, in the study by Badora*et al.*, 2016 [12], the median NLR & PLR were 8 and 62.

In the present study the inflammatory burden based on NLR & PLR was analysed and these two factors were evaluated for risk of recurrence (Table 4). In the univariate analysis, based on the pretreatment, median cut off NLR of 11 & PLR of 59, women were categorized in the early and late recurrence group analysis. In women with a pre-treatment NLR > 11 and PLR> 59 a significant number had an early relapse (p= 0.004 & 0.093). However, we did not find any significance of a normalized post IDSNLR & PLR with recurrence (p more than 0.05). Many studies evaluated the prognostic role of NLR and PLR in advanced stage ovarian cancer, however there is in consistency in the methodology process. Some used the cut off values of NLR and PLR based on ROC which varied from 3-5, though these studies included patients of all stages and all histologies. The higher NLR & PLR in the present study could be because of the high-grade serous histology andthe highly metastatic disease on presentation. The higher the NLR, the more aggressive the disease, the higher the burden, less chemo response which led to early recurrence.

The influence of abnormal inflammatory markers on the prognosis was observed in the present study. An elevated Pre NACT NLR>11 and PLR>59 significantly effected relapse This is in accordance with numerous studies done in this regard.Severalstudies done so far have substantiated the effect of anelevated pre-treatment NLR and PLR on the prognosis, however there has been in consistent choice of high cutoff values (79-81). The present study comprised of a homogeneous population from a single institute (all high grade serous in advanced stage), thus our median cut off of NLR was higher as compared to previous studies.

Amongst the biochemical parameters an elevated pre NACTNLR>11 (P=0.003), Pre NACTPLR>59 (P=0.001) and Pre recurrence elevated NLR>9 (P<0.0001) was significant.Thus, on univariatecoxhazard ratio analysis demonstrated pre recurrence NLR of > 9 (HR 2.6, P=0.001), and a pre NACT NLR >11(HR 2.1, P=0.004), significantly was associated with an unfavourable prognosis. Factors of moderate risk were pre NACTPLR>59 (HR1.5, P=0.127). The reported pooled hazardratios for NLR and OS have ranged from (1.9-2.6) in literature [7, 9, 13].

CONCLUSION

Presently, the estimate of oncologic outcomes in patients with ovarian cancer mainly relies on conventional clinico-pathological variables, such as TNM stage, CA125 and CA 19.9 levels. These parameters, reflecting cancer behaviour and presentation in biology, may notrepresent the actual burden of patients with ovarian cancer. The blood-based indexes canserveascomplementaryitems forthe predictive models inpatients with ovarian cancer. Recently, the NLR has been proposed to be significant prognosis predictors Yet, the cutoff value of the NLR is inconsistent instudies, which reduces its clinical applicability. In the present study the chosen median cutoff value of pre NACTNLR > 11(HR:2) and PLR> 59 (HR:1.5) and a pre recurrence NLR> 9 (HR:2.6) had a significant impact on thepost-recurrence survival. A pre recurrence NLR> 9 wasalso a poor predictor of survival. The impact of an elevated NLR has been explored as a continuous explanatory variable and it is affected by the patients baselines and therapeutic approaches.

REFERENCES

1. He, W., Yin, C., Guo, G., Jiang, C., Wang, F., Qiu, H., ...& Xia, L. (2013). Initial neutrophil lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. *Medical Oncology*, *30*, 1-6.
2. Jung, M. R., Park, Y. K., Jeong, O., Seon, J. W., Ryu, S. Y., Kim, D. Y., & Kim, Y. J. (2011). Elevated preoperative neutrophil to lymphocyte ratio predicts poor survival following resection in late stage gastric cancer. *Journal of surgical oncology*, *104*(5), 504-510.
3. Baert, T., Van Camp, J., Vanbrabant, L., Busschaert, P., Laenen, A., Han, S., ...&Coosemans, A. (2018). Influence of CA125, platelet count and neutrophil to lymphocyte ratio on the immune system of ovarian cancer

patients. *Gynecologic Oncology*, *150*(1), 31-37.
4. Kwon, B. S., Jeong, D. H., Byun, J. M., Lee, T. H., Choi, K. U., Song, Y. J., ... & Kim, K. H. (2018). Prognostic value of preoperative lymphocyte-monocyte ratio in patients with ovarian clear cell carcinoma. *Journal of Cancer*, *9*(7), 1127-1134.
5. Lin, Q., Ding, S. J., Zhu, T. H., Li, T. T., Huang, X. F., & Zhang, X. M. (2018). Role and clinical significance of coagulation and inflammatory factors in moderate and severe ovarian endometriosis. *Zhonghua Fu Chan KeZaZhi*, *53*(3), 167-171.
6. Zhu, Y., Zhou, S., Liu, Y., Zhai, L., & Sun, X. (2018). Prognostic value of systemic inflammatory markers in ovarian Cancer: a PRISMA-compliant meta-analysis and systematic review. *BMC cancer*, *18*, 1-10.
7. Cho, H., Hur, H. W., Kim, S. W., Kim, S. H., Kim, J. H., Kim, Y. T., & Lee, K. (2009). Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. *Cancer immunology, immunotherapy*, *58*, 15-23.
8. Williams, K. A., Labidi-Galy, S. I., Terry, K. L., Vitonis, A. F., Welch, W. R., Goodman, A., & Cramer, D. W. (2014). Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. *Gynecologic oncology*, *132*(3), 542-550.
9. Wang, Y., Liu, P., Xu, Y., Zhang, W., Tong, L., Guo, Z., & Ni, H. (2015). Preoperative neutrophil-to-lymphocyte ratio predicts response to first-line platinum-based chemotherapy and prognosis in serous ovarian cancer. *Cancer chemotherapy and pharmacology*, *75*, 255-262.
10. Feng, Z., Wen, H., Bi, R., Ju, X., Chen, X., Yang, W., & Wu, X. (2016). Preoperative neutrophil-to-lymphocyte ratio as a predictive and prognostic factor for high-grade serous ovarian cancer. *PLoS One*, *11*(5), e0156101.
11. Eitan, R., Salman, L., Sabah, G., Jakobson-Setton, A., Raban, O., Yeoshoua, E., &Tsoref, D. (2019). Neutrophil-to-lymphocyte ratio as a prognostic factor in advanced stage ovarian carcinoma treated with neoadjuvant chemotherapy. *Gynecologic Oncology*, *154*, 269-270.
12. Badora-Rybicka, A., Nowara, E., &Starzyczny-Słota, D. (2016). 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*, *1*(2), e000039.
13. Miao, Y., Yan, Q., Li, S., Li, B., &Feng, Y. (2016). 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 Biomarkers*, *17*(1), 33-40.