Chirurgia (2023) 118: 417-425
No. 4, July - August

http://dx.doi.org/10.21614/chirurgia.2023.v.118.i.4.p.417

Platelet to Lymphocyte Ratio as a Predictive Tool for the Perioperative and Postoperative Outcomes in Advanced Stage Ovarian Cancer

Irina Balescu[1‡], Iulian Brezean[2,3], Victor Cauni[4], Sorin Petrea[2,3], Camelia Diaconu[5,6], Bogdan Gaspar[2,7‡], Adriana Ciuvica[8,9‡], Claudiu Eduard Nistor[10,11], Adrian Ciuche[10,11], Valentin Varlas[8,12], Nicolae Bacalbasa[2,13*]

[1]PhD Student, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2]Department of Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3]Department of Surgery, Ion Cantacuzino Clinical Hospital, Bucharest, Romania
[4]Department of Urology, Colentina Clinical Hospital, Bucharest, Romania
[5]Department of Internal Medicine, Floreasca Clinical Emergency Hospital, Bucharest, Romania
[6]Department of Internal Medicine Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[7]Department of Visceral Surgery, Floreasca Clinical Emergency Hospital, Bucharest, Romania
[8]Department of Obstetrics and Gynecology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[9]Department of Obstetrics and Gynecology National Institute of Mother and Child Care Alessandrescu-Rusescu, Bucharest, Romania
[10]Cardio-Thoracic Pathology, Thoracic Surgery Discipline, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[11]Thoracic Surgery Department, Carol Davila Central Emergency University Military Hospital, Bucharest, Romania
[12]Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania
[13]Department of Visceral Surgery, Center of Excellence in Translational Medicine "Fundeni" Clinical Institute, Bucharest, 022328, Romania

***Corresponding author:**
Nicolae Bacalbasa, MD
Department of Visceral Surgery
Center of Excellence in Translational Medicine, Fundeni Clinical Institute
Bucharest, 022328, Romania
E-mail: nicolaebacalbasa@gmail.com

‡Authors with equal contributions.

Received: 09.06.2023
Accepted: 15.08.2023

Rezumat

Raportul trombocite/limfocite ca unealtă de predicție a evoluției perioperatorii și postoperatorii în neoplasmele de ovar avansate

Scop: raportul trombocite/limfocite reprezintă un factor semnificativ de prognostic în cazul diferitelor malignități. Scopul studiului de față este de a investiga corelația dintre valorile preoperatorii ale acestui raport şi evoluția postoperatorie a pacientelor cu neoplasme ovariene.

Metodă: am condus un studiu retrospectiv pe un grup de 57 paciente supuse chirurgiei citoreducționale în perioada 2014-2020. Am determinat valoarea optimă de cut off a acestui raport pentru a avea valoare predictivă pentru supraviețuire la 350. Ulterior pacienții au fost clasificați în funcție de valoarea acestui raport.

Rezultate: au fost 37 pacienți cu valoarea raportului de sub 350 şi respectiv 20 pacienți cu valoare de peste 350, pacienții din cel de-al doilea grup prezentând o vârstă semnificativ mai înaintată, o rată mai mare a complicațiilor postoperatorii, al numărului trombocitelor, al CA 125 şi respectiv un nivel mai mic al limfocitelor şi al

hemoglobinei. În acelaşi timp pacienții din cel de-al doilea grup au raportat o rată semnificativ mai mica a supraviețuirii libere de boală şi respectiv globale.
Concluzii: pacienții cu niveluri crescute ale raportului trombocite/limfocite tind să aibă un prognostic mai prost pe termen scurt şi la distanță. Drept urmare, în astfel de cazuri, terapii sistemice mai agresive ar putea fi necesare.

Cuvinte cheie: neoplasme ovariene avansate, raport trombocit/limfocit, supraviețuire medie globală, complicații postoperatorii

Abstract
Background: platelet to lymphocyte ratio remains a significant prognostic factor in different malignancies. The aim of the current paper is to study the correlation between the preoperative values of platelet to lymphocyte ratio (PLR) and the postoperative outcomes in ovarian cancer patients.
Method: we conducted a retrospective study on 57 patients submitted to cytoreductive surgery between 2014-2020. We determined the optimal cut off value of PLR for predicting survival outcomes by using the Receiver Operating Characteristic curve a value of 350 being obtained. The patients were further classified in two groups according to the PLR value.
Results: there were 37 patients with PLR<350 and respectively 20 patients with PLR>350. Patients in the second group were significantly older and presented significantly higher rates of perioperative complications, a significantly higher level of circulating platelets, of CA125 and respectively a significantly lower level of circulating lymphocytes and of preoperative hemoglobin level. Meanwhile, patients in the second group reported a significantly poorer disease free and overall survival.
Conclusions: ovarian cancer patients with higher preoperative levels of PLR trend to have a poorer early and long-term postoperative outcome. Therefore, in such cases more aggressive systemic therapies might be needed.

Key words: advanced stage ovarian cancer, platelet to lymphocyte ratio, mean overall survival rate, postoperative complications

Introduction

Despite progress reported in the field of cytoreductive surgery, ovarian cancer remains one of the most important causes of cancer related death among women worldwide. Therefore, it is estimated that ovarian cancer ranks third in prevalence among gynecologic malignancies, being responsible for 125000 cancer related deaths yearly (1,2). The high amount of cancer related deaths is mainly explained through the fact that until now no significant screening system could be identified in order to provide an early diagnostic of this malignancy. In the last decade an association between biological tests (CA125 measurement) and imagistic studies (vaginal ultrasound) has been proposed but the benefits remain scarce (3). However, CA125 has been recognized as the most important tool for diagnostic and follow up in advanced stages of this disease. In such cases, the standard therapeutic protocol remains cytoreductive surgery followed by adjuvant platinum and taxanes based chemotherapy (4). Even though a significant number of cases

will recur and will report poor rates of survival. Therefore, it is estimated that less than 30% of women diagnosed with advanced stage ovarian cancer will achieve a 5-year rate of survival (3). In this respect, attention was focused on identifying new prognostic factors which might provide a better selection of cases submitted to per primam surgery (5-7).

During the last decade particular interest was focused on studying the possible correlation between the circulating number of platelets and respectively other inflammation markers and the aggressiveness of ovarian cancer (8-10). It has been widely demonstrated that inflammation plays a crucial role in tumorigenesis by stimulating cancer cells proliferation, invasion, dissemination as well as angiogenesis (11-15). On the other hand, modifications of complete blood cells formula by decreasing the number of circulating lymphocites and increasing neutrophils seem to induce a particular environment which diminishes the host capacity to protect against tumoral dissemination. Moreover, it seems that the presence of a lower rate of lymphocytes is usually associated with terminal stage cancer. In this respect, different prognostic markers have been proposed such as platelet to lymphocyte ratio, monocyte to lymphocyte ratio or neutrophil to lymphocyte ratio (16-20).

Although the correlation between the number of the circulating platelets and the overall prognostic in ovarian cancer patients has been widely studied, little is known about the possible correlation between this malignancy and platelet to lymphocyte ratio (PLR). The aim of the current paper was to study the influence of the PLR on the short term and respectively long-term outcomes of patients diagnosed with advanced stage ovarian cancer and submitted to cytoreductive surgery.

Material and Method

After receiving the Ethics Committee of I. Cantacuzino clinical hospital approval, data of patients submitted to surgery for advanced stage ovarian carcinoma were retrospectively reviewed. Inclusion criteria were represented by: patients' age over 18 years, histopathological confirmed stage IIIc or IV ovarian cancer and submission to surgery with curative intent. Exclusion criteria were: age under 18 years, the absence of a histopathological confirmation of FIGO stage IIIC or IV ovarian cancer, prior neoadjuvant therapy, previous history of splenectomy as well as the presence of any associated infection, hematological or rheumatoid disorder which might influence the complete blood count. Initially, 85 such cases were identified; however, after analyzing the histopathology of the surgical specimens, eight cases were excluded due to the fact that there were finally classified as having FIGO IIIA or FIGO IIIB lesions while, other 20 cases were excluded due to the fact that they associated cutaneous or urinary infections.

Finally, 57 patients were considered as being eligible for this study. In all cases a preoperative complete blood count was retrieved 24 hours before the surgical procedure. Preoperative data regarding complete blood count, CA125 level and age were analyzed in each case. Complete debulking surgery was defined as the absence of any visible residual tumor and was tempted in all cases.

Receiver Operating Characteristic (ROC) curve was used with Youden index [maximum (sensitivity + specificity-1)], a cut off value of the platelet to lymphocyte ratio in order to predict the radicality of the resection being determined at 350 (with a sensibility of 0.9 and a specificity of 0.78, area under the curve of 0.94 (*Fig. 1*).

Progression free survival was defined as the interval between the data of the initial surgical procedure and the data when recurrent disease was diagnosed while overall survival was defined as the interval between the time of the initial surgery and the moment in which cancer related death occurred. Univariate analysis was performed by using the Cox proportional hazard model. Multivariate analysis was performed by using the multivariate Cox proportional hazard mode, factors showing statistical significance in univariate analysis being entered into the Cox proportional hazard model

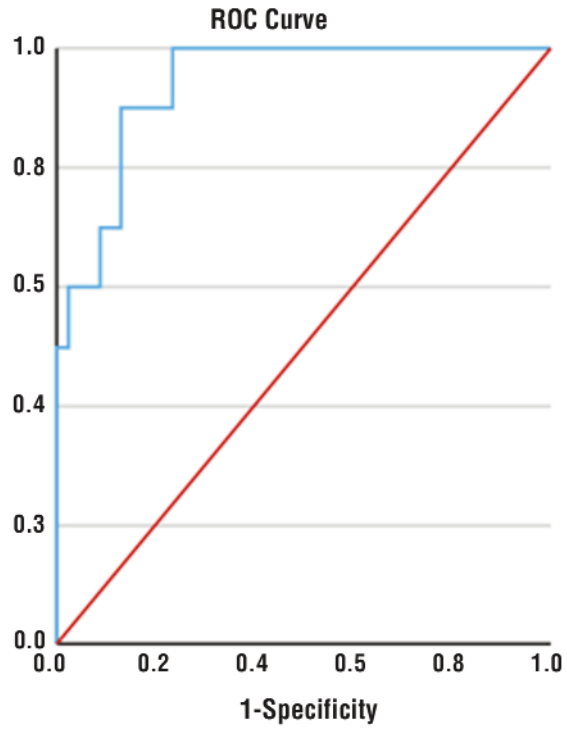

Figure 1. The ROC curve to determine the cut-off value for platelet to lymphocyte ratio to predict the completeness of the resection

for multivariate analysis. For the purpose of this study, independent variables where $p \leq 0.05$ were considered significant. The median overall survival curves were obtained by applying the Kaplan Meyer analysis and compared using the Log-rank test . All data was analyzed by using the SPSS statistical software version 18.0 (SPSS Inc. Chicago, IL, USA).

Results

By using the cut off value of 350, the group of 57 patients was further subdivided in two groups: cases with a preoperative value of PLR<350 which included 37 patients and cases with a preoperative value of PLR>350 which included 20 patients respectively.

The mean age if the patients at the time of entering the study was 56 years (range 25-83 years) while the value of PLR ranged between 73 and 853.

The clinical, biochemical and pathological characteristics of the two subgroups of patients (divided according to the preoperative PLR value) are presented in *Table 1.*

As it can be observed, patients with lower than 350 PLR value were significantly younger and were more frequently submitted to complete resections when compared to cases with a higher than 350 PLR value. Meanwhile, cases in the first subgroup developed a significantly lower rate of post-operative complications when compared to those in the second subgroup. However, the length of hospital in stay was similar between the two groups. When analyzing the correlation ship between the preoperative level of PLR and other biomarkers, we observed that a higher PLR level was significantly corelated with a higher value of CA125, with a higher number of circulating platelets, a lower number of circulating lymphocytes and respectively a lower level of hemoglobin.

As expected, patients with a lower PLR also had a significant benefit in terms of survival. Therefore, in patients with PLR<350 the mean progression free survival rate was of 22.5 months (95% confidence interval [CI] 20.1-29.3 months), while in cases with PLR >350, the mean progression free survival rate was of only 7.7 months (95% confidence interval [CI] 6.5-10.4 months) (p=0.01). Meanwhile, when investigating the mean overall survival rate, we observed that in patients with PLR<350 the mean overall survival rate was of 38.89 months (95% confidence interval [CI] 31-43 months) while in cases with PLR>350, the mean progression free survival rate was of only 13.7 months (95% confidence interval [CI] 11.2-16.4 months) (p=0.01).

The Kaplan Meyer curves of survival for the two groups (with PLR, 350 versus PLR > 350) are represented in *Fig. 2.* As expected, the difference between the two groups was statistically significant.

In univariate analysis CA125, platelet number, lymphocyte number, PLR, and the radicality of the surgical procedure had a significant influence on survival. Data regarding the univariate analysis results are presented in *Table 2.*

Table 1. Clinical, biochemical and pathological findings of patients submitted to cytoreductive surgery and further classified according to the preoperative level of PLR

	PLR<350 (n=37)	PLR>350 (n=20)	P value
Age (years, mean)	53	62	P=0.015
Stage:			P=0.119
IIIC	36	17	
IV	1	3	
Histopathology:			P=0.539
Serous	26	13	
Endometroid	3	1	
Mucinous	2	1	
Clear cell	5	1	
Other histologies	1	4	
Grade:			P=0.449
I	4	2	
II	12	3	
III	21	15	
Residual disease:			P<0.000001
R0	36	9	
R1	1	13	
Postoperative complications:			P=0.0026
Yes	4	10	
No	33	10	
Associated comorbidities:			P=0.9
Yes	14	8	
No	23	12	
Length of hospital in stay (days, mean)	10.3	10.5	P=0.9
CA125 (U/ml, mean)	334	2518	P<0.001
Platelet (*1000/microL, mean)	312575	469466	P<0.001
Lymphocyte (/microL, mean)	1781	897	P<0.001
Hemoglobin (g/dl)	12.39	10.34	P=0.004

When performing multivariate analysis CA125 level, platelet number, platelet to lymphocyte ratio and the radicality of procedure negatively impacted the overall survival rate.

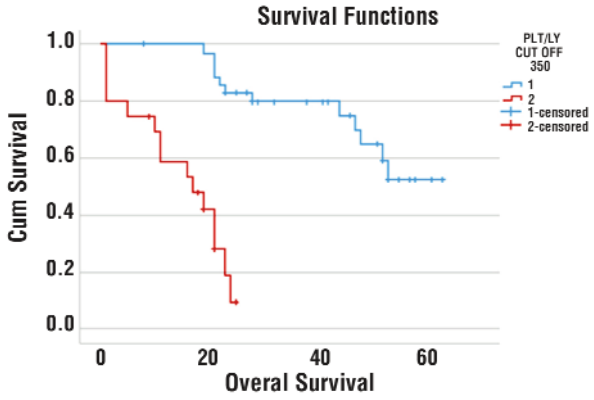

Figure 2. The Kaplan Meyer curves of survival for the two categories (with PLR < 350 versus PLR > 350) demonstrating a significant benefit in terms of survival for cases in the first category

When performing the univariate analysis by Cox proportional hazard model for progression free survival, CA125 level, platelet number, OLR and the radicality of the surgical procedure significantly influenced this parameter; p values, hazard ratio and confidence intervals are shown in *Table 3*.

As for the influence on the disease-free survival, the multivariate analysis demonstrated that only the number of circulating platelets and the PLR significantly influenced this parameter

Table 2. Univariate analysis by Cox proportional hazard model for the overall survival rate

Parameter	P value	HR	95% CI
Age	P=0.23	1.1	0.8-1.9
CA125	P=0.002	2.1	1.2-3.4
Platelet number	P=0.002	1.9	1.1-2.8
PLR	P=0.001	2.6	1.2-3.9
Radicality	P=0.015	1.6	1.3-3.3
Lymphocyte number	P=0.021	1.8	1.1-3.4

Table 3. Univariate analysis by Cox proportional hazard model for the progression free survival rate

Parameter	P value	HR	95% CI
Age	P=0.872	1	0.8-3.2
CA125	P=0.011	1.8	1.2-3.2
Platelet number	P=0.001	2.1	1.3-3.8
PLR	P=0.009	1.9	1.2-3
Radicality	P=0.012	1.7	1.1-2.9
Lymphocyte number	P=0.234	1.1	0.6-2.5

(HR=2.3, 95% CI=1.8-4.6 and p= 0.023 for the circulating platelets and respectively HR=3.8, 95%CI=1.7-7 and p=0.045 for PLR).

Discussions

Although CA125 has been widely recognized as the most important biological marker for ovarian cancer diagnosis, it has been also demonstrated that the rates of false positive cases are high; therefore, attention was focused on identifying other potential prognostic markers which could provide a better identification of ovarian cancer patients in less advanced stages as well as the cases who should be rather submitted to neoadjuvant chemotherapy than to per primam cytoreductive surgery (21). PLR seems to be a promising such marker, which has the great advantage of being associated with a low cost and high quality (22). A higher number of circulating platelets as well as a higher value of PLR seems to be associated with a higher level of angiogenesis and with a higher capacity of tumoral spread. As expected, a higher value of PLR is usually associated with higher levels of CA125 pointing out therefore the presence of a more biologically aggressive tumor (21). The presence of a higher number of circulating platelets also seems to be associated with a higher amount of circulating proangiogenic factors such as tumor growth factors and interleukines which will further stimulate tumoral cells migration, growth and will inhibit tumoral apoptosis. Meanwhile, it has been widely demonstrated that lymphocytes are responsible for the immune defense against neoplastic cells; therefore, once the number of circulating lymphocytes decreases, a favorable tumoral environment develops and tumoral progression occurs (23,24). In our study the presence of a higher PLR was associated not only with a higher risk of incomplete debulking surgery but also with a poorer long term outcome, defined through a significantly lower progression free survival rate and respectively a significantly lower overall survival rate. Moreover, both univariate and multivariate analysis demonstrated a significant correlation ship between PLR and overall survival. Interestingly, the preoperative level of PLR was significantly corelated not only with CA 125 levels, but also with the preoperative level of hemoglobin; this aspect might be explained through the fact that anemia is currently associated with more advanced or more aggressive malignancies. Therefore, cases presenting these biological particularities should be rather submitted to neoadjuvant chemotherapy followed by interval debulking surgery than to per primam attempt of cytoreduction (25).

An interesting study which aimed to investigate the correlation ship between platelet to lymphocyte ratio and the overall prognosis of ovarian cancer patients was conducted by Badora-Rybicka et al and included 315 newly diagnosed ovarian cancer patients submitted to surgery followed by adjuvant taxanes and platinum-based chemotherapy. In all cases PLR was determined after surgery and before initiation of adjuvant chemotherapy; other investigated parameters were represented by neutrophil to lymphocyte ratio and CA125 levels. When it comes to the FIGO stages, 59% of cases were diagnosed in stage III of the disease, 19.4% of cases were diagnosed in FIGO stage I of the disease, 9.5% of cases were diagnosed in FIGO stage II of the disease and the remaining 12.1% of cases were diagnosed in FIGO stage IV of the disease; meanwhile, when discussing about the rate of complete debulking surgery, the authors underlined the fact that it was achieved in 57.8% of cases. Overall, a higher pretreatment PLR was associated with longer progression free survival interval. When analyzing the influence of this parameter on different stages of the disease,

the authors demonstrated that among patients diagnosed in FIGO stage I a higher pretreatment PLR was associated with an increased overall survival (p=0.005); a similar result was also found when studying the influence of PLR on the progression free and overall survival in FIGO stage II of the disease, a higher value of this parameter being significantly corelated with improved survival outcomes. However, when investigating the influence of pretreatment PLR on the overall outcomes in stage III of the disease, higher PLR were negative prognostic factors for both progression free and overall survival rates (26).

A paper which aimed to investigate the influence of PLR on the response to chemotherapy was conducted by Winarno et al and was published in 2021; the study included 116 patients diagnosed with stage I-III ovarian cancer submitted to surgery followed by chemotherapy who were further classified according to their response to chemotherapy into platinum sensitive and respectively platinum resistant. According to the results of this study, platinum sensitivity was strongly associated with a higher PLR value; however, a detailed analysis on FIGO stages of the disease was not performed (27).

A systematic review conducted by Prodromidou et al and published in 2017 came to demonstrate that PLR could not only predict the presence of a more advanced stage of the disease among ovarian cancer patients but it can also distinguish between healthy controls, borderline ovarian lesions and ovarian cancer, a higher trend being observed between the three categories (28). A larger meta-analysis conducted on this issue which included six retrospective studies came to demonstrate that PLR has a stable unfavorable influence on the long term outcomes of ovarian cancer patients; a similar trend was observed when investigating the influence of neutrophil to lymphocyte ratio on the long term outcomes of these patients. Therefore, the authors underlined the fact that the association of neutrophil to lymphocyte ratio with PLR should be considered as an effective predictor factor for overall prognosis in ovarian cancer patients (29).

When it comes to the influence of the circulating platelets on the overall prognostic in ovarian cancer, it seems that an increased number of thrombocytes predispose to a higher risk of postoperative embolism and therefore it also increases the perioperative morbidity and mortality. In such an instance, the adjuvant treatment will by delayed and therefore the risk of relapse will increase. In order to prevent this scenario, certain authors recommend the association of antiaggregant therapies with promising results (29-32).

Our paper comes to demonstrate the utility of using this ratio in order to better identify and select cases who could benefit most from per primam surgery and meanwhile, to exclude from surgery cases in which an incomplete surgical procedure is to be expected. However the main limitation of our study is related to the low number of cases included in the current study; in order to minimize the influence of these factors, larger studies including a higher number of patients are still needed.

Conclusions

PLR seems to be a promising factor in order to better identify ovarian cancer patients and to predict the response to therapy especially in advanced stages of the disease (29,30). When it comes to the advanced stages of the disease, a higher PLR seems to be predictive for incomplete debulking surgery, for poorer chemotherapeutic response as well as for poorer rates of progression free and respectively overall survival rates. Therefore, in such cases association of neoadjuvant therapy might be useful in order to improve the long-term outcomes. Moreover, in cases presenting a significantly higher number of platelets maybe an antiaggregant therapy should be added in order to minimize the risks related to cancer related thrombocytosis complications such as thromboses and embolisms.

Author's Contributions

Conceptualization: Irina Balescu, Nicolae Bacalbasa. Project administration: Iulian Brezean. Data curation: Victor Cauni, Sorin Petrea, Camelia Diaconu, Bogdan Gaspar.
Software: Irina Balescu.
Investigation: Adriana Ciuvica.
Resources: Claudiu Eduard Nistor.
Supervision: Iulian Brezean, Nicolae Bacalbasa. Validation: Claudiu Eduard Nistor.
Visualization: Adrian Ciuche. Writing original draft: Irina Balescu, Valentin Varlas.
Writing - review & editing: Nicolae Bacalbasa.

Conflicts of Interest

The authors have no conflicts of interest to declare and received no grants or funding for this study.

Funding

No funding was received.

Ethical Statement

Ethical approval no 83/2023 of the Ion Cantacuzino clinical hospital was obtained before beginning the study.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, 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.
2. Huang Q, Du T, Qu QX. Tea polyphenol decreased growth and invasion in human ovarian cancer cells. Eur J Inflamm. 2016;14: 206-211.
3. Moyer VA. Screening for ovarian cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2012; 157(12):900-904.
4. Querleu D, Planchamp F, Chiva L, Fotopoulou C, Barton D, Cibula D, et al. European Society of Gynaecological Oncology (ESGO) guidelines for ovarian cancer surgery. Int J Gynecol Cancer. 2017;27(7):1534-1542.
5. Fan HY, Duan DM, Liu YF. The diagnostic value of determination of serum GOLPH3 associated with CA125, CA19.9 in patients with ovarian cancer. Eur Rev Med Pharmacol Sci. 2017;21(18):4039-4044.
6. Ocana A, Nieto-Jiménez C, Pandiella A, Templeton AJ. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer. 2017; 16(1):1-7.
7. Olsson A-K, Cedervall J. The pro-inflammatory role of platelets in cancer. Platelets. 2018;29(6):569-573.
8. Macciò A, Madeddu C. Inflammation and ovarian cancer. Cytokine. 2012; 58(2):133-147.
9. Kim HS, Choi HY, Lee M, Suh DH, Kim K, No JH, et al. Systemic inflammatory response markers and CA-125 levels in ovarian clear cell carcinoma: a two center cohort study. Cancer Res Treat. 2015;48(1): 250-258.
10. Crasta JA, Premlatha TS, Krishnan SM, Vallikad E, Rameshkumar K. Significance of preoperative thrombocytosis in epithelial ovarian cancer. Indian J Pathol Microbiol. 2010;53(1): 54-56.
11. Guo ZS, Qu Z. PDLIM2: Signaling pathways and functions in cancer suppression and host immunity. Biochim Biophys Acta Rev Cancer. 2021;1876(2): 188630.
12. Pankowska KA, Bedkowska GE, Chociej-Stypułkowska J, Rusak M, Dabrowska M, Osada J. Crosstalk of Immune Cells and Platelets in an Ovarian Cancer Microenvironment and Their Prognostic Significance. Int J Mol Sci. 2023;24(11):9279
13. Stepien S, Olczyk P, Gola J, Komosinska-Vassev K, Mielczarek-Palacz A. The Role of Selected Adipocytokines in Ovarian Cancer and Endometrial Cancer. Cells. 2023;12(8):1118.
14. Barth MC, Häfner N, Runnebaum IB, Weigand W. Synthesis, Characterization and Biological Investigation of the Platinum(IV) Tolfenamato Prodrug-Resolving Cisplatin-Resistance in Ovarian Carcinoma Cell Lines. Int J Mol Sci. 2023;24(6):5718
15. Guo ZS, Qu Z. PDLIM2: Signaling pathways and functions in cancer suppression and host immunity. Biochim Biophys Acta Rev Cancer. 2021;1876(2): 188630.
16. Sánchez-Prieto M, Sánchez-Borrego R, Lubián-López DM, Pérez-López FR. Etiopathogenesis of ovarian cancer. An inflamm-aging entity? Gynecol Oncol Rep. 2022;42:101018
17. Zhang CL, Jiang XC, Li Y, Pan X, Gao MQ, Chen Y et al. Independent predictive value of blood inflammatory composite markers in ovarian cancer: recent clinical evidence and perspective focusing on NLR and PLR. J Ovarian Res. 2023;16(1):36.
18. Zhu Y, Zhou S, Liu Y, Zhai L, Sun X. Prognostic value of systemic inflammatory markers in ovarian Cancer: a PRISMA-compliant meta-analysis and systematic review. BMC Cancer. 2018;18(1):443.
19. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1204-12
20. Mu J, Wu Y, Jiang C, Cai L, Li D, Cao J. Progress in Applicability of Scoring Systems Based on Nutritional and Inflammatory Parameters for Ovarian Cancer. Front Nutr. 2022;9:809091.
21. Wang N, Li C, Yang Y, Guan Y, Wang F, Wang Y, et al. The Use of Platelet/Lymphocyte Ratio and Cancer Antigen 125 Combined with Magnetic Resonance Diffusion-Weighted Imaging in Diagnosis of Recurrent Ovarian Cancer and Neuropathic Pain. World Neurosurg. 2021;149:502-510.
22. Lee M, Chang MY, Yoo H, Lee KE, Chay DB, Cho H, et al. Clinical significance of CA125 level after the first cycle of chemotherapy on survival of patients with advanced ovarian cancer. Yonsei Med. 2016;57(3):580-587.
23. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: a meta-analysis. J Cancer. 2018; 9(18): 3295–3302.
24. Yan Q, Ertao Z, Zhimei Z, Weigang D, Jianjun P, Jianhui C et al. Systemic

immune-inflammation index (SII): a more promising inflammation-based prognostic marker for patients with synchronic colorectal peritoneal carcinomatosis. J Cancer. 2020;11(18):5264–5272.
25. Ramón-Rodríguez J, De-Armas-Conde N, Jaén-Torrejimeno I, Prada-Villaverde A, Rojas-Holguín A, López-Guerra D, et al. Prognostic value of pre-operative systemic immune-inflammation index and platelet to lymphocyte ratio in peritoneal carcinomatosis of ovarian origin. Surg Oncol. 2022; 42:101750.
26. Badora-Rybicka A, Nowara E, 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(2):e000039.
27. Winarno GNA, Pasaribu M, Susanto H, Nisa AS, Harsono AB, Yuseran H, et al. The Platelet to Lymphocyte and Neutrophil to Lymphocyte Ratios in Predicting Response to Platinum-based Chemotherapy for Epithelial Ovarian Cancer. Asian Pac J Cancer Prev. 2021;22(5):1561-1566.
28. 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.
29. 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.
30. Tian C, Song W, Tian X, Sun Y. Prognostic significance of platelet-to-lymphocyte ratio in patients with ovarian cancer: A meta-analysis. Eur J Clin Invest. 2018;48)5):12917.
31. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, MehtaZ. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet. 2012;379(9826):1591-1601.
32. Stevenson JL, Varki A, Borsig L. Heparin attenuates metastasis mainly due to inhibition of P- and L-selectin, but non-anticoagulant heparins can have additional effects. Thromb Res. 2007;120(Suppl 2):S107-S111.