RESEARCH ARTICLE

Diagnostic Value of NLR and PLR for Malignancy in Ovarian Tumor: Feasible Markers in Low-resource Setting

Muhammad Ary Zucha[1], Ardhanu Kusumanto[2], Siti Salima[3], Ali Budi Harsono[4], Andi Kurniadi[5]

Received on: 08 August 2024; *Accepted on:* 20 September 2024; *Published on:* 03 February 2025

Abstract

Aim and background: Most ovarian cancer patients are diagnosed at a late stage, which correlates with a poorer prognosis. Systemic inflammation plays an important role in tumor initiation and progression. Therefore, systemic inflammation markers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are extensively studied. However, the applicability of PLR and NLR as malignancy predictors and the diagnostic accuracy in ovarian malignancy need to be clarified. The study aimed to investigate the diagnostic accuracy of PLR and NLR for malignant ovarian tumors.

Methods: We included 161 patients who underwent surgery on an indicated ovarian tumor. Histopathologic confirmation of malignancy was used as a gold standard. Preoperative PLR and NLR values were compared to pathologic confirmation of malignancy. A threshold of NLR ≥3.0 was defined as high NLR, while PLR value ≥160 was considered high. The area under the curve (AUC) value of the receiver operator characteristic (ROC) curve was used to distinguish between benign and malignant individuals. Area under the curve above 0.7 is considered an acceptable diagnostic performance.

Results: We found that both preoperative PLR and NLR had significantly greater values in ovarian cancer than in benign ovarian tumors ($p < 0.001$). High NLR patients showed greater possibility of malignancy (OR = 5.32; 95% CI: 2.52–11.21; $p < 0.001$). Patients with high PLR also showed comparable odds ratio for malignancy (OR = 4.03; 95% CI:1.95–8.31; $p < 0.001$). The sensitivity of NLR was 66.3% and specificity was 72.9%, while PLR sensitivity and specificity were 78.76 and 52.08%, respectively. The accuracy of NLR was 68.32% (AUC = 0.743) and PLR was 60.54% (AUC = 0.733).

Conclusion: Both PLR and NLR have valuable accuracy in differentiating ovarian malignancies from benign ovarian tumors. These results may be important evidence to support the applicability of these cheap markers to indicate ovarian malignancy in low-resource settings.

Keywords: Accuracy, Neutrophil-to-lymphocyte ratio, Ovarian malignancy, Platelet-to-lymphocyte ratio, Systemic inflammation.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2545

Introduction

Ovarian malignancy is a major health problem, as one of the cancers with high incidence and mortality.[1] In 2020, ovarian cancer is considered the third highest prevalence of gynecologic malignancy globally with a total incidence of 313,959 and 207,252 annual deaths. It is estimated 4.2 mortality per 1,00,000 are related to ovarian malignancy.[1] It is mainly due to late diagnosis of the disease. Ovarian cancer is considered the silent lady killer because most patients are diagnosed at a late stage, which leads to poor outcomes. Patients in the advanced stage tend to have higher recurrence and poorer response to chemotherapy.[2] The investigation of the underlying mechanism of ovarian cancer pathobiology is important.

Inflammation is considered an important factor in oncogenesis. After being postulated by Rudolf Virchow, the importance of inflammation in tumor development, progression, and association with clinical outcomes was studied extensively.[3] An inflammatory condition in aging women is considered etiopathogenesis of ovarian cancer.[4] Inflammatory condition in the tumor microenvironment facilitates sustained proliferation and tumor progression.[5,6] Systemic inflammation further leads to immune cell recruitment which is mediated by their soluble factors that promote tumor growth by maintaining proliferation, increasing angiogenesis, and metastasis.[6] This cancer progression is also facilitated by immune suppression in inflammatory conditions.[5] Therefore, markers of systemic inflammatory response may indicate tumor progression.

The neutrophil-to-lymphocyte ratio (NLR) is one of the feasible biochemical markers that are widely studied to indicate systemic inflammation.[7] Several reports have mentioned the applicability of NLR for diagnosis or disease stratification in infection and sepsis. It is also increased in critical condition. Differentiating NLR value may be used as a tool to differentiate severity of illness. The dramatic increase of NLR correlates with serious inflammatory illness with poor prognosis.[8,9] Current evidence also indicates that elevated NLR

[1]Department of Obstetrics and Gynecology, Division of Oncology Gynecology, Universitas Padjadaran, Bandung, West Java; Department of Obstetrics and Gynecology, Division of Oncology Gynecology, Universitas Gadjah Mada – Sardjito Central Hospital, Sleman, Yogyakarta, Indonesia

[2]Department of Obstetrics and Gynecology, Division of Oncology Gynecology, Universitas Gadjah Mada – Sardjito Central Hospital, Sleman, Yogyakarta, Indonesia

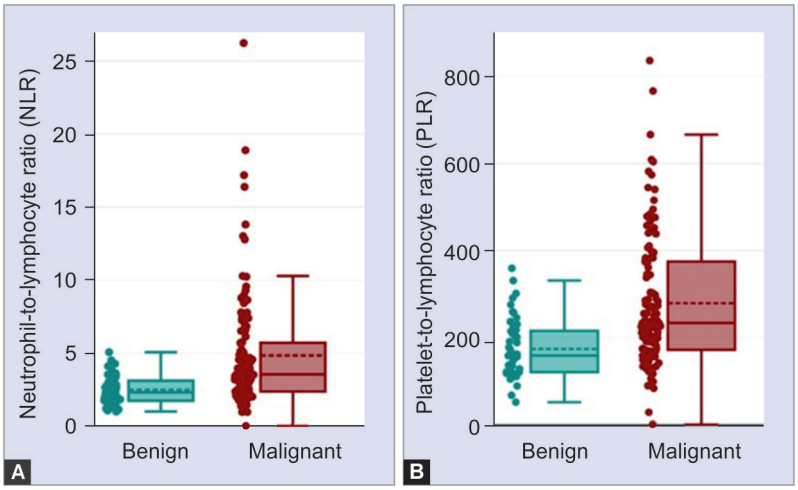
[3–5]Department of Obstetrics and Gynecology, Division of Oncology Gynecology, Universitas Padjadaran, Bandung, West Java, Indonesia

Corresponding Author: Andi Kurniadi, Department of Obstetrics and Gynecology, Division of Oncology Gynecology, Universitas Padjadaran, Bandung, West Java, Indonesia, Phone: +6281220286197, e-mail: andikur1978@gmail.com

How to cite this article: Zucha MA, Kusumanto A, Salima S, *et al*. Diagnostic Value of NLR and PLR for Malignancy in Ovarian Tumor: Feasible Markers in Low-resource Setting. J South Asian Feder Obst Gynae 2024;16(Suppl 3):S229–S233.

Source of support: Nil

Conflict of interest: None



Figs 1A and B: Box plot of NLR and PLR value in benign ovarian tumor vs malignant ovarian cancer

may correlate with poorer clinical outcomes in various malignancies. Most systematic reviews have found that cut-off value of high NLR to indicate poor prognosis was more than 3.0. It is also associated with tumor size, staging, and metastatic features in solid tumors.[10,11]

In addition to NLR, PLR was also associated with poor survival in several malignancies, including lung, hepatocellular, colorectal, and gastric cancer.[12–14] Platelet activation was an important mechanism in tumor initiation and progression. Platelet also promotes the activation of soluble growth factors, such as vascular endothelial growth factor (VEGF) that promote progression and metastasis.[14] Therefore, it is understandable PLR elevation correlates with a poorer prognosis, which also indicates tumor progression.[15]

Even though PLR and NLR have been evaluated in various solid tumors, the association between NLR and ovarian malignancy remains inconsistent.[16] The current study aimed to understand the diagnostic value of PLR and NLR to identify ovarian malignancy. The wide availability of these markers may help clinicians to predict malignancy in ovarian tumor patients.

Methods

The study was conducted according to ethical approval by the Joint Commission of Ethical Review Board at Universitas Gadjah Mada–Sardjito Central Hospital, following the Declaration of Helsinki. We collected data from 161 ovarian tumor patients who underwent primary surgery. Patients were excluded if they performed neoadjuvant therapy prior to surgery, or if they have another gynecologic malignancy. A routine hematologic test was done within 2 weeks prior to surgery to analyze the results with several clinical parameters and histopathologic diagnosis.

The definition of NLR was an absolute ratio between neutrophil count divided by lymphocyte count. Blood samples to evaluate NLR were taken prior to surgery. A threshold of NLR ≥3.0 was applied to determine a high NLR, while a PLR value ≥160 was considered high.

Statistical analysis of this study was done with SPSS software and Graphpad (Prism). Mean differences were assessed with an independent *t*-test, while numeric data Pearson's analysis was performed to study the correlation between two numeric variables. The predictive value of PLR and NLR was evaluated according to the area under the curve (AUC) in receiver operator characteristic (ROC) analysis. The value of $p < 0.05$ was considered statistically significant.

Table 1: Clinical parameter differences between malignant and benign ovarian tumors

	Ovarian tumor		
Variable	*Malignant (Mean ± SD)*	*Benign (Mean ± SD)*	*p-value*
Age at diagnosis (year old)	51.73 ± 13.0	45.48 ± 15.24	0.009
CA-125 level	518.78 ± 904.06	120.13 ± 125.44	0.238
NLR	4.86 ± 3.95	2.51 ± 1.02	<0.001
PLR	279.40 ± 153.15	174.43 ± 68.03	<0.001

Results

PLR and NLR Differences in Benign and Malignant Ovarian Tumor

Compared to the benign group, patients with malignant ovarian cancer showed significantly greater levels of PLR and NLR (Fig. 1). The levels (mean ± SD) of NLR and PLR were 4.86 ± 3.95 vs 2.51 ± 1.02 and 279.40 ± 153.15 vs 174.43 ± 68.03, respectively. Interestingly, we also found that CA-125 was not a significant marker to differentiate malignancy in ovarian tumor patients. This widely used marker did not differ from malignant from benign ovarian tumors ($p = 0.238$). In contrast, both PLR and NLR had significant differences between benign and malignant ovarian tumors ($p < 0.001$) (Table 1).

Applicability of PLR and NLR to Predict Ovarian Cancer

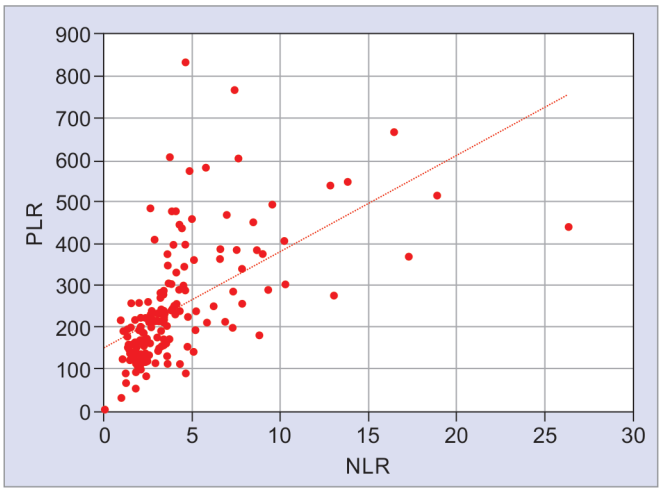
We found that PLR and NLR both had significant values in predicting ovarian malignancy. High NLR patients had a higher probability of having a malignancy diagnosis (OR = 5.32; 95% CI: 2.52–11.21; $p < 0.01$). In addition, PLR also showed comparable results (OR = 4.03; 95% CI: 1.95–8.31; $p < 0.01$) (Table 2). Interestingly, we also found that both parameters were positively correlated. Pearson's correlation analysis of PLR and NLR showed a positive correlation (Pearson's correlation score = 0.5763; $p < 0.001$) (Fig. 2).

Accuracy of PLR and NLR in Ovarian Cancer Diagnosis

The diagnostic performance of PLR and NLR in ovarian malignancy is presented in Table 3. With cut-off value ≥3.0, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of NLR were 66.37, 72.92, 85.23, and 47.95%,

Table 2: NLR and PLR as predictive factors for ovarian malignancy

	Ovarian tumor				
Parameter	*Malignant*	*Benign*	*Total*	*OR (95% CI)*	*p-value*
NLR					
High (≥3.0)	75	13	88	5.32 (2.52–11.21)	<0.001
Low (<3.0)	38	35	73		
PLR					
High (≥160)	89	23	94	4.03 (1.95–8.31)	<0.001
Low (<160)	24	25	38		
Total	113	48			



Pearson correlation coefficient (R)	Coefficient of determination (R^2)	*p*-value
0.5763	0.3321	<0.001

Fig. 2: Value of NLR and PLR showed a moderate correlation

Table 3: Diagnostic performance of NLR and PLR for ovarian malignancy

	NLR		*PLR*	
Statistics	*Value*	*95% CI*	*Value*	*95% CI*
Sensitivity	66.37%	56.88–74.99	78.76%	70.07–85.89
Specificity	72.92%	58.15–84.72	52.08%	37.19–66.71
Positive likelihood ratio	2.45	1.51–3.97	1.64	1.21–2.24
Negative likelihood ratio	0.46	0.34–0.63	0.41	0.26–0.64
PPV	85.23%	78.08–90.33	79.46%	73.94–84.07
NPV	47.95%	40.29–55.70	51.02%	39.99–61.96
Accuracy	68.32%	60.54–75.42	70.81%	63.13–77.70

respectively. Analysis of accuracy for NLR showed acceptable results (accuracy = 68.32%; AUC = 0.743) (Fig. 3). High PLR (≥160) also had a definite diagnostic value for ovarian malignancy with sensitivity of 78.76%, specificity of 52.08%, PPV of 79.46%, and NPV of 51.02%. Diagnostic accuracy for PLR was 70.81% (AUC = 0.733) (Fig. 4).

Discussion

The highlight of inflammation in tumorigenesis was first presented by Virchow in 1963. Currently, the more thorough understanding of inflammation roles in tumor initiation and progression is better understood, as one of the hallmarks of cancer.[3,4] Within the

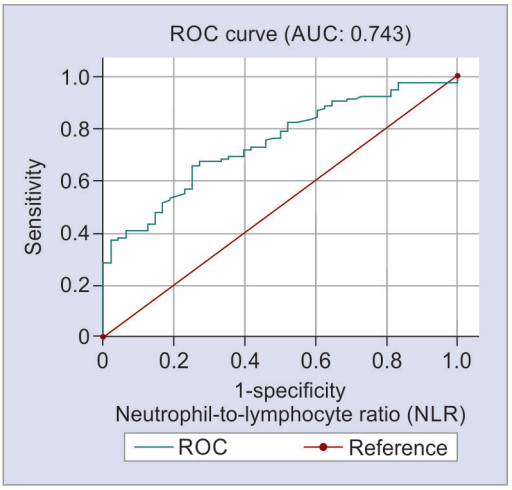


Fig. 3: Receiver operator characteristic curve of NLR to diagnose ovarian malignancy

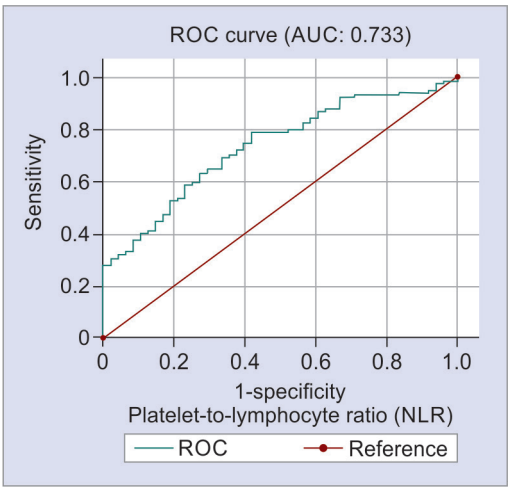


Fig. 4: Receiver operator characteristic curve of PLR to diagnose ovarian malignancy

tumor microenvironment, tumor cells secrete several soluble cytokines, chemokines, and other substances that may orchestrate the immune response, as well as promote cell proliferation and progression. Secreted inflammatory cytokines may also promote tumor angiogenesis and mediate distant metastasis.[9,17,18] Therefore, tumor-related inflammatory markers are important indicators for tumor initiation and progression.

Some of the widely known markers for systemic inflammation are PLR and NLR. These markers are widely available, cheap, and routinely examined before operation, thus they may serve as feasible markers of malignancy before surgery. High levels of PLR and NLR may be used for ovarian malignancy prediction in patients with ovarian tumors without extra cost so that they are potential malignancy predictor markers in a low-resource setting.[15]

We performed diagnostic analysis of preoperative PLR and NLR to predict and diagnose ovarian malignancy. The ratio of neutrophils to lymphocytes represents systemic inflammation and also indicates a higher protumorigenic inflammatory response, rather than an anti-inflammatory response. Therefore, NLR elevation may indicate increased pro-tumorigenic condition. In addition, the higher level of neutrophils may also indicate tumor progression,

as neutrophils may secret VEGF that promotes neovascularization and metastasis.

The suppression of lymphocytes correlates with the down-regulation of lymphokine-activated killer cells with a higher tendency of cancer progression. Lymphocytes are important white blood cells that play key roles in immune defense mechanisms. Reduction of lymphocyte counts indicates suppression of cytotoxic CD8+ T-cells.[17] The reduction of cytotoxic activity means a weakened immune defensive capacity, including against tumor cells. Therefore, the reduction of platelets was an important prognostic factor in various malignancies. In addition, the relative lymphocyte proliferation indicates cancer progression and represents the treatment response for malignant tumors.[14]

The ratio of neutrophils to lymphocytes may be influenced by age, race, medication, and some chronic conditions that alter the relative value. Pathologic conditions that may affect NLR are stroke, diabetes, heart disease, obesity, psychiatric diagnosis, cancers, anemia, and chronic stress. Normally, adults have NLR ranges between 1.0 and 2.0. Several studies mentioned a threshold of pathologic NLR greater than 3.0. The value between 2.3 and 3.0 is considered grey zone that may be seen as an early warning of disorders.[12,13,19,20] We found that patients with ovarian malignancy had significantly higher NLR ($p < 0.001$) (Table 1). Our results were consistent with reported evidence that highlighted the higher NLR value in solid cancers. Meta-analyses have investigated the prognostic value of NLR in various cancers and have found out threshold value of NLR greater than 3.0 (IQR 2.5–5.0). Various studies also mentioned that high NLR correlates with tumor size, stage, and metastasis status. Therefore, a higher NLR indicates poorer overall survival and disease-free survival.

We also found that NLR has the potential to differentiate ovarian malignancy from benign ovarian tumors. High NLR had a sensitivity of 66.37%, specificity of 72.92%, PPV of 85.23%, and NPV of 47.95%. The diagnostic accuracy of NLR was 68.32% (AUC = 0.743). Clinical confirmation in several studies showed the diagnostic accuracy of NLR in systemic infection, sepsis, and bacteremia, as well as in oncology cases. It also correlates with the severity of illnesses, and a significant increase in critical condition. A dramatic increase above 11 was found in serious condition. Therefore, the higher level of NLR in ovarian tumors indicates malignant disease and an even higher NLR value may predict the progression.[13,21]

Inflammatory reactions may be reflected by some biochemical markers, including PLR and NLR, which are inexpensive and widely available. Previous reports have assessed the prognostic value of these systemic inflammation markers in various solid tumors, including breast, lung, gastrointestinal, and hepatocellular cancer.[12,13,22–24] In addition to NLR, PLR also shows promising significance as a malignancy marker. We found that patients with ovarian malignancy had higher PLR values (279.40 ± 153.15 vs 174.43 ± 68.03; $p < 0.001$). The odds ratio of high PLR had malignant diagnosis was (OR = 4.03; 95% CI: 1.95–8.31; $p < 0.01$). The comparable value of high NLR and high PLR was assessed quantitatively with Pearson's correlation score. We found that PLR and NLR had a moderate positive correlation (Pearson's correlation score = 0.5763; $p < 0.001$). This significant result indicates the consistency of systemic inflammation in ovarian cancer progression.

Platelet-to-lymphocyte ratio is a valuable marker that reflects systemic inflammatory conditions. Elevated platelet number reflects the higher ability to deliver various angiogenic factors to tumors, thereby stimulating angiogenesis. In gynecologic cancer, a meta-analysis of nine articles mentioned that high PLR was associated with poor overall survival in endometrial cancer. Platelet-to-lymphocyte ratio also showed significant diagnostic accuracy in distinguishing endometrial pathology and malignancy. In addition, higher PLR was found win patients with poorer treatment response.[21]

Our study highlights the diagnostic accuracy of PLR and NLR to define ovarian malignancy. We found the sensitivity, specificity, PPV, and NPV of NLR were 66.37, 72.92, 85.23, and 47.95%, respectively. Analysis of accuracy for NLR showed acceptable results (accuracy = 68.32%; AUC = 0.743) (Fig. 3). Platelet-to-lymphocyte ratio also had a certain diagnostic value for ovarian malignancy. The sensitivity of high PLR (≥160) was 78.76%, specificity = 52.08%, PPV = 79.46%, and NPV = 51.02%. Diagnostic accuracy for PLR was 70.81% (AUC = 0.733) (Fig. 4). These comparable results between PLR and NLR indicate the diagnostic value of both markers for ovarian cancer. Both PLR and NLR have several advantages, including availability, and inexpensiveness, thereby posing as potential markers in low-resource settings. The applicability of PLR and NLR to distinguish malignancy may benefit patients with ovarian cancer to get better and more comprehensive management.

Conclusion

Preoperative PLR and NLR are higher in ovarian cancer patients than those in the benign group, which indicates valuable diagnostic accuracy. In addition, both PLR and NLR showed abilities for ovarian cancer preoperative prediction. The applicability of PLR and NLR in low-resource settings may become important markers that help clinicians to predict ovarian malignancy before surgery, so as to provide better treatment strategies.

Orcid

Muhammad Ary Zucha https://orcid.org/0000-0001-9337-8237

References

1. Huang J, Chan, WC, Ngai CH, et al. Worldwide burden, risk factors, and temporal trends of ovarian cancer: A global study. Cancers (Basel) 2022;14:2230. DOI: 10.3390/cancers14092230.
2. Gaitskell K, Hermon C, Barnes I, et al. Ovarian cancer survival by stage, histotype, and pre-diagnostic lifestyle factors, in the prospective UK Million Women Study. Cancer Epidemiol 2022;76:102074. DOI: 10.1016/j.canep.2021.102074
3. Turizo-Smith AD, Córdoba-Hernandez S, Mejía-Guarnizo LV, et al. Inflammation and cancer: Friend or foe? Front Pharmacol 2024;15. DOI: 10.3389/fphar.2024.1385479.
4. Sánchez-Prieto M, Sánchez-Borrego R, Lubián-López DM. et al. Etiopathogenesis of ovarian cancer. An inflamm-aging entity? Gynecologic Oncology Reports 2022;42. DOI: 10.1016/j.gore.2022.101018.
5. Korniluk A, Koper O, Kemona H, et al. From inflammation to cancer. Irish J Med Sci 2017;186:57–62. DOI: 10.1007/s11845-016-1464-0.
6. Hibino S Kawazoe T, Kasahara H, et al. Inflammation-induced tumorigenesis and metastasis. Int J Mol Sci 2021;22:5421. DOI: 10.3390/ijms22115421.
7. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratis Med J 2021;122:474–488. DOI: 10.4149/BLL_2021_078.
8. Okada F. Inflammation-related carcinogenesis: Current findings in epidemiological trends, causes and mechanisms. Yonago Acta Med 2014;57:65–72. PMID: 25324587.
9. Lamkanfi M, Dixit, V.M. Mechanisms and functions of inflammasomes. Cell 2014;157:1013–1022. DOI: 10.1016/j.cell.2014.04.007.

10. Cha YJ, Park EJ, Baik SH., et al. Clinical significance of tumor-infiltrating lymphocytes and neutrophil-to-lymphocyte ratio in patients with stage III colon cancer who underwent surgery followed by FOLFOX chemotherapy. Sci Rep 2019;9:11617. DOI: 10.1038/s41598-019-48140-1.
11. Mazaki J, Katsumata K, Kasahara K, et al. Neutrophil-to-lymphocyte ratio is a prognostic factor for colon cancer: A propensity score analysis. BMC Cancer 2020;20:922. (2020). DOI: 10.1186/s12885-020-07429-5.
12. Zhou K, Cae J, Lin H, et al. Prognostic role of the platelet to lymphocyte ratio (PLR) in the clinical outcomes of patients with advanced lung cancer receiving immunotherapy: A systematic review and meta-analysis. Front Oncol 2022;12:962173. DOI: 10.3389/fonc.2022.962173.
13. Zheng J, Cae J, Li H, et al. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic predictors for hepatocellular carcinoma patients with various treatments: A meta-analysis and systematic review. Cell Physiol Biochem 2018;44:967–981. DOI: 10.1159/000485396.
14. Chan KS, Shelat VG. The role of platelet-lymphocyte ratio in hepatocellular carcinoma: A valuable prognostic marker. Transl Cancer Res 2022;11:4231–4234. DOI: 10.21037/tcr-22-2343.
15. Dinca AL, Diaconu A, Birla RD, et al. Systemic inflammation factors as survival prognosis markers in ovarian neoplasm and the relationship with cancer-associated inflammatory mediators—a review. Int J Immunopathol Pharmacol 2023;37:3946320231178769. DOI: 10.1177/03946320231178769.
16. Yin X, Wu L, Yang H, et al. Prognostic significance of neutrophil-lymphocyte ratio (NLR) in patients with ovarian cancer: A systematic review and meta-analysis. Medicine 2019;98:e17475. DOI: 10.1097/MD.0000000000017475.
17. Savant SS, Sriramkumar S, O'hagan HM. The role of inflammation and inflammatory mediators in the development, progression, metastasis, and chemoresistance of epithelial ovarian cancer. Cancers 2018;10:251. DOI: 10.3390/cancers10080251.
18. Kumari N, Dwarakanath BS, Das A, et al. Role of interleukin-6 in cancer progression and therapeutic resistance. Tumor Biol 2016;37:11553–11572. DOI: 10.1007/s13277-016-5098-7.
19. Okada F, Izutsu R, Goto K, et al. Inflammation-related carcinogenesis: Lessons from animal models to clinical aspects. Cancers 2021;13:1–37. DOI: 10.3390/cancers13040921.
20. Yi YS. Regulatory roles of flavonoids on inflammasome activation during inflammatory responses. Mol Nutr Food Res 2018;62. DOI: 10.1002/mnfr.201800147.
21. Ni L, Tao J, Xu J, et al. Prognostic values of pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in endometrial cancer: A systematic review and meta-analysis. Arch Gynecol Obstet 2020;301:251–261. DOI: 10.1007/s00404-019-05372-w.
22. Gou M, Zhang Y. Pretreatment platelet-to-lymphocyte ratio (PLR) as a prognosticating indicator for gastric cancer patients receiving immunotherapy. Discov Oncol 2022;13:118. DOI: 10.1007/s12672-022-00571-5.
23. Kim HY, Kim TH, Yoon HK, et al. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in predicting neoadjuvant chemotherapy response in breast cancer. J Breast Cancer 2019;22:425–438. DOI: 10.4048/jbc.2019.22.e41.
24. Diany H. Platelet-to-lymphocyte ratio (plr) profile and neutrophil-to-lymphocyte ratio (nlr) in lung cancer patients in ulin general hospital Banjarmasin 2017-2018. Berkala Kedokteran 2020;16:31–34. DOI: 10.20527/jbk.v16i1.8101.