Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2020 Oct 20; 8(B):1058-1063.
https://doi.org/10.3889/oamjms.2020.5336
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Oncology*

OPEN ACCESS

Pretreatment Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as a Stage Determination in Breast Cancer

Sinta Wiranata[1], Ida Ayu Widya Anjani[1], I Putu Gede Septiawan Saputra[1], I Gusti Ayu Stiti Sadvika[1], I Putu Yuda Prabawa[2], I Gede Supadmanaba[3], Desak Made Wihandani[3], Putu Anda Tusta Adiputra[4], I Wayan Sudarsa[4], Anak Agung Wiradewi Lestari[2]*

[1]Medical Student, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia; [2]Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia; [3]Department of Biochemistry, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia; [4]Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Udayana University, Sanglah General Hospital, Bali, Indonesia

Edited by: Ksenija Bogoeva-Kostovska
Citation: Wiranata S, Anjani IAW, Saputra IPGS, Sadvika IGAS, Prabawa IPY, Supadmanaba IG, Wihandani DM, Adiputra PAT, Sudarsa IW, Lestari AAW. Pretreatment Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as a Stage Determination in Breast Cancer. Open Access Maced J Med Sci. 2020 Oct 20; 8(B):1058-1063. https://doi.org/10.3889/oamjms.2020.5336
Keywords: Breast cancer; Platelet lymphocyte ratio; Staging
***Correspondence:** Anak Agung Wiradewi Lestari, Department of Clinical Pathology, Faculty of Medicine, Udayana University, Sanglah General Hospital, Bali, Indonesia.
E-mail: wiradewilestari@gmail.com.
Received: 31-Jul-2020
Revised: 04-Oct-2020
Accepted: 10-Oct-2020

Funding: The authors themselves supported the funding without the involvement of grants, research scholarships, or other funding sources
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Breast cancer tends to respond differently to treatments, which are usually determined by clinicopathological characteristics. Several studies evaluated the role of the peripheral blood test as diagnostic and prognostic markers in several types of solid cancer and neutrophil-to-lymphocyte ratio (NLR) and platelet-tolymphocyte ratio (PLR) are two of them which already tested. However, the evidence in breast cancer is still lacking.

AIM: Therefore, the study aimed to investigate the value of NLR and PLR as biomarkers concerning breast cancer stage.

METHODS: A retrospective study was conducted using breast cancer patients' medical records from 2014 to 2019 at Sanglah General Hospital. The histopathological records and complete blood counts of the patients were collected and analyzed risk analysis model, receiver operator characteristics analysis, and correlation of NLR and PLR with cancer staging analysis used correlation test.

RESULT: One hundred five patients data were used in this study, with 35 subjects had early-stage breast cancer while 70 subjects had an advanced stage. Breast cancer staging with NLR and PLR showed significant associations ($p < 0.001$). Both NLR and PLR had area under the curve >0.7 ($p < 0.001$). The cutoff, sensitivity, and specificity values of NLR and PLR were 2.504 (71%; 70%) and 157.1 (73%; 70%). Advanced stage of breast cancer was mostly found in high NLR and PLR value with (OR: 4.231; CI = 1.791-9.995, $p < 0.001$) and (OR: 3.949; 95% CI = 1.679–9.287; $p < 0.001$).

CONCLUSION: From this preliminary study, pretreatment NLR and PLR values might determine the breast cancer stage. Further research is needed to evaluate the association between grade and patient survival.

Introduction

Breast cancer is the most common cancer, followed by cervical cancer in women. The incidence rate associated with breast cancer is about 11.6% of cancer worldwide and currently in second place after lung cancer. The mortality rate of breast cancer is the highest in women worldwide [1]. Futhermore, breast cancer in Indonesia has the most number of new cases (30.9%) in all ages among woman. It's become the most prevalence cancer in both sex (16.7%) [2].

Treatment outcomes in breast cancer depend on several variables and clinicopathological characteristics are among the most substantial factors in determining management and survival [3], [4]. However, in some cases, even early-stage cancer could lead to severe outcomes, while advanced stage cancer could also progress slowly. Overall, it remains a challenge for the scientist to predict the outcome of breast cancer. Some predictive markers have been investigated, but molecular detection is still regarded as expensive and affordable in developing countries [5].

Inflammation recognizes as one of the hallmarks of cancer in the recent decade. Inflammation plays an essential role in enhancing tumor growth, angiogenesis, and metastasis. Localized inflammation in cancer tissue also extends systemically and reflects peripheral white blood cell composition change [5]. Recently, scientists put some interest in hematological markers of inflammation as predictive markers in cancer. Several studies had investigated the role of some markers such as platelet, lymphocyte, and monocytes in a peripheral blood test as a prognostic tool in cancer assessment [6], [7], [8]. According to the Lasorda study was found platelet-to-lymphocyte ratio (PLR) significant with tumor size ($p = 0.04$), meanwhile contrast with neutrophil-to-lymphocyte ratio (NLR) ($p = 0.7$) [9]. These hematologic

markers are inexpensive and widely applicable in clinical practice. Among these markers, NLR and PLR are considered hematological markers correlated with unfavorable outcomes in some solid tumors such as lung cancer and colorectal cancer [10]. Prabawa *et al*. (2019) also showed that NLR's median value was significantly higher at the advanced stage than early-stage cervical cancer (r = 0.638; p = 0.001) [11]. Studies by Noh *et al*. (2013) showed a direct association between NLR values above 2.5 with tumor size, young age (<40 years old), and HER2 +breast cancer [12]. A study by Prabawa *et al*. (2019) also showed a significant association between PLR and FIFO stage (p < 0.001) in cervical cancer patients [11]. A meta-analysis study reported a significant increase in having an advanced tumor in breast cancer patients with high PLR (OR = 1.86, 95% CI = 1.2–2.9) [13]. However, there are still limited resources about the link between pretreatment NLR and PLR with the breast cancer stage. The revelation of their association will strengthen the basis to validate their application in a clinical setting. Therefore, this study aimed to investigate the link between pretreatment NLR and PLR with the stage of breast cancer.

Patients and Methods

Patient selection and ratio calculation

In this study, after all, samples were selected according to the inclusion and exclusion criteria. There were 105 eligible samples. This study's inclusion criteria were complete medical and pathological data for all variables and demographic data. The patients were diagnosed in 2014 and 2019 in Sanglah General Hospital, Bali, Indonesia, had not received treatment yet. The exclusion criteria were as follow: Patients who had infectious diseases, autoimmune diseases, steroid administration, and relapse of breast cancer that have gotten treatment.

After that, data input was carried out based on determined variables before the patients received any treatments and have been diagnosed with breast cancer, such as chronological age, clinical stages that classified into early-stage (I-II) and advanced stage (III-IV), parity was classified into nullipara, primipara, multipara, grande para, histopathological types as a microscopic classification, menarche and menopausal age after diagnosed in breast cancer, but has not received any treatment yet, grade (I-III), hematologic markers in 10^9/L such as white blood cell, neutrophil, monocyte, lymphocyte, basophil, eosinophil, and platelet. Furthermore, the absolute count of platelet, neutrophil, basophil, monocyte, and eosinophil each is divided with an absolute count of lymphocyte to produce PLR, NLR, basophil to lymphocyte ratio (BLR), monocyte to lymphocyte ratio (MLR), and eosinophil to lymphocyte ratio (ELR).

Statistical analysis

The study was analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 25. The normality of continuous variable distribution was determined by the Kolmogorov–Smirnov test (KS-test). The data were reported as mean ± standard deviation, ratio, 95% IC, cutoff value, sensitivity, and specificity. The associations between stage with NLR, PLR, MLR, BLR, and ELR were assessed using the Mann–Whitney test. Categorical data were analyzed by chi-square. The cutoff point for the ratio was determined using the receiver operating characteristic (ROC) curve by considering the value of sensitivity and specificity. $p \leq 0.005$ is considered as statistically significant.

Results

Subject characteristics

Regarding the subjects' age, both groups have comparable mean age (advance stage group: 50.82 ± 11.274 years-old; early-stage group: 52.30 ± 10.364 years-old). Surprisingly, there was also no significant difference between both groups in terms of histopathological characteristics. However, variability was observed when comparing the hematological parameters in which both groups differ significantly in neutrophil, lymphocyte, and platelet counts. As predicted, the NLR and PLR were also significantly different. Table 1 summarizes the subjects' demographical, pathological, and hematological characteristics and compares early and late-stage groups.

Table 1: Breast cancer characteristic, histopathological features, and blood parameters

Characteristic	Early (n = 35)	Advanced (n = 70)	p
Age (years)	52.30 ± 10.364	50.82 ± 11.274	0.71
Menarche (years)	10.44 ± 6.318	9.43 ± 6.77	0.25
Menopause (years)	22.03 ± 24.47	16.50 ± 23.11	0.67
Parity (n, %)			0.26
Nullipara	10 (9.5%)	25 (23.8%)	
Primipara	3 (2.9%)	3 (2.9%)	
Multipara	19 (18.1%)	41 (39%)	
Grande para	3 (2.9%)	1 (1%)	
Grade (n, %)			0.36
1	3 (2.9%)	4 (3.8%)	
2	21 (20%)	22 (21%)	
3	19 (18.1%)	36 (34.3%)	
Histopathology (n, %)			0.97
Invasive carcinoma of no special type	39 (37.1%)	57 (54.3%)	
Invasive lobular carcinoma	2 (1.9%)	2 (1.9%)	
Non-invasive carcinoma	1 1%)	1 (1%)	
Special type carcinoma	1 (1%)	2 (1.9%)	
Blood parameters			
White blood cell (10^9/L)	7.35 ± 1.896	6.71 ± 3.228	0.09
Neutrophil (10^9/L)	4.06 ± 1.875	3.98 ± 2.195	0.04*
Monocyte (10^9/L)	0.51 ± 0.135	0.49 ± 1.999	0.6
Lymphocyte (10^9/L)	1.52 ± 1.144	1.94 ± 1.238	0.02*
Basophils (10^9/L)	0.06 ± 0.043	0.07 ± 0.035	0.63
Eosinophil (10^9/L)	0.18 ± 0.073	0.22 ± 0.273	0.19
Platelet (10^9/L)	101.92 ± 1.687	247.92 ± 3.873	0.04*
NLR	1.62 ± 0.779	2.46 ± 1.756	0.003*
PLR	115.94 ± 3.799	169.91 ± 2.930	0.002*
MLR	0.20 ± 0.051	0.32 ± 0.202	0.07
BLR	0.02 ± 0.017	0.046 ± 0.022	0.34
ELR	0.07 ± 0.030	0.11 ± 0.085	0.10

*Statistically significant (p < 0.05); SD: Standard deviations, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, BLR: Basophil-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio.

ROC curve of sensitivity and specificity of NLR, PLR, MLR, BLR, and ELR as hematological markers in the breast cancer stadium

A ROC analysis performed the NLR, PLR, MLR, BLR, and ELR predictive value and identified their diagnostic values (sensitivity and specificity). According to the ROC curve, NLR and PLR emerged as potential markers since their area under the curve (AUC) value was >0.70, which indicated an excellent predictive parameter. The cutoff point of each ratio was also identified through ROC analysis, and it was shown that NLR had 71% sensitivity, 70% specificity, with a cutoff value of 2.504 while PLR had 73% sensitivity, 70% specificity, and a cutoff value of 157.1. Table 2 presents the detail of ROC analysis.

Table 2: Advanced stage of AUC, cutoff value, sensitivity, and specificity for NLR, PLR, MLR, BLR, and ELR in breast cancer patients

Stage	Parameter	AUC	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)	p
Advanced	NLR	0.733	0.632 – 0.833	2.504	71	70	<0.001*
	PLR	0.735	0.636 – 0.833	157.1	73	70	<0.001*
	MLR	0.681	0.575 – 0.788	0.246	67	60	0.003*
	BLR	0.681	0.578 – 0.784	0.042	59	57	0.003*
	ELR	0.625	0.520 – 0.730	0.093	60	60	0.037*

*Statistically significant ($p < 0.05$); NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, BLR: Basophil-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, AUC: Area under the curve, CI: Confidence interval.

Risk analysis model of hematological markers as a predictive value in the advance stage of breast cancer

Using the cutoff value from ROC analysis, a two-step risk analysis was performed using cross-tabulation to assess each variable, odds ratio (OR), and logistic regression to identify the adjusted OR (Figure 1). Bivariate risk analysis showed that NLR, PLR, and MLR significantly associated with a higher risk of having advanced tumor stadium, with NLR, possessed the highest OR value (OR: 4.231; 95%CI: 1.791-9.995; p = 0.001). However, multivariate regression analysis showed that only NLR and PLR could predict advanced tumor stadium while MLR was proved to be not significant (Table 3).

Discussion

In this study, we strengthen the findings from the previous study, and we also compared four different ratios instead of focusing on one. Our study found that there were already significant differences in neutrophil, lymphocyte, and platelet between patients with early-stage compared to an advanced stage even from the absolute counts. The values tended to be higher in the advanced stage than in the early stage, except for neutrophil count. Thus, the NLR and PLR were also significantly different between the two groups.

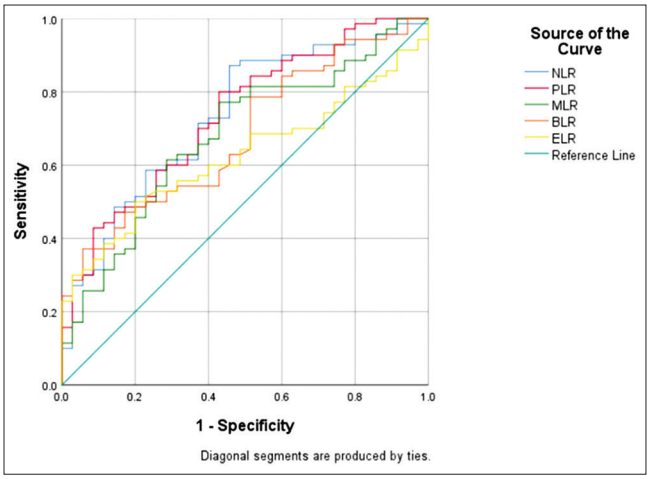

Figure 1: Receiver operating characteristic analysis of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio, basophil-to-lymphocyte ratio, and eosinophil-to-lymphocyte ratio as predictive values in the advanced stage of breast cancer. The diagonal reference line is an indicator of no diagnostic value. Among those ratios, NLR and PLR were the only variables that had area under the curve value > 0.70.

These findings are in line with several other studies that also assess the diagnostic or predictive value of lymphocyte ratios. For example, Elyasinia *et al*. (2017) found a significant relationship between neutrophil and platelet with breast cancer staging [14]. Theoretically, the number of lymphocytes is correlated with tumor stage because of its inherent nature as a cellular-based immune response in eliminating cancer [15]. However, a higher number is not always associated with the greater immune response since cancer cells can modulate the immune response through immune-tolerance cytokines production of tumor micro environment. As for platelet, its higher count is often associated with a higher tumor cell migration rate as it protects circulating tumor cells and provides necessary growth factors needed when tumor cells arrived in the target organ [16]. Therefore, a higher ratio of platelet lymphocytes can be considered an indicator of tumor progression, especially in vascular invasion proven in breast cancer [14].

Some previous studies also showed a significant relationship between NLR and PLR with the stage of several types of cancer. Studies by Noh *et al*. (2013) conducted a direct association between NLR values above 2.5 with tumor size, young age (<40 years old), and HER2 + breast cancer [12]. In addition, Prabawa *et al*. (2019) also showed that NLR's median value was significantly higher at the advanced stage than early-stage cervical cancer (r = 0.638; p = 0.001) [11]. This association was also confirmed in a meta-analysis by Huang *et al*. (2017), which found a significant association between NLR with tumor stadium in esophageal squamous cell carcinoma patients [17]. However, Aslan *et al*. (2016) found no significant relationship between NLR with the clinicopathological aspects of follicular lymphoma, but the lymphoma's

Table 3: Risk analysis model of NLR, PLR, BLR, and MLR in advanced breast cancer

Hematologic markers	Univariate model		Bivariate model		Multivariate model	
	Early (%)	Advanced (%)	OR (95% CI)	p	Adjusted OR (95% CI)	p
NLR			4.231 (1.791 – 9.995)	0.001*	3.024 (1.207 – 7.580)	0.018*
High	13 (20.6)	50 (47.6)				
Low	22 (21.0)	20 (19.0)				
PLR			3.949 (1.679 – 9.287)	0.001*	2.737 (1.092 – 6.859)	0.032*
High	13 (12.4)	47 (44.8)				
Low	21 (20.0)	23 (21.9)				
MLR			3.065 (1.323 – 7.102)	0.008*	1.461 (0.521 – 4.095)	0.47
High	14 (13.3)	47 (44.8)				
Low	7 (6.7)	23 (21.9)				
BLR			1.885 (0.829 – 4.285)	0.13	0.815 (0.296 – 2.244)	0.82
High	15 (14.3)	41 (39.0)				
Low	20 (19.0)	29 (27.6)				
ELR			2.250 (0.983 – 5.151)	0.053	1.623 (0.650 – 4.057)	0.3
High	14 (13.3)	42 (40.0)				
Low	21 (20.0)	28 (26.7)				

Univariate analysis was conducted using cross-tabulation analysis; multivariate analysis was performed using binary logistic regression; *Significant at $p < 0.05$.

hematological nature might cause this finding [18]. Therefore, NLR can still be considered as one of the potential hematological biomarkers of concrete cancer. The Explanation of neutrophil pathological role by looking into a histologic tumor sample where neutrophil is often present at the tumor rim as tumor-associated neutrophils (TAN) can release pro-tumorigenic molecules that support angiogenesis, invasion, and migration of cancer cells [17].

On the other hand, PLR also has been shown to significantly associate with tumor stadiums, as reported by Yersal *et al*. [19]. In addition, Prabawa *et al*. (2019) also showed a significant association between PLR and FIFO stage ($p < 0.001$) in cervical cancer patients [11]. A study by Krenn-Pilko *et al*. (2014) and Graziano *et al*. (2019) showed that high PLR value was related to larger tumor size [20], [21]. A meta-analysis study reported a significant increase in having an advanced tumor in breast cancer patients with high PLR (OR = 1.86, 95% CI = 1.2 – 2.9) [13]. However, Zhu *et al*. (2017) reported no relationship between PLR with breast cancer stadium [10]. Therefore, there are still some un-resolving issues regarding the role of PLR as a diagnostic or predictive marker in breast cancer. However, pathologically, platelets support tumor progression by shielding tumor cells from natural killer cells and producing angiogenic and growth factors, including vascular endothelial growth and platelet-derived growth factors [22], [23], [24], [25].

Regarding the diagnostic value, our study showed that NLR and PLR had the highest level of sensitivity and specificity, among other variables at a specific cutoff point. In line with this study, a systematic review and meta-analysis by Ethier *et al*. (2017) reported that NLR predicted overall survival and disease-free survival of breast cancer patients with a cutoff value of 1.9–5.0 (median cutoff value 3.0) [26] findings. Ulas *et al*. (2015) obtained significant results at a cutoff value of 161 [27]. Furthermore, Yao *et al*. (2014) obtained significant results at a cutoff value of 107 [28]. Separately, Cihan *et al*. (2014) found similar findings using a cutoff value at 1.60, which was linear with Ulas *et al*. and Yao *et al*. [28] that research shows that the NLR and PLR are promising and potential biomarkers in breast cancer, but the cutoff values need to be validated [27], [28], [29]. Additional evidence by Orditura *et al*. (2016) showed a further role of NLR as a predictive marker of distant metastasis-free survival of a breast cancer patient [30].

Aside from predicting tumor stadium, PLR and NLR are also associated with breast cancer patient's mortality rates. Patients with an NLR >5.64 only had a 5-year survival rate at 51.1%, while patients with PLR >215 had a 5-year survival rate at 53.2% [15]. Gynecologic evidence also revealed that baseline values of NLR ≥4.1 and PLR ≥0.3 were associated with a higher risk of metastases compared to patients with below cutoff point NLR and PLR [31]. Other than these, NLR and PLR were also associated with tumor stadium and metastasis in osteosarcoma and chemosensitivity in gastric cancer [32], [33], [34].

However, this study has several limitations, which are essential to be considered in generalizing the findings. First, this study used a retrospective cohort design, which is prone to bias. Selective sample selection we used to reduce the bias according to inclusion and exclusion criteria. In addition, hematological markers are susceptible to a patient's condition and are affected by several factors, including nutrition and bone metastasis. Nevertheless, hematologic biomarkers have several advantages worth considering, such as affordable and applicable, which can benefit oncologists in developing countries.

Conclusion

PLR and NLR are the potential to determine cancer staging in breast cancer. However, a further study is needed to assess the optimal cutoff point and its associated factors as well as a further study involving recurrence rate and chemoresistance.

Ethics approval

The research was approving by the Research Ethics Committee, Faculty of Medicine of Udayana

University - Sanglah General Hospital (REC Approval File No. 1412/UN14.2.2.VII.14/LP/2019).

Acknowledgments

We would like to show our gratitude to the RISE-Search Oncology Group that provided insight expertise greatly assisted and supported the study.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53. https://doi.org/10.1002/ijc.31937
   PMid:30350310
2. The Global Cancer Observatory. Indonesia Fact Sheets. Globocan; 2018. Available from: https://www.gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf. [Last accessed on 2020 Oct 07].
3. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol. 2010;28(10):1684-91. https://doi.org/10.1200/jco.2009.24.9284
   PMid:20194857
4. Dong G, Wang D, Liang X, Gao H, Wang L, Yu X, *et al*. Factors related to survival rates for breast cancer patients. Int J Clin Exp Med. 2014;7(10):3719-24.
   PMid:25419424
5. Esbah O, Oksuzoglu B. Prognostic & predictive factors for planning adjuvant chemotherapy of early-stage breast cancer. Indian J Med Res. 2017;146(5):563-71.
   PMid:29512598
6. Multhoff G, Molls M, Radons J. Chronic inflammation in cancer development. Front Immunol. 2012;2:98. https://doi.org/10.3389/fimmu.2011.00098
   PMid:22566887
7. Cuello-López J, Fidalgo-Zapata A, López-Agudelo L, Vásquez-Trespalacios E. Platelet-to-lymphocyte ratio as a predictive factor of complete pathologic response to neoadjuvant chemotherapy in breast cancer. PLoS One. 2018;13(11):e0207224. https://doi.org/10.1371/journal.pone.0207224
   PMid:30427884
8. Zhang H, Xia H, Zhang L, Zhang B, Yue D, Wang C. Clinical significance of preoperative neutrophil-lymphocyte vs platelet-lymphocyte ratio in primary operable patients with non-small cell lung cancer. Am J Surg. 2015;210(3):526-35. https://doi.org/10.1016/j.amjsurg.2015.03.022
   PMid:26105800
9. Losada B, Guerra JA, Malón D, Jara C, Rodriguez L, Del Barco S. Pretreatment neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, and neutrophil/monocyte ratios and outcome in elderly breast cancer patients. Clin Transl Oncol. 2019;21(7):855-63. https://doi.org/10.1007/s12094-018-1999-9
   PMid:30506134
10. Zhu Y, Si W, Sun Q, Qin B, Zhao W, Yang J. Platelet-lymphocyte ratio acts as an indicator of poor prognosis in patients with breast cancer. Oncotarget. 2017;8(1):1023-30. https://doi.org/10.18632/oncotarget.13714
    PMid:27906679
11. Prabawa IP, Bhargah A, Liwang F, Tandio DA, Tandio AL, Lestari AA, *et al*. Pretreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as a predictive value of hematological markers in cervical cancer. Asian Pac J Cancer Prev. 2019;20(3):863-8. https://doi.org/10.31557/apjcp.2019.20.3.863
    PMid:30912405
12. Noh H, Eomm M, Han A. Usefulness of pretreatment neutrophil to lymphocyte ratio in predicting disease-specific survival in breast cancer patients. J Breast Cancer. 2013;16(1):55-9. https://doi.org/10.4048/jbc.2013.16.1.55
    PMid:23593082
13. Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High platelet-to-lymphocyte ratio predicts poor prognosis and clinicopathological characteristics in patients with breast cancer: A meta-analysis. Biomed Res Int. 2017;2017:9503025. https://doi.org/10.1155/2017/9503025
14. Elyasinia F, Keramati MR, Ahmadi F, Rezaei S, Ashouri M, Parsaei R, *et al*. Neutrophil-lymphocyte ratio in different stages of breast cancer. Acta Med Iran. 2017;55(4):228-32.
    PMid:28532133
15. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, *et al*. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer. 2015;113(1):150-8. https://doi.org/10.1038/bjc.2015.183
    PMid:26022929
16. Pilatova K, Zdrazilova-Dubska L, Klement GL. The role of platelets in tumour growth. Klin Onkol. 2012;25 (Suppl 2):2S50-7.
    PMid:23581017
17. Huang Y, Sun Y, Peng P, Zhu S, Sun W, Zhang P. Prognostic and clinicopathologic significance of neutrophil-to-lymphocyte ratio in esophageal squamous cell carcinoma: Evidence from a meta-analysis. Onco Targets Ther. 2017;10:1165-72. https://doi.org/10.2147/ott.s126637
18. Aslan C, Eren R, Doğu MH, Yokuş O, Suyanı E. Relationship between neutrophil-lymphocyte ratio and clinicopathological parameters in follicular lymphoma. İstanbul Med J. 2016;17:150-1. https://doi.org/10.5152/imj.2016.93546
19. Yersal Ö, Çetinkünar S, Aktimur R, Aziret M, Özdaş S, Erdem H, *et al*. Neutrophil/lymphocyte and platelet/lymphocyte ratios are not different among breast cancer subtypes. Asian Pac J Cancer Prev. 2017;18(8):2227-31.
    PMid:28843260
20. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, *et al*. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer. 2014;110(10):2524-30. https://doi.org/10.1038/bjc.2014.163
    PMid:24675383
21. Graziano V, Grassadonia A, Iezzi L, Vici P, Pizzuti L, Barba M, *et al*. Combination of peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. Breast. 2019;44:33-8. https://doi.org/10.1016/j.breast.2018.12.014
    PMid:30611095
22. Suzuki K, Aiura K, Ueda M, Kitajima M. The influence of platelets on the promotion of invasion by tumor cells and inhibition by antiplatelet agents. Pancreas. 2004;29(2):132-40. https://doi.org/10.1097/00006676-200408000-00008

PMid:15257105

23. Tsuji T, Sawai T, Yamashita H, Takeshita H, Nakagoe T, Shindou H, *et al*. Platelet-derived endothelial cell growth factor expression is an independent prognostic factor in colorectal cancer patients after curative surgery. Eur J Surg Oncol. 2004;30(3):296-302. https://doi.org/10.1016/j.ejso.2003.11.019
24. Palumbo JS, Talmage KE, Massari JV, La Jeunesse CM, Flick MJ, Kombrinck KW, *et al*. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood. 2005;105(1):178-85. https://doi.org/10.1182/blood-2004-06-2272

    PMid:15367435
25. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer. 2011;11(2):123-34. https://doi.org/10.1038/nrc3004

    PMid:21258396
26. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: A systematic review and meta-analysis. Breast Cancer Res. 2017;19(1):2. https://doi.org/10.1186/s13058-016-0794-1

    PMid:28057046
27. Ulas A, Avci N, Kos T, Cubukcu E, Olmez OF, Bulut N, *et al*. Are neutrophil/lymphocyte ratio and platelet/lymphocyte ratio associated with prognosis in patients with HER2-positive early breast cancer receiving adjuvant trastuzumab? J BUON. 2015;20(3):714-22. https://doi.org/10.7314/apjcp.2015.16.4.1643
28. Yao M, Liu Y, Jin H, Liu X, Lv K, Wei H, *et al*. Prognostic value of preoperative inflammatory markers in Chinese patients with breast cancer. Onco Targets Ther. 2014;7:1743-52. https://doi.org/10.2147/ott.s69657

    PMid:25328407
29. Cihan YB, Arslan A, Cetindag MF, Mutlu H. Lack of prognostic value of blood parameters in patients receiving adjuvant radiotherapy for breast cancer. Asian Pac J Cancer Prev. 2014;15(10):4225-31. https://doi.org/10.7314/apjcp.2014.15.10.4225

    PMid:24935375
30. Orditura M, Galizia G, Diana A, Saccone C, Cobellis L, Ventriglia J, *et al*. Neutrophil to lymphocyte ratio (NLR) for prediction of distant metastasis-free survival (DMFS) in early breast cancer: A propensity score-matched analysis. ESMO Open. 2016;1(2):e000038. https://doi.org/10.1136/esmoopen-2016-000038

    PMid:27843594
31. Abu-Shawer O, Abu-Shawer M, Hirmas N, Alhouri A, Massad A, Alsibai B, *et al*. Hematologic markers of distant metastases and poor prognosis in gynecological cancers. BMC Cancer. 2019;19(1):141. https://doi.org/10.1186/s12885-019-5326-9

    PMid:30755184
32. Ohe Y, Fushida S, Yamaguchi T, Kinoshita J, Saito H, Okamoto K, *et al*. Peripheral blood platelet-lymphocyte ratio is good predictor of chemosensitivity and prognosis in gastric cancer patients. Cancer Manag Res. 2020;12:1303-11. https://doi.org/10.2147/cmar.s241069

    PMid:32110104
33. Thio QC, Goudriaan WA, Janssen SJ, Paulino Pereira NR, Sciubba DM, Rosovksy RP, *et al*. Prognostic role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with bone metastases. Br J Cancer. 2018;119(6):737-43. https://doi.org/10.1038/s41416-018-0231-6

    PMid:30116026
34. Xia WK, Liu ZL, Shen D, Lin QF, Su J, Mao WD. Prognostic performance of pre-treatment NLR and PLR in patients suffering from osteosarcoma. World J Surg Oncol. 2016;14:127. https://doi.org/10.1186/s12957-016-0889-2