International Journal of Research and Reports in Gynaecology

Volume 6, Issue 1, Page 71-78, 2023; Article no.IJRRGY.108948

Predictive Value of Pretreatment Haematological Markers in Cervical Cancer at a Third Level Health Institution

Justina Omoikhefe Alegbeleye [a*] and Merry Alali Jaja [b]

[a] University of Port Harcourt Teaching Hospital, Rivers State, Nigeria.
[b] Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/108948

Original Research Article

Received: 10/09/2023
Accepted: 15/11/2023
Published: 20/11/2023

ABSTRACT

Background: Inflammatory biomarker measurement is a low-cost method of identifying patients with advanced disease, and the risk of recurrence after treatment.
Objectives: To investigate if the pretreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used in predicting the stage of cervical cancer.
Materials and Methods: A cross-sectional analysis of seventy-eight women newly diagnosed with cervical cancer managed at the University of Port Harcourt Teaching Hospital between January 1, 2019, and December 31, 2022. A data collection form was used to collect socio-demographic and clinical characteristics from the patients after informed consent was obtained. Blood samples were collected and used to determine the pretreatment levels of NLR and PLR. The Receiver Operating Characteristic (ROC) curve was used to assess the predictive accuracy of the different haematological parameters for late-stage cervical cancer.

**Corresponding author: E-mail: justina.alegbeleye@uniport.edu.ng; drefe_2@yahoo.co.uk;*

Results: PLR was significantly higher in advanced-stage cancer (p = 0.041). There was no statistically significant strong positive correlation between NLR (r = 0.195) and PLR (0.078) with cervical cancer staging (p > 0.05). None of the haematological parameters could be used as predictive markers for advanced-stage cervical cancer.
Conclusion: Pretreatment NLR and PLR did not predict the stage of cervical cancer in this study.

Keywords: Cervical cancer; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; predictive value; Port Harcourt.

1. INTRODUCTION

"Cervical cancer is an important public health issue especially in low-and middle-income countries, yet largely preventable" [1,2]. "It is the fourth most common cancer in women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020" [3]. Cervical cancer incidence and mortality rates vary widely by geographic region [4,5]. The highest incidence rates are found in sub-Saharan Africa, followed by Latin America and the Caribbean, and Southeast Asia. The lowest rates are found in North America, Western Europe, and Australia [6,7,8].

Many studies in recent years have shown that systemic inflammatory responses play a role in cancer patient prognosis [9]. Inflammation influences every stage of cancer development, from tumour formation to progression and metastasis [10].

"Changes in the microenvironment are caused by the host's response to malignant tumours that cause systemic alterations. Several studies have shown that systemic inflammation plays a role in cancer progression at multiple stages, including initiation, promotion, invasion, and metastasis" [10]. Systemic inflammation can be detected in a complete blood count (CBC) as neutrophilia, thrombocytopenia, and relative lymphocytopenia [10]. Routine laboratory tests for haematological biomarkers are easily accessible and inexpensive.

Many studies have shown that there is an association between several inflammatory markers in the peripheral blood, such as neutrophil count, lymphocyte count, thrombocyte, and C-reactive protein, and the prognosis of various cancers [11,12].

Cervical cancer haematological markers are important predictors because they may be helpful in early detection, monitoring, and prognosis. Individuals at risk of cervical cancer should have regular screening tests, including haematological markers, to detect the disease early and improve their chances of treatment success [13,14].

"Neutrophils and platelets provide angiogenic, epithelial, and stromal growth factors, as well as matrix-remodeling enzymes, which are required for neoplastic progression" [10,15]. "Furthermore, an imbalance in the innate and adaptive immune systems, as evidenced by lymphocytopenia and an impaired T lymphocytic response, reduces the effectiveness of host-tumour immune responses" [16]. "Neutrophils, platelets, and lymphocytes may be involved in the progression of cancer. The progression of cancers to the advanced stage is characterized by neutrophilia, thrombocytosis, and lymphocytopenia. As a result, the combination of lymphocytes, neutrophils, and platelets has been studied as an independent prognostic factor in the progression of cancer" [17].

"Neutrophils and lymphocytes are the main elements of the tumour-related stroma that are linked to local inflammation and immune responses as well as reflect the balance between pro- and anti-tumour status" [18,19]. Furthermore, IL-1, IL-2, and IL-6 are the main pro-inflammatory mediators that indirectly correlate with an elevated platelet count to indicate the severity of inflammation in cancer.

"The most frequently studied parameters are neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Several studies have found that an increased peripheral neutrophil-to-lymphocyte ratio (NLR) is a poor prognostic indicator in various cancers" [20]. PLR has also been linked to a poor outcome in various malignant tumours [20,21].

Pre-treatment NLR and PLR values have been shown to be predictive and prognostic in patients with cervical cancer [7,22-30]. Han et al. discovered that a high NLR was an independent predictor of poor overall survival in patients with cervical cancer [30]. Similarly, Long et al.

observed that having a high PLR was associated with a lower progression free survival (PFS) and overall survival (OS) in cervical cancer patients [31]. However, the use of NLR and PLR as predictive markers in cervical cancer has not yielded a consistent conclusion. The findings from these studies are contradictory, and the prognostic significance of NLR and PLR in cervical cancer remains unknown [1,2,28]. As a result, the study sought to investigate NLR and PLR as haematological markers for predicting the stage of cervical cancer.

2. MATERIALS AND METHODS

2.1 Study Population

This cross-sectional study included 78 patients with newly diagnosed clinical stage IB to IVA cervical cancer who were managed at the University of Port Harcourt Teaching Hospital between January 1, 2019, and December 31, 2022, according to the 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system. Squamous cell carcinoma (SCC), adenocarcinoma, and adenosquamous carcinoma of the uterine cervix were histologically confirmed in all patients. After obtaining informed consent, the patients' information was collected using a data collection tool and data was entered in a sequential order. Patients' baseline characteristics, laboratory results, and histopathology reports were all included in the data. Each participant was assigned a unique identity to ensure anonymity and ease of identification. The data collection tools were checked daily for accuracy and completeness. Patients with early cervical cancer with microscopic lesions (IA1 and IA2), as well as those with concurrent haematologic or infectious diseases, were excluded from this study.

2.2 Pretreatment Assessment and Analysis of Inflammatory Markers

At the time of admission, all patients underwent physical and gynaecological pelvic examinations. LN involvement and distant metastasis were assessed using pelvic MRI (Magnetic Resonance Imaging) and/or CT (Computed Tomography). The initial complete blood count was performed prior to the start of treatment at the time of admission. Absolute white blood cell (WBC) counts (AWC), absolute lymphocyte counts (ALC), absolute neutrophil counts (ANC), absolute monocyte counts (AMC), and absolute platelet counts (APC) were among the haematological parameters measured. PLR was calculated by dividing the absolute platelet count (APC) by the absolute lymphocyte count (ALC). NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC). Thereafter, the patients all had examination under anaesthesia, staging, and biopsy to determine the clinical stage of the disease. The biopsy specimen was sent to the histopathologists to determine the histological type, depth of invasion and grading of the tumour.

2.3 Data Analysis

The data was summarized using mean and standard deviation as appropriate. Spearman Rank correlation was used to assess the correlation between stage of cervical cancer and NLR, PLR, BLR, and MLR. The discriminative role and cut-off values of NLR, PLR, BLR, and MLR were determined using Receiver Operating Curve (ROC) analysis with Area under the Curve (AUC). The cut-off values were used to determine the sensitivity and specificity of each haematological parameter. The p-value was set at ≤ 0.05 for statistical significance, and data analysis was done using SPSS version 25 at 95% confidence interval.

3. RESULTS

The mean age of the patients was 57.21 ± 12.39 years. There was no significant difference found in age between the advanced stage group II (56.1 ± 12.7), III (57.3 ± 12.6), and IV (57.2 ± 12.34) using One-Way Anova. Haematological parameters such as PLR was significantly higher in the advanced-stage cancer groups compared to the early-stage group ($p = 0.041$) using the non-parametric Kruskal Wallis test. In contrast, NLR, BLR, and MLR were not different (Table 1). Partial correlation was used to analyze the correlation between blood parameters (NLR, PLR, BLR, and MLR) against the staging of cervical cancer by controlling for age and parity. There was no statistically significant strong positive correlation between NLR ($r = 0.195$), PLR ($r = 0.078$), BLR ($r = 0.154$), MLR ($r = 0.188$), and cervical cancer stage ($p > 0.05$). These findings illustrate that the increase in NLR, PLR, BLR, and MLR only had a mild positive correlation with the stage of cervical cancer. This is shown in Table 2.

Predictive models were performed through ROC curve analysis on NLR, PLR, BLR, and MLR

parameters against advanced stage of cervical cancer as shown in Fig. 1. NLR has a sensitivity value of 81% and specificity of 82% with a cut-off value of 1.38. PLR has a sensitivity of 88% and specificity of 94% with a cutoff value of 3.91 (Table 3). However, none of the parameters was feasible to be used as a predictive model because they have an area under the curve (AUC) of less than < 0.7. This means that there is a less than 70% chance of the model correctly classifying patients in this study.

Table 1. Patients haematological parameters

Variables	Mean ±SD	p-value
Age	57.21 ±12.39	0.264
NLR	2.56 ± 3.01	0.110
PLR	7.30 ± 1.70	0.041*
BLR	0.01 ± 0.00	0.615
MLR	0.22 ± 0.03	0.205

**Statistically significant (p≤0.05), NLR: Neutrophil-lymphocyte ratio, PLR: Platelets-lymphocyte ratio, BLR: Basophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio*

Table 2. Correlation between haematological markers with stage of cancer after adjustment for age and parity

Haematological Parameters	FIGO stage (correlation coefficient)	p-value
NLR	0.195	0.096
PLR	0. 078	0.511
BLR	0.154	0.220
MLR	0.188	0.108

NLR: Neutrophil-to-lymphocyte ratio; BLR: Basophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio

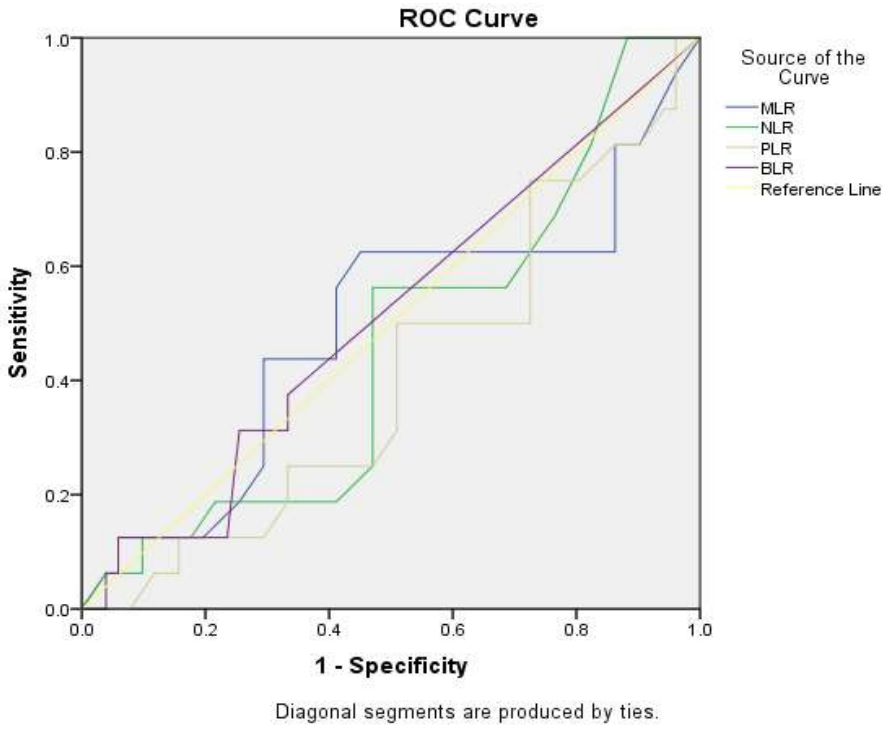

Fig. 1. ROC analysis of NLR, PLR, MLR, and BLR as predictive values in advanced stage cervical cancer

Table 3. AUC, cut-off value, sensitivity, specificity for NLR, PLR, MLR, and BLR in cervical cancer patients

Parameter	AUC	95% CI	Cut-off	Sensitivity %	Specificity %	p-value
NLR	0.456	0-30-0.61	1.38	81	82	0.60
PLR	0.406	0.25-0.56	3.91	88	94	0.26
BLR	0.510	0.35-0.67	0.02	31	26	0.90
MLR	0.491	0.32-0.67	0.19	63	71	0.91

NLR: Neutrophil-to-lymphocyte ratio; BLR: Basophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; AUC: Area Under the Curve; CI: Confidence Interval

4. DISCUSSION

The relationship between cancer and immunity has been one of the most widely discussed topics in recent times [9,10,32]. Many studies have shown that systemic inflammatory response plays a significant role in cancer development [32]. Many cancers are caused by environmental factors and develop in areas of chronic irritation and inflammation [10,26]. In general, neutrophilia, thrombocytosis, and relative lymphopenia are markers of systemic inflammation in peripheral blood [10]. These immune cells and inflammatory mediators play a significant role in the tumour microenvironment.

The mechanism by which increased neutrophil and decreased lymphocyte counts cause tumour progression is unknown. Neutrophils produce a variety of inflammatory cytokines, including vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9, causing DNA damage, inhibiting apoptosis, and promoting angiogenesis. Lymphocytes inhibit tumour cell proliferation by secreting interleukin-2, which stimulates the proliferation of cytotoxic lymphocytes while inhibiting tumour cell proliferation, thereby mediating antitumour immune responses [10,24,33].

The release of both angiogenic and anti-angiogenic factors by activated platelets results in stimulation of tumour angiogenesis because of platelet endothelial interaction [34]. Platelet activation causes release of angiogenic and anti-angiogenic factors, and the overall effect of platelet endothelial interaction is stimulation of tumour angiogenesis [34]. To predict the development of several cancers, various combinations of these inflammatory markers are currently being assessed as independent prognostic factors.

Clinicians are increasingly using haematological parameters to determine prognosis and management of cervical cancer [35]. NLR has been proposed for estimating cervical cancer mortality and recurrences. A high NLR is associated with poor prognosis in patients with cervical carcinoma [22,35,36]. The NLR can provide a reliable prediction of the prognosis of a patient with stage IIB cancer and lymph node metastasis [13]. “Furthermore, the NLR may be useful in determining the severity of cervical cancer. It is proposed that the NLR can be used as a predictor of cancer invasion” [13].

The PLR is dependent on the systemic inflammatory response, which is significantly influenced by cancer and other inflammatory conditions [37]. “These conditions can lead to misdiagnosis and ineffective, if not harmful, treatment. It is used to predict lymph node metastasis in cervical cancer and to improve the categorization of risk for predicting survival. In addition, the PLR provides a simple and easily accessible test for predicting the severity of cervical cancer” [38].

According to the findings of the current study, pretreatment NLR and PLR could not be used as predictive haematological markers to stage cervical cancer, implying that the models would be unreliable in correctly classifying patients. The small patient population could explain the non-significant association. Similarly, some researchers also observed that neither NLR nor PLR had a significant predictive value for overall survival, disease-free survival, or recurrence-free survival in patients with early-stage cervical cancer [27]. As a result, they concluded that although preoperative NLR and PLR are not clinically useful in predicting prognosis in early-stage cervical cancer, they may be useful in determining the risk for adjuvant therapy.

However, the study by Ergen et al., found that cervical cancer patients with high pretreatment NLR values had a more advanced stage, larger tumour size (> 4cm), and poorer treatment response. The cancer stages of patients with

high PLR values were also more advanced [1]. Increased NLR has been described as a sign of poor prognosis in many earlier studies. According to Lee et al., NLR could be used to calculate the mortality and recurrence rates in cervical cancer patients [22]. “They opined that in patients with locally advanced cervical cancer treated with radical chemoradiotherapy, post-treatment haematological parameters rather than pre-treatment haematological parameters may be used as a prognostic indicator” [29]. These conflicting outcomes could be the result of various patient characteristics, study designs, and sample size. The small sample size may have been the reason we could not determine the predictive values of NLR and PLR.

Furthermore, there is no validated threshold value for NLR or PLR. In each study, a different value (median value or ROC cut-off value) is used. In general, the NLR and PLR values used in these studies ranged from 2 to 5 and from 150 to 300 [11,12,39,40]. These are general inflammatory markers. At the same time, because these are systemic inflammation parameters, they may be difficult to interpret in the presence of concurrent chronic illness.

The fact that this study is prospective, that it is the first to assess the predictive value of haematological markers in cervical cancer patients at the centre, and that our cohort was exclusively made up of patients with a histologic diagnosis of the disease are some of its strengths. Complete blood counts are routinely performed at low cost before and during treatment, as well as during follow up visits; as a result, they are regarded as a practical and reproducible laboratory parameter.

The clinical significance of pretreatment NLR and PLR can therefore be a helpful predictive indicator for cancer stage if it is well defined. The study does, however, have some drawbacks, such as the small sample size and the fact that it was conducted in a single centre, so the results cannot be generalized. Larger multicentre clinical studies should be carried out to confirm the predictive values and cutoff values of NLR and PLR.

5. CONCLUSION

We were unable to establish the predictive value of pre-treatment NLR and PLR in this study. However, pretreatment NLR and PLR can be used as a simple and cost-effective biomarker in the future, particularly in developing countries where cervical cancer remains a major public health concern. In addition to clinical stage, it may be useful for stratifying patients at high risk of recurrence and death from cervical cancer.

ETHICAL APPROVAL AND CONSENT

The research and ethics committee of the University of Port Harcourt Teaching Hospital granted ethical approval for the study. Prior to their inclusion in the study, participants provided written informed consent. Personal identifying information was kept confidential.

ACKNOWLEDGEMENT

The authors acknowledge all the women with gynaecological cancers who despite their challenges, personal and financial struggles gave consent for the study. We also acknowledge Dr. Solace Omoruyi who helped with the data collection.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ergen S, Barlas C, Dagdelen M, Can G, Sahinler I. The prognostic role of the pretreatment peripheral neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in patients with cervical cancer. Ann Med Res 2021;28 (4):778-785.
2. Koulis TA, Kornaga EN, Banerjee R, Phan T, Ghatage P, Magliocco AM, et al. Anemia, leukocytosis, and thrombocytosis as prognostic factors in patients with cervical cancer treated with radical chemoradiotherapy: A retrospective cohort study. Clin Transl Radiat Oncol 2017;4: 51-56.
3. Jia W, Yuan L, Ni H, Xu B, Zhao P. Prognostic Value of Platelet-to-Lymphocyte Ratio, Neutrophil-to-Lymphocyte Ratio, and Lymphocyte-to-White Blood Cell Ratio in Colorectal Cancer Patients Who Received Neoadjuvant Chemotherapy. Technol Cancer Res Treat. 2021;20: 15330338211034291.
4. Gavrilescu MM, Hutanu I, Ioanid N, Musina, AM, Mihaela BA, Moscalu M, et al. Clinical Value of Hematological Biomarkers in Uterine Cervical Cancer. Chr. 2016;111 (6):493-499.

5. Palaia I, Tomao F, Di Pinto A, Pernazza A, Santangelo G, D'Alessandris N, et al. Response to Neoadjuvant Chemotherapy in Locally Advanced Cervical Cancer: The Role of Immune-related Factors. In Vivo 2021;35(2):1277–1283.
6. Adejumo R. 339 Ovarian cancer epidemiology in Jigawa, Nigeria. A 4-year review. Int J Gynecol Cancer 2020; DOI: 10.1136/ijgc-2020-IGCS.291.
7. George S, Omotoso A, Pinto A, Mustapha A, Sanchez-Covarrubias AP, Umar UA, et al. An Assessment of Ovarian Cancer Histotypes Across the African Diaspora. Front Oncol 2021;11, DOI:10.3389/fonc.2021.732443.
8. Kim YW, Choi EH, Kim BR, Ko WA, Do YM, Kim IY. The impact of delayed commencement of adjuvant chemotherapy (eight or more weeks) on survival in stage II and III colon cancer: a national population-based cohort study. Oncotarget. 2017;10;8(45):80061-80072.
9. Balkwill F, Mantovani A. Inflammation, and cancer: back to Virchow? Lancet. 2001;357(9255):539-545.
10. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140(6):883-899.
11. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106(6):dju124. DOI: 10.1093/jnci/dju124
12. Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, et al. Prognostic value of PLR in Various Cancers: A Meta-Analysis. PLoS One. 2014;9:e101119.
13. Kose M, Celik F, Kose SK, Arioz DT, Yilmazer M. Could the Platelet-to-Lymphocyte Ratio be a Novel Marker for Predicting Invasiveness of Cervical Pathologies? Asian Pac J Cancer Prev 2015;16(3):923-926.
14. Yildirim MA, Seckin KD, Togrul C, Baser E, Karsli MF, Gungor T, et al. Roles of Neutrophil/ Lymphocyte and Platelet/Lymphocyte Ratios in the Early Diagnosis of Malignant Ovarian Masses. Asian Pac J Cancer Prev. 2014;15 (16):6881-6885.
15. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-674.
16. Roxburgh CS, Salmond JM, Horgan PG, Oien KA, McMillan DC. Comparison of the prognostic value of inflammation-based pathologic and biochemical criteria in patients undergoing potentially curative resection for colorectal cancer. Ann Surg. 2009;249(5):788-793.
17. Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013; 13: 350.
18. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013; 88(1):218-230.
19. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers. 2012;17(3):216-222.
20. Hong X, Cui B, Wang M, Yang Z, Wang L, Xu Q. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J Exp Med 2015;236(4) ;297-304.
21. Gunaldi M, Goksu S, Erdem D, Gunduz S, Okuturlar Y, Tiken E, et al. Prognostic impact of platelet/lymphocyte and neutrophil/lymphocyte ratios in patients with gastric cancer: a multicenter study. Int J Clin Exp Med 2015;8(4):5937-5942.
22. Lee YY, Choi CH, Kim HJ, Kim T J, Lee JW, Lee JH, et al. Pretreatment neutrophil: lymphocyte ratio as a prognostic factor in cervical carcinoma. Anticancer Res. 2012;32(4):1555-1561.
23. Zhang Y, Wang L, Liu Y, Wang S, Shang P, Gao Y, et al. Preoperative neutrophil-lymphocyte ratio before platelet-lymphocyte ratio predicts clinical outcome in patients with cervical cancer treated with initial radical surgery. Int J Gynecol Cancer 2014;24(7):1319-1325.
24. Nakamura K, Nishida T, Haruma T, Haraga J, Omichi C, Ogawa C, et al. Pretreatment platelet-lymphocyte ratio is an independent predictor of cervical cancer recurrence following concurrent chemoradiation

therapy. Mol Clin Oncol. 2015;3(5):1001-1006.
25. Mizunuma M, Yokoyama Y, Futagami M, Aoki M, Takai Y, Mizunuma H. The pretreatment neutrophil-to-lymphocyte ratio predicts therapeutic response to radiation therapy and concurrent chemoradiation therapy in uterine cervical cancer. Int J Clin Oncol. 2015;20(5):989-996.
26. Wu J, Chen M, Liang C, Su W. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio in cervical cancer: a meta-analysis and systematic review. Oncotarget. 2017;8(8):13400-13412.
27. Nuchpramool P, Hanprasertpong J. Preoperative Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio Are Not Clinically Useful in Predicting Prognosis in Early-Stage Cervical Cancer. Surg Res Pract. 2018;2018:9162921.
28. Prabawa IPY, Bhargah A, Liwang F, Tandio DA, Tandio AL, Lestari AAW, 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):863-868.
29. Lee HJ, Kim JM, Chin YJ, Chong GO, Park SH, Lee YH, et.al. Prognostic Value of Hematological Parameters in Locally Advanced Cervical Cancer Patients Treated with Concurrent Chemoradiotherapy. Anticancer Res. 2020; 40(1):451-458.
30. Han X, Liu S, Hosseinifard H, Imani S, Yang G, Yang L, et al. Descriptive statistics of dataset from the meta-analysis and meta-regression analysis on prognostic significance of pre-treatment systemic hemato-immunological indices of cervical cancer patients. Data in Brief. 2021;35:106925.
31. Long Y, Zhang Y, Ni L, Yuan X, Liu Y, Tao J, et al. Prognostic value of platelet-to-lymphocyte ratio in neoadjuvant chemotherapy for solid tumors: A PRISMA-compliant meta-analysis. Medicine. 2021; 100(29):e26202.
32. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454 (7203):436-444.
33. Valle-Mendiola A, Gutiérrez-Hoya A, Lagunas-Cruz MDC, Weiss-Steider B, Soto-Cruz I. Pleiotropic Effects of IL-2 on Cancer: Its Role in Cervical Cancer. Mediators Inflamm. 2016;2849523.
34. Sabrkhany S, Griffioen AW, oude Egbrink MG. The role of blood platelets in tumor angiogenesis. Biochim Biophys Acta. 2011; 1815(2):189-196.
35. Nakamura K, Nakayama K, Tatsumi N, Minamoto T, Ishibashi T, Ohnishi K, et al. Prognostic significance of pre-treatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in non-surgically treated uterine cervical carcinoma. Mol Clin Oncol. 2018;9(2):138-144.
36. Chun S, Shin K, Kim KH, Kim HY, Eo W, Lee JY, et al. The neutrophil-lymphocyte ratio predicts recurrence of cervical intraepithelial neoplasia. J Cancer. 2017; 8(12):2205-2211.
37. Sun P, Zhang F, Chen C, Bi X, Yang H, An X, et al. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China. Oncotarget 2016; 7 (27): 42650-42660.
38. Chen L, Zhang F, Sheng X-G, Zhang SQ, Chen YT, Liu BW, et al. Peripheral platelet/ lymphocyte ratio predicts lymph node metastasis and acts as a superior prognostic factor for cervical cancer when combined with neutrophil: Lymphocyte. Medicine. 2016;95(32):e4381.
39. Zhang X, Wang Y, Zhao L, Sang S, Zhang L. Prognostic value of platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: A systematic review and meta-analysis. Int J Biol Markers. 2018;1724600818766889.
40. Wu J, Chen M, Liang C, Su W. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio in cervical cancer: a meta-analysis and systematic review. Oncotarget. 2017;8(8):13400-13412.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/108948