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Comparison of Hematologic Parameters Between Early Stage and Advanced Stage Cervical Cancer Patients: Cross sectional Study

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Abstract

Background

Cervical cancer is the fourth most common malignancy among women worldwide. Systemic inflammation associated with cancer progression may lead to hematologic alterations such as anemia, thrombocytosis, neutrophilia, and lymphopenia. These hematologic parameters may have potential value as simple biomarkers to identify advanced stage cervical cancer. This study aimed to compare hematologic parameters between early stage and advance stage cervical cancer patients

Methods

This analytical observational study used a cross sectional design and included cervical cancer patients treated at Dr. Mohammad Hoesin General Hospital between August 2022 and July 2023. A total of 153 patients were included and categorized into early stage (FIGO I–IIA) and advanced stage (FIGO IIB–IV) groups. Demographic characteristics, histopathological findings, complete blood count parameters, and hematologic indices including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were analyzed. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut off values and categorize variables for comparative analysis. Multivariable logistic regression analysis was performed to assess the association between hematologic parameters and cervical cancer stage.

Results

Hemoglobin level, platelet count, NLR, and PLR were significantly associated with the clinical stage of cervical cancer ($p < 0.001$). Patients with advanced stage disease had lower hemoglobin levels and higher platelet counts and NLR. Logistic regression analysis showed that hemoglobin < 11.55 g/dL, platelet count ≥ 367.5×10³/μL, and NLR ≥ 2.64 were significantly associated with advanced stage cervical cancer.

Conclusion

Hematologic parameters, particularly hemoglobin level, platelet count, and NLR, differed significantly between early stage and advanced stage cervical cancer patients and may reflect disease progression.

1. Introduction

Cervical cancer is the 4th most common cancer in women globally, with nearly 94% of 350,000 annual deaths occurring in low- and middle-income countries due to limited screening and HPV vaccination access. It is highly preventable, yet inequitable healthcare access means high-risk areas bear the highest

mortality burden.[1] Persistent infection with high-risk human papillomavirus is the primary cause of cervical cancer and contributes to disease progression from precancerous lesions to invasive carcinoma.[2]

The clinical stage of cervical cancer at diagnosis is a key determinant of treatment strategy and prognosis.[3] Early-stage disease is generally managed surgically, whereas advanced-stage disease often requires chemoradiotherapy. However, many patients present at advanced stages, especially in resource-limited settings, highlighting the need for simple indicators associated with disease severity.[4]

Systemic inflammation in cervical cancer is associated with various hematologic alterations, including anemia, neutrophilia, thrombocytosis, and lymphopenia. Cancer-related anemia is partly mediated by immune activation, which increases the production of reactive oxygen species (ROS). Excessive ROS can disrupt erythropoiesis and reduce erythrocyte survival, ultimately contributing to decreased hemoglobin levels.[5] Neutrophilia in cancer reflects an enhanced systemic inflammatory response driven by tumor–host interactions. Activated neutrophils may undergo polarization into the N1 phenotype, which exerts antitumor effects through the recruitment and activation of CD8 + cytotoxic T lymphocytes. This process is mediated by the release of pro-inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12), which collectively enhance antitumor immune responses.[6] Lymphocytes play a crucial role in cancer progression, primarily through their involvement in antitumor immune responses. They contribute to tumor suppression by mediating cytotoxic activity against malignant cells and regulating immune surveillance. A decrease in lymphocyte levels may reflect impaired immune function, resulting in a reduced ability to control tumor growth and progression.[7] In addition, platelet levels may increase due to cytokine stimulation, particularly interleukin-1 (IL-1), interleukin-3 (IL-3), and interleukin-6 (IL-6), which promote thrombopoiesis. Platelets also play an important role in cancer progression by protecting circulating tumor cells from natural killer (NK) cell-mediated cytotoxicity during metastasis, thereby facilitating tumor cell survival in the circulation and enabling their dissemination to distant metastatic sites.[8, 9]

Previous studies conducted in Indonesia have demonstrated significant associations between hematologic parameters—including hemoglobin level, neutrophil count, platelet count, and lymphocyte count—as well as hematologic indices such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), and the clinical stage of cervical cancer.[10] A study published in Scientific Reports by Zou reported that pre-treatment neutrophil-to-lymphocyte ratio (NLR) was significantly associated with tumor grade and advanced FIGO stage.[11] In addition, a study by Zhu et al. reported that platelet-to-lymphocyte ratio (PLR) was significantly associated with tumor invasion depth and FIGO stage. The study also found that both neutrophil-to-lymphocyte ratio (NLR) and PLR were associated with patient age.[12]

Previous studies have reported associations between hematologic parameters and cancer progression, but evidence regarding their relationship with cervical cancer stage remains limited, particularly in

Indonesian populations to support early detection of cervical cancer and ultimately improve patient outcomes by utilizing easily accessible biomarkers. Therefore, this study aimed to compare hematologic parameters between early-stage and advanced-stage cervical cancer patients.

2. Methods

2.1. Study Design

This analytical observational study used a cross-sectional design. Data were collected from cervical cancer patients treated at Dr. Mohammad Hoesin General Hospital between August 2022 and July 2023. The study protocol was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya (Protocol No. 301–2023).

2.2. Study Population

Patients aged ≥ 18 years who were newly diagnosed with cervical cancer were included. Patients with other malignancies, hematologic disorders, or a history of blood transfusion within the previous 14 days were excluded. The clinical staging of cervical cancer was determined based on the FIGO 2018 classification system, which categorizes the disease into four stages: I, II, III, and IV. A total of 153 patients were included and categorized into two groups: early-stage (FIGO stage I–IIA) and advanced-stage (FIGO stage IIB–IV)

2.3. Data Collection

The collected variables included demographic characteristics (age, marital status, parity, and hormonal contraceptive use), histopathological type, complete blood count parameters (hemoglobin, leukocyte count, neutrophil count, lymphocyte count, monocyte count, and platelet count), and hematologic indices including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count, whereas the platelet-to-lymphocyte ratio (PLR) was obtained by dividing the platelet count by the lymphocyte count. The systemic inflammation response index (SIRI) was calculated by multiplying the monocyte count by the neutrophil count and dividing the result by the lymphocyte count. The systemic immune-inflammation index (SII) was calculated by multiplying the platelet count by the neutrophil count and dividing it by the lymphocyte count. The haematological analysis was conducted using a Sysmex XN-1000 machine.

2.4. Statistic Analysis

Statistical analyses were performed using IBM SPSS software version 26.0 (Armonk, NY: IBM Corp), with statistical significance defined as a p-value < 0.05. Data normality was assessed using the Kolmogorov–Smirnov test for samples exceeding 50 participants. Descriptive analysis was performed to summarize patient characteristics. The chi-square test was used to evaluate the association between independent variables and cervical cancer stage. Receiver operating characteristic (ROC) curve analysis was

conducted to determine optimal cut-off values for hematologic parameters. These cut-off values were used to categorize variables for subsequent comparative analysis. Variables with $p < 0.25$ in the bivariate analysis were included in the multivariable logistic regression was performed to assess the association between hematologic parameters and cervical cancer stage. Adjusted relative risk (RR) with 95% confidence intervals were reported.

3. Result

A total of 153 cervical cancer patients were included in this study, consisting of 117 patients with advanced-stage disease and 36 patients with early-stage disease. Most patients were aged over 42 years (68.6%) and the majority were married (98.7%). Squamous cell carcinoma was the most common histopathological type (68%). Bivariate analysis showed that hemoglobin level, leukocyte count, neutrophil count, monocyte count, platelet count, NLR, and PLR were significantly associated with cervical cancer stage ($p < 0.05$).

Table 1
The association between demographic, histopathological, and hematological status with the clinical stage of cervical cancer.

No	Variable	Total (n = 153)	Advanced Stage (n = 117)	Early Stage (n = 36)	P-Value
Demographic Status					
1	Age (year)				
	• > 42 years	105 (68,60%)	83 (70,9%)	22 (61,1%)	0,365
	• ≤ 42 years	48 (31,40%)	34 (29,1%)	14 (38,9%)	
2	Marital Status				1,000
	• Married	151 (98,70%)	115 (98,30%)	36 (100%)	
	• Not married	2 (1,30%)	2 (1,7%)	0 (0%)	
3	Parity History				0,164
	• > 4	21 (13,70%)	19 (16,20%)	2 (5,60%)	
	• ≤ 4	132 (86,30%)	98 (83,80%)	34 (94,40%)	
4	History of Hormonal Contraceptive Use (n = 173)				1,000
	• Yes	5 (2,90%)	4 (3,10%)	1 (2,30%)	
	• No	168 (97,1%)	125 (96,90%)	43 (97,70%)	
Histopathological Examination					
5	Histopathology				
	• Squamous Cell Carcinoma				1,000
	− Yes	104 (68%)	80 (68,4%)	24 (66,7%)	
	− No	49 (32%)	37 (31,6%)	12 (33,3%)	
	• Adenocarcinoma, Mixed, and Others				1,000

*Significant

No	Variable	Total (n = 153)	Advanced Stage (n = 117)	Early Stage (n = 36)	P-Value
Demographic Status					
	– Yes	49 (32%)	37 (31,6%)	12 (33,3%)	
	– No	104 (68%)	80 (68,4%)	24 (66,7%)	
Complete Hematological Examination					
6	*Complete Blood Count*				
	• Hemoglobin (g/dL)				< 0,001*
	< 11,55	96 (62,7%)	88 (75,2%)	8 (22,2%)	
	≥ 11,55	57 (37,3%)	29 (24,8%)	28 (77,8%)	
	• Leukocyte (×10³/mm³)				0,001*
	≥ 9,37	81 (52,9%)	71 (60,7%)	10 (27,8%)	
	< 9,37	72 (47,1%)	46 (39,3%)	26 (72,2%)	
	• Neutrophil (×10³/mm³)				0,001*
	≥ 7,14	61 (39,9%)	56 (47,9%)	5 (13,9%)	
	< 7,14	92 (60,1%)	61 (52,1%)	31 (86,1%)	
	• Monocyte (×10³/mm³)				0,037*
	≥ 0,99	23 (15,0%)	22 (18,8%)	1 (2,8%)	
	< 0,99	130 (85,0%)	95 (81,2%)	35 (97,2%)	
	• Lymphocyte (×10³/mm³)				0,829
	≥ 2,37	64 (41,8%)	50 (42,7%)	14 (38,9%)	
	< 2,37	89 (58,2%)	67 (57,3%)	22 (61,1%)	

*Significant

No	Variable	Total (n = 153)	Advanced Stage (n = 117)	Early Stage (n = 36)	P-Value
Demographic Status					
	• Platelet (×10³/µL)				< 0,001*
	≥ 367,5	81 (52,9%)	73 (62,4%)	8 (22,2%)	
	< 367,5	72 (47,1%)	44 (37,6%)	28 (77,8%)	
	• Neutrophil Lymphocyte Ratio				< 0,001*
	≥ 2,64	85 (55,6%)	76 (65%)	9 (25,0%)	
	< 2,64	68 (44,4%)	41 (35%)	27 (75,0%)	
	• Platelet Lymphocyte Ratio				< 0,001*
	≥ 153,67	89 (58,2%)	78 (66,7%)	11 (30,6%)	
	< 153,67	64 (41,8%)	39 (33,3%)	25 (69,4%)	
	• Systemic Immune-inflammation Index (SII)				< 0,001*
	≥ 1022	76 (49,7%)	71 (60,7%)	5 (13,9%)	
	< 1022	77 (50,3%)	46 (39,3%)	31 (86,1%)	
	• Systemic Inflammation Response Index (SIRI)				< 0,001*
	≥ 2,94	53 (34,6%)	50 (42,7%)	3 (8,3%)	
	< 2,94	100 (65,4%)	67 (57,3%)	33 (91,7%)	
*Significant					

Table 2
ROC Analysis

Parameter	AUC	Sensitivity	Specificity	Cut off Point	P-Value	95% CI
Age	0,528	70,9%	38,9%	42	0,606	0,421-0,636
Parity	0,497	16,2%	94,4%	5	0,961	0,396-0,599
Hemoglobin	0,774	77,80%	75,20%	11,55	< 0,001*	0,684–0,864
Leukocyte	0,686	60,70%	72,20%	9,37	0,001*	0,588–0,783
Neutrophil	0,706	47,90%	86,1%	7,14	< 0,001*	0,613–0,798
Monocyte	0,551	18,8%	97,2%	0,99	0,36	0,449–0,652
Lymphocyte	0,442	42,7%	61,1%	2,37	0,29	0,341–0,542
Platelet	0,762	62,40%	77,8%	367,5	< 0,001*	0,679–0,846
NLR	0,708	65,00%	75%	2,64	< 0,001*	0,621–0,795
PLR	0,741	66,7%	69,4%	153,67	< 0,001*	0,69 – 0,85
SIRI	0,685	42,7%	91,7%	2,94	0,001	0,595–0,776
SII	0,772	61,5%	86,1%	1022	< 0,001*	0,693–0,851

Receiver operating characteristic (ROC) analysis showed that hemoglobin, platelet count, and SII had the highest discriminative ability for advanced-stage cervical cancer, with AUC values of 0.774, 0.762, and 0.772, respectively. NLR and PLR also demonstrated moderate performance, with AUC values above 0.70. In contrast, age, parity, monocyte, and lymphocyte counts exhibited poor discriminatory capacity and were not statistically significant. The optimal cut-off values identified were 11.55 g/dL for hemoglobin, 367.5×10³/μL for platelet count, and 2.64 for NLR. The ROC curves had significant differences based on the clinical stage of cervical cancer are shown in Fig. 1.

Tabel 3. Multivariable logistic regression analysis of factors associated with advanced-stage cervical cancer

Variables	OR	95% CI	P-Value
Hemoglobin	6,72	2,58–17,49	< 0,001
NLR	2,92	1,11–7,65	0,029
Platelet	4,45	1,69–11,71	0,002

Multivariable logistic regression analysis identified hemoglobin level, neutrophil-to-lymphocyte ratio (NLR), and platelet count as independent factors associated with advanced-stage cervical cancer. Hemoglobin level was associated with a more than six-fold increase in the likelihood of advanced-stage

disease (OR = 6.72; 95% CI: 2.58–17.49; p < 0.001), while elevated platelet count and NLR were associated with approximately four-fold (OR = 4.45; 95% CI: 1.69–11.71; p = 0.002) and nearly three-fold increases (OR = 2.92; 95% CI: 1.11–7.65; p = 0.029), respectively.

4. Discussion

This study found a significant correlation (p < 0.001) between hemoglobin levels and the clinical stage of cervical cancer. This is consistent with research conducted by Gennigens et al., which found a negative correlation (r=-0.38; P = 0.001) between hemoglobin and tumor size in cervical cancer.[13] Other studies also say that hemoglobin levels before therapy are negatively correlated with tumor size (R = − 0,77; R2=-1,55; P = 0,0001).[14] The decrease in hemoglobin is mediated by the release of cytokines resulting from the complex interaction of tumor cells and the immune system. Excessive production of proinflammatory cytokines (IFN-γ, TNF-α, IL-1, and IL-6) leads to a shortened erythrocyte lifespan, crushed erythrocyte, and impaired erythropoiesis.[5, 15]

This study showed a significant correlation (p < 0.001) between platelet count and the clinical stage of cervical cancer. These results are consistent with a study by Wang et al., which found that pre-treatment platelet count correlated significantly (p < 0.046) with the FIGO stage of cervical cancer.[16] Another study conducted by Abu-Zaid et al., also stated that there was a significant relationship (p = 0.001) between platelets and the FIGO stage of cervical cancer.[17] Platelet elevation in malignancy occurs because megakaryocytopoiesis is stimulated by IL-6, which is mediated by tumor-derived humoral factor, resulting in thrombopoiesis. Increased hepatic thrombopoietin synthesis can occur in response to IL-6, which is the basis for thrombocytosis in malignancy. Platelet elevation plays a role in protecting cancer from immune system attacks.[8, 18]

This study also found a significant relationship (p < 0.001) between the Neutrophil Lymphocyte Ratio and the clinical stage of cervical cancer. This is in line with research conducted by Lee, which found a significant relationship (p < 0.001) between the NLR and the clinical stage of cervical cancer.[19] Elevated neutrophil-to-lymphocyte ratio (NLR) has been reported to be significantly associated with cervical cancer. Higher NLR levels were observed in patients with malignant outcomes, and increasing NLR values were linked to a higher likelihood of cancer.[20] Malignancy can result in an increased number of neutrophils in the blood. GM-CSF production is a possible mechanism in some types of cancer. In addition, other cytokines such as granulocyte colony-stimulating factor (G-CSF), IL-1, and IL-6 are produced by tumors.[21, 22] Lymphocytes also play a crucial role in suppressing tumor growth and tumor cell death.[23]

This study shows a significant difference between PLR and the clinical stage of cervical cancer. This is in line with Zhu et al., who found a significant relationship (p = 0.004) between PLR and the clinical stage of cervical cancer.[12] Another study conducted in Istanbul also showed that PLR was significantly associated (p = 0.036) with the stage of cervical cancer.[24] Platelets can play a role in tumor growth by increasing angiogenesis through the release of the cytokine vascular endothelial growth factor (VEGF).

Furthermore, the release of the cytokines IL-1, IL-3, IL-11, and granulocyte-macrophage colony-stimulating factor can stimulate thrombopoiesis, which plays a role in protecting cancer cells from immune system attacks.[8, 25–27] Meanwhile, lymphocytes play a crucial role in the immune system, identifying and defending against cancer. Cancer can cause suppression of regulatory T cells and activation of chemokines, leading to tumor cell growth and metastasis.[28, 29]

In the present study, inflammatory indices, particularly the systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI), demonstrated notable differences across clinical stages of cervical cancer. Elevated levels of these markers likely reflect an enhanced systemic inflammatory response associated with tumor progression.[30] Previous studies have reported that higher SII and SIRI are associated with poorer clinical outcomes, including increased risk of recurrence and reduced survival in patients with cervical cancer and other malignancies.[12, 31] The systemic immune-inflammation index (SII) has been shown to differentiate prognosis across various FIGO stages, serving as a valuable complement to the FIGO staging system and improving the identification of high-risk patients for more appropriate treatment strategies. [32, 33]A prognostic nomogram incorporating SIRI, FIGO stage, and lymphovascular invasion has been shown to provide superior predictive accuracy, achieving a concordance index (c-index) of 0.80, significantly outperforming the FIGO staging system alone ($p < 0.001$). Moreover, a post-treatment increase in SIRI exceeding 75% at eight weeks after surgical resection was associated with a significantly higher risk of mortality, and these patients exhibited the worst survival outcomes (hazard ratio = 3.30; 95% CI: 2.08–5.25; $p < 0.001$).[34]

In Low and Middle Income Countries (LMICs), where advanced diagnostic imaging (MRI, PET-CT) is often limited[35], simple, cost-effective biomarkers derived from routine hematologic tests can effectively help clinicians identify patients at high risk of advanced-stage disease and prioritize them for further diagnostic evaluation.

5. Conclusion

Hematologic parameters, including hemoglobin level and leukocyte, platelet, neutrophil, monocyte, and lymphocyte counts, as well as inflammatory ratios (NLR and PLR) and indices (SII and SIRI), differed significantly across clinical stages of cervical cancer. These markers may reflect underlying disease severity. Future research is warranted to further investigate their potential role in assessing treatment response and prognosis.

6. Recommendations

Future studies are recommended to include additional clinical variables derived from physical examination, such as vital signs and body mass index (BMI), other biomarkers, to provide a more comprehensive assessment. Furthermore, prospective studies evaluating treatment response and prognostic outcomes in cervical cancer patients are warranted.

Declarations

Ethical Approval and consent to participate

This study was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Universitas Sriwijaya (Protocol No. 301–2023). The requirement for informed consent was waived by the Ethics Committee due to the retrospective design of the study and the use of anonymized patient data.

Consent for Publication

Not Applicabale

Funding

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Author Contribution

H.G.S. and M.A.T.P. contributed to the study conception and design. H.G.S. performed data collection and data curation. H.G.S. and M.A.T.P. conducted the statistical analysis. M.A.T.P. and R.N. drafted the manuscript. All authors reviewed and approved the final manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request, in accordance with institutional and ethical regulations.

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Figures

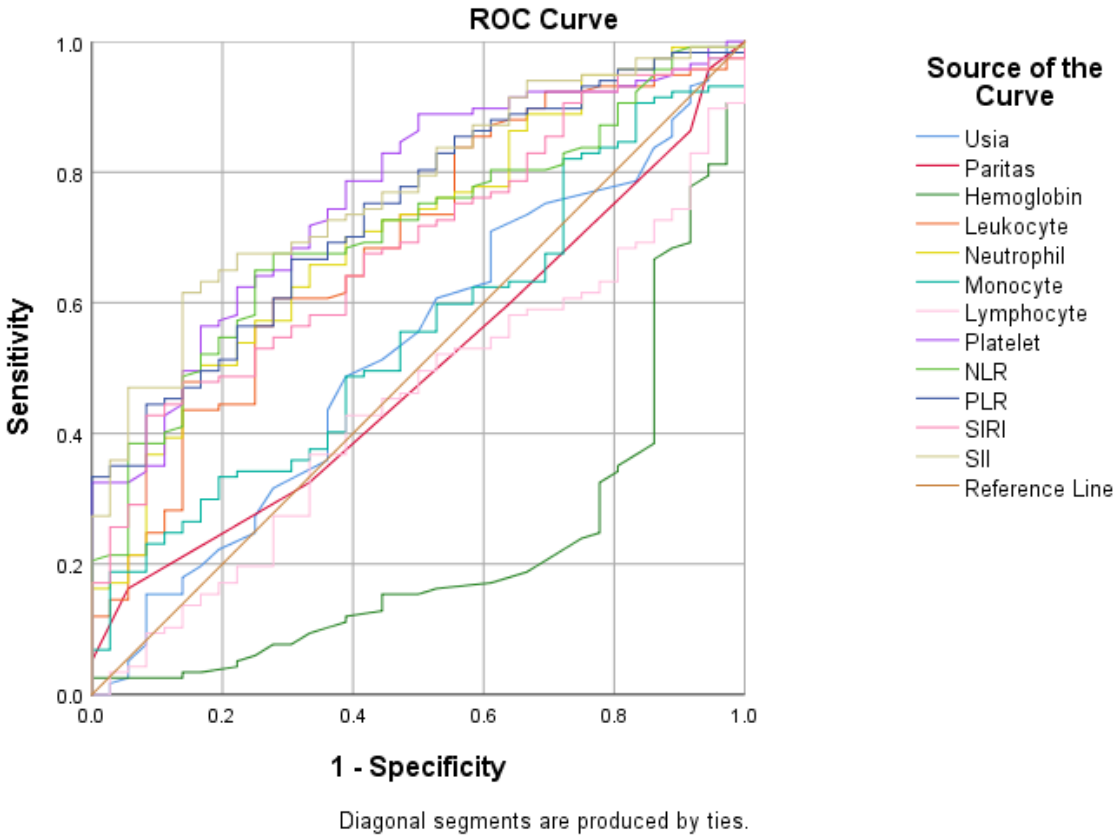


Figure 1

ROC curve for cut of point variable based on cancer stage