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Neutrophil-to-lymphocyte and Platelet-to-lymphocyte Ratio as Predictors of CD4 Count among People Living with HIV

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection remains a global health concern characterized by the reduction of CD4 lymphocyte cells and weakened immune systems. Knowing the CD4 count and the factors affecting it is crucial for assessing the immune status of HIV patients. Hematological markers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have been recognized as prognostic tools that were associated with CD4 Count. The goal of this study was to determine the impact of NLR and PLR on CD4 count among people living with HIV (PLHIV). This study used analytic observational method with a cross-sectional on HIV-positive individuals who were treated at Moewardi Hospital, Surakarta, Indonesia. The Chi-Square and Pearson correlation tests were performed to identify the correlation between variables and the linear regression test was done to investigate the association between NLR and PLR with CD4 count. A total of 80 PLHIV were identified for this study, with the median CD4 count of 103 cells/mm3. NLR and PLR were found to be 3.06 and 181.03, respectively. This study found that opportunistic infection, duration on ARV treatment, body mass index, total lymphocyte count, and hemoglobin were significantly associated with CD4 count. The Pearson correlation test revealed a strong correlation between NLR and PLR to CD4 count. Linear regression analyses showed that NLR and PLR could predict the CD4 count. These findings indicate that NLR and PLR could serve as alternative prognostic parameters for monitoring treatment outcomes in PLHIV, particularly in health facilities where access to CD4 count testing is limited.

Keywords: HIV, Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, CD4 count, and prognostic factor.

Highlights: This study confirms the predictive role of NLR and PLR in CD4 count as the indicator of immune status in PLHIV. Both of these are widely available markers that can aid clinicians in monitoring HIV patients' immune status, thereby reducing morbidity and mortality from HIV infection.

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INTRODUCTION

Human Immunodeficiency Virus (HIV) infection has become a health challenge with increasing case rates worldwide. According to UNAIDS data, a total of 39 million people worldwide had HIV and approximately 1.3 million of them were newly diagnosed in 2022.[1] Since the first cases were officially reported in 1981, a total of 84.2 million cases of HIV have been found.[2] The primary targets of HIV infection are the Cluster of Differentiation 4 (CD4) and chemokine receptors, both of which can be found in several human immune system cells.[3] These cells include helper T lymphocytes, dendritic cells, and macrophages.[3] Viruses attached to receptors on target cells will proceed with membrane fusion, allowing the viral components to enter the cells and replicate.[4] Continued replication will destroy target cells, decreasing CD4 levels.[5] This leads to impaired immunity and susceptibility to various opportunistic infections.[6]

Examining CD4 counts needs to be done regularly to determine the immune status of HIV patients.[6] However, there are several obstacles in conducting the examination, such as high examination fees and limited availability of this service in health facilities.[7] For this matter, it is crucial to discover alternatives to CD4 tests to monitor the immune status of HIV patients. Over the past few years, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have emerged as systemic inflammatory indicators and predictive factors of death in the general population.[8] NLR reflects both types of the body's immune response, neutrophils as an innate response and lymphocytes as an adaptive response.[9] Meanwhile, PLR simultaneously connects inflammatory pathways and aggregation.[10]

HIV infection is linked with immune hyperactivation and chronic inflammation, characterized by rising levels of various proinflammatory cytokines and hypercoagulable biomarkers.[11] High NLR and PLR have been shown to reflect severity and were linked with increased mortality in PLHIV as a result of the immunosuppression linked to low CD4 count.[9] One of the challenges in the clinical management of PLHIV is the limited access to CD4 count service in primary healthcare facilities while there is hematologic testing in these facilities. Despite the potential role of NLR and PLR to predict CD4 count, there is limited evidence in this area. Therefore, the goal of this study was to determine the correlation between NLR and PLR on CD4 count among PLHIV.

MATERIALS AND METHODS

This research is characterized as a cross-sectional study carried out at the Voluntary Counselling and Testing Polyclinic of Moewardi Hospital, Surakarta, Central Java, Indonesia, involving patients with HIV from 2017 – 2023. The participant inclusion criteria included patients diagnosed with HIV aged 18 - 65. The exclusion criteria encompassed patients with malignancy; patients with chronic diseases such as cardiovascular disease, liver cirrhosis, chronic kidney failure, and hematological disorders; patients with a history of autoimmune or currently undergoing immunosuppressant therapy; and patients with herpes simplex virus (HSV) co-infection. The sample selection involved purposive random sampling, with a minimum requirement of 60 subjects. The variables investigated within this study consisted of NLR and PLR as independent variables and CD4 as the dependent variable.

Laboratory Testing

The NLR and PLR were derived from routine hematology examination results using a hematology analyzer based on flow cytometry. The calculation of the NLR

involved dividing the total of neutrophils by the total of lymphocytes, while the PLR was determined by dividing the total of platelet count by the total of lymphocytes.

CD4 counts were also obtained using the flow cytometry method. All data were sourced from medical records, selecting patients who underwent both routine hematology test and CD4 test within a close period. For this study, a total of 80 patients were included.

Statistical Analysis

Statistical analyzes were conducted on both the main variables and patients' characteristic variables. The characteristics of the research subjects encompassed demographic variables such as age and gender, along with clinical variables including opportunistic infections, duration on ARV treatment, body mass index, total lymphocyte count, and hemoglobin. A normality test was conducted on continuous variables. Those that followed a normal distribution were presented as mean ± SD, whereas variables with a non-normal distribution were reported as median (interquartile range). Statistical analysis of categorical variables was conducted using the Chi-Square test, while continuous variables were analyzed using the Pearson test. The Pearson test was also performed to asses the correlation between NLR and PLR with CD4 count, and linear regression analysis was employed to identify the impact of NLR and PLR on CD4 count. To be considered as a statistically significant finding, the p-value should be <0.05.

RESULTS AND DISCUSSION

HIV Patients Characteristics

Table 1 shows the demographic and clinical profiles of research subjects. A total of 80 HIV patients were included. The majority of patients were ≥35 years old (53.8%), male (66.3%), had a normal BMI (51.3%), and had opportunistic infection (75%). Fifty-five (68.8%) of the patients had duration of ARV treatment for ≤3 months and 48 (60%) used tenofovir-lamivudine-efavirenz (TDF + 3TC + EFV) ARV regimen. Most of patients had CD4 count <200 cells/mm^3 (61.3%), had normal AST (71.3%), and had normal ALT (90%). Also, 44 (55%) patients were anemic.

Table 2 shows the hematological characteristics of the research subjects including neutrophils, lymphocytes, platelets, leukocytes, NLR, PLR, CD4, TLC, hemoglobin, AST, and ALT. The median CD4 at presentation was 103 (2 – 927) cells/mm^3, with the median NLR and PLR were 3.06 (0.87 – 15.94) and 181.03 (69.17 – 741.26), respectively.

Table 3 shows that opportunistic infection, body mass index (BMI), total lymphocyte count (TLC), duration on ARV treatment, and hemoglobin (Hb) were significantly associated with CD4 count.

Table 1. Demographic and Clinical Profiles of HIV Patients

Variables	Frequency (n)	Percentage (%)
Age		
<35 years	37	46.3
≥35 years	43	53.8
Sex		
Male	53	66.3
Female	27	33.8
BMI		
Underweight (<18,5 kg/m^2)	25	31.3
Normal (18,5 – 24,9 kg/m^2)	41	51.3
Overweight (≥25 kg/m^2)	14	17.5

CD4 count		
<200 cells/mm^3	49	61.3
≥200 cells/mm^3	31	38.8
Opportunistic infection		
Without opportunistic infection	20	25
With opportunistic infection	60	75
Candidiasis	19	31.7
Wasting syndrome	19	31.7
Pulmonary tuberculosis	6	10
Pneumonia	4	6.7
Toxoplasmosis	8	13.3
Cytomegalovirus	2	3.3
Pruritic papular eruption	4	6.7
Duration of ARV treatment		
≤3 months	55	68.8
>3 months	25	31.3
ARV regimen		
TDF + 3TC + EFV	48	60
TDF + 3TC + DTG	20	25
AZT + 3TC + NVP	10	12.5
TDF + FTC + EFV	1	1.3
AZT + 3TC + EFV	1	1.3
Liver function test		
Normal AST (5 - 40 µ/l)	57	71.3
High AST (>40 µ/l)	23	28.8
Normal ALT (7 - 56 µ/l)	72	90
High ALT (>56 µ/l)	8	10
Hematological characteristics		
Anemia (<13 g/dl in men, <12 g/dl in women)	44	55
Thrombocytosis (>450 × 10^3/µl)	4	5
Thrombocytopenia (<150 × 10^3/µl)	5	6.3
Lymphopenia (<1000 cells/mm^3)	29	36.4

Table 2. Hematological Characteristics of HIV Patients.

Variables	**Mean ± SD or Median (Range)**
Neutrofil (%)	65.15 ± 12.16*
Limfosit (%)	22.62 ± 10.07*
Platelet (10^3/µl)	287.43 ± 97.01*
Leukosit (10^3/µl)	6.5 (2.4 – 16.3)#
NLR	3.06 (0.87 – 15.94)#
PLR	181.03 (69.17 – 741.26)#
CD4 (cells/mm^3)	103 (2 – 927)#
TLC	1475.6 (3672 – 4661.8)#
Hb (g/dl)	12.25 (8.4 – 16.9)#
ALT (µ/l)	24 (8 – 190)#
AST (µ/l)	29 (15 – 208)#

*) Data with normal distribution are presented in mean ± SD

#) Data with abnormal distribution are presented in median (interquartile range)

Table 3. HIV Patients Characteristics Based on CD4 Count

Variables	CD4 Count				p-value
	<200 cells/mm^3		≥200 cells/mm^3		
	n	%	n	%	
Age					
<35 years	23	46.9	14	45.2	0.877[a]
≥35 years	26	53.1	17	54.8	
Sex					
Male	33	67.3	20	64.5	0.794[a]
Female	16	32.7	11	35.5	
Opportunistic infection					
Without opportunistic infection	4	8.2	16	51.6	0.000[a]
With opportunistic infection	45	91.8	15	48.4	
Duration on ARV treatment					
≤3 months	45	91.8	10	32.3	0.000[a]
>3 months	4	8.2	21	67.7	
Total lymphocyte count					
Normal	20	40.8	31	0	0.000[b]
Lymphopenia	29	59.2	0	100	
Hemoglobin					
Normal	15	30.6	21	67.7	0.000[b]
Anemia	34	69.4	10	32.3	
Body Mass Index (kg/m^2)					
Underweight	20	40.8	5	16.1	0.002[b]
Normal	21	42.9	20	64.5	
Overweight	8	16.3	6	25.8	

Bivariate analysis: a. Chi-Square; b. Pearson Correlation

This study found that the majority of characteristic variables of the patients were associated with CD4 count, except age and gender. This finding is consistent with the cohort study conducted in Cipto Mangunkusumo Hospital, Indonesia, which showed that age and gender were not linked with the increase of CD4 count (p = 0.112; p = 0.554).[12] A cohort study in Africa also proved that age was not a factor that significantly influenced the recovery of CD4 count after undergoing ARV therapy.[13] However, these findings are in contrast to the results of a cohort study in Iran, which revealed that older age affected lower CD4 count.[14] The aging process is linked with the atrophy of the thymus and reduced production of T and B lymphocytes.[15,16] Therefore, older patients can face a higher risk of HIV complications than younger patients due to weakened immune system.[14]

In terms of gender, the majority of the study participants (66.3%) were male. This is consistent with a research by Sajadipour et al.[17] , which found that males had higher rates of HIV infection than females because they engaged in riskier sexual behavior.[17] According to the Chi-Square test analysis results, there was no significant association between gender and CD4 count (p = 0.794). Similarly, study by Yogani et al.[12] also stated that gender was not related to an increase in CD4 count (p = 0.544).[12] In addition, a cohort study in Tanzania has proven that men and women have similar immunological and clinical conditions after one year of ARV treatment.[18]

This study displayed that most patients who have CD4 count lower than 200 cells/mm^3 had opportunistic infections. The bivariate analysis results using the Chi-Square test indicated a significant association

between opportunistic infections and CD4 count (p = 0.000). This result aligns with previous studies, that low CD4 levels were predictor of opportunistic infections.[19,20,21] Patients with CD4 <200 cells/mm^3 were shown to be 4.9 times higher of getting opportunistic infections than patients with CD4 >350 cells/mm^3.[19] The reduction in CD4 T lymphocytes can lead to impaired humoral and cellular immune responses, putting patients with low CD4 levels at risk of being more susceptible to various pathogenic infections.[22]

According to the duration of ARV treatment, it was found that the majority of patients with CD4 count <200 cells/mm^3 were patients undergoing therapy for ≤3 months, while those with CD4 count >200 cells/mm^3 were dominated by patients undergoing therapy for >3 months. The bivariate analysis using the Chi-Square test indicated a significant relationship between the duration of ARV treatment and CD4 count (p = 0.000). CD4 count can increase especially in the first 3 months after ARV initiation and continue to increase for up to 10 years of therapy.[23] This finding is also supported by study by Hidayat et al.[24] which found that ARV therapy for 6, 12, and 24 months had a significant effect on increasing CD4 levels in HIV patients.[24]

A cross-sectional study by Kwantwi et al.[14] in Ghana, West Africa revealed that total lymphocyte count (TLC), hemoglobin (Hb), and body mass index (BMI) could provide prognostic information about CD4 count in HIV patients.[25] Therefore, this study analyzed the relationship between TLC, Hb, and BMI with CD4 count. The analysis using the Pearson test showed that TLC, Hb, and BMI had a significant positive correlation with CD4 count. TLC has a strong positive correlation with CD4 count with a correlation coefficient of r = 0.767. Similar results were found in the study by Ola Wuan et al.[26] involving 121 HIV patients in Kupang, a strong positive correlation was found between TLC and CD4 count (r = 0.799).[26] This finding is also supported by several studies showing that TLC can be a predictor of CD4 levels.[27,28] The study conducted by Chen et al.[26] showed that TLC <1570 cells/mm^3 could be a predictor of CD4 levels <350 cells/mm^3 with a sensitivity of 65% and a specificity of 80%.[27]

This study found a moderate positive correlation between BMI and CD4 count (r = 0.422). Correspondingly, study conducted by Dwiadnyana et al.[29] showed a strong positive correlation between Hb and CD4 count (r = 0.698).[29] The occurrence of cytokine dysregulation, especially the increase in TNF, IL-6, and IFN-γ in HIV infection inhibits the process of erythropoiesis so that Hb levels can decrease along with decreased CD4 levels during the course of infection.[30] As a result, anemia is one of the hematological symptoms that occurs most frequently HIV infection.[31]

This study also found a weak positive correlation between BMI and CD4 count (r = 0.342). Matching results were found in the study of Kwantwi et al.[25], which stated a positive correlation between BMI and CD4 (r = 0.301).[25] Another research by Widiyanti et al.[32] also stated that the BMI value significantly affected increasing CD4 count.[32] BMI is an indicator for assessing nutritional status, which can be a predictor of immune status in HIV patients.[33] A study in China proved that HIV patients with higher baseline BMI had a better immune recovery process.[34]

Correlation between NLR and PLR with CD4 Count

As displayed in Table 4 and Figure 1, this study indicated a strong negative correlation between NLR to the CD4 count (r = -0.648; p = 0.000) and between PLR to the CD4 count (r = -0.668; p = 0.000).

Table 4. Correlation between NLR and PLR with CD4 Count.

Variables	Coefficient Correlation (r)	p-value
NLR	-0.648	0.000
PLR	-0.668	0.000

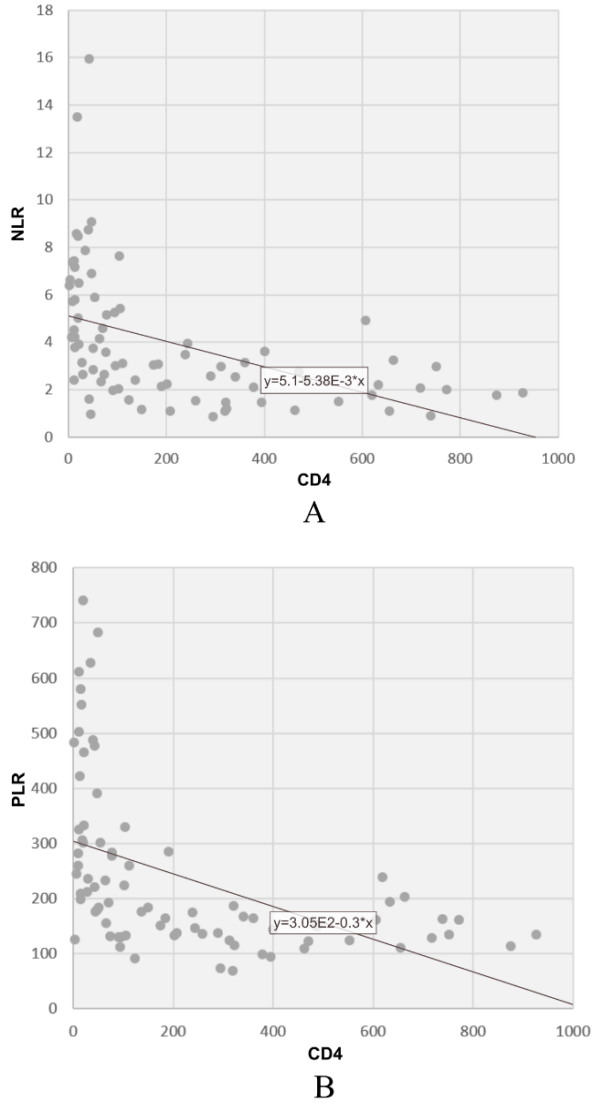

Figure 1. Scatter plot of the correlation between NLR and CD4 (A), PLR and CD4 (B)

Correlation between NLR and CD4 Count

Neutrophil-to-lymphocyte Ratio (NLR) refers to the ratio between neutrophils and lymphocytes which is used as a marker of the progression of various diseases including HIV. NLR combines both types of the body's immune response, lymphocytes as the adaptive immune response and neutrophils as the innate immune response. The Spearman correlation analysis between NLR and CD4 count yielded a correlation value of r = -0.648 which means that the higher the NLR value, the lower the CD4 count. This finding is in accordance with the research carried out by Handayani et al.[35], which found a negative correlation between NLR and CD4 count (r = -0.321; p <0.001).[35]

The discovery of a negative correlation between NLR values and CD4 count is backed by Nugraha dan Suryana's (2021) study on the association between NLR and CD4 with opportunistic infections.[36] The study proved that NLR has a positive correlation with opportunistic infections (r = 0.47; p <0.001), while CD4 has a negative correlation with opportunistic infections (r = -0.69; p <0.001).[36] Opportunistic infections are more common at higher clinical stages and lower CD4 levels.[19] Meanwhile, HIV patients with bacterial infection demonstrated a higher NLR compared to HIV patients who are not infected with bacteria due to an increase in neutrophils, especially during the beginning phases of the inflammatory response.[37] This shows that the increase in NLR occurs linearly with the decrease in CD4.

The opposite result was found in the study of Wande et al.[38] which showed that NLR had a weak positive correlation with CD4 (r = 0.375).[38] NLR values can be influenced by various factors including age, BMI, side effects of treatment for chronic infections such as hepatitis C and hepatitis B, and various chronic conditions, including cancer, diabetes, stroke, malnutrition, and coronary heart disease.[39,40] In addition, neutrophil levels can also decrease in advanced-stage HIV patients due to the cytotoxic effects of the virus and damage to hematopoietic stem cells which causes pancytopenia.[41] This decrease in neutrophil levels can cause a decrease in NLR values along with the decrease in CD4 count as HIV infection develops. Therefore, the use of NLR as a biomarker should consider the factors that can influence it, including medication usage and other medical conditions that affect hematology.

The standard NLR value typically falls within the range of 1 to 2.[40] Contrarily, an NLR value greater than three can indicate pathological conditions like cancer, inflammation, and infection.[40] Our study showed that the median of NLR was 3.06 (0.87 – 15.94) cells/mm^3, which means it has increased from the normal value. Correspondingly, research conducted by Emokpae et al.[42] also found higher NLR values in subjects with HIV compared to the control group.[42]

Increased NLR in HIV infection can occur from increased neutrophil or reduced lymphocyte counts. The increase in neutrophils happens due to basal hyperactivation of polymorphonuclear cells, driven by a greater release of proinflammatory cytokines, including IL-18, IL-22, TGF-B, and IL-8 during chronic inflammation.[43] On the other hand, the decrease in lymphocytes can occur from the decrease in CD4 T lymphocytes as a cytopathic effect of the virus through several mechanisms such as apoptosis, pyroptosis, or direct destruction by viruses.[5] Therefore, the increase in NLR in HIV infection occurs linearly with the decrease in CD4 count.

Correlation between PLR and CD4 Count

Platelet-to-Lymphocyte Ratio (PLR) is the ratio between platelets and lymphocytes which is used as an indicator to assess the progression of various diseases including HIV. A high PLR value can reflect the level of systemic inflammation and infection.[44] The Spearman test finding established a strong negative correlation between PLR and CD4 ($r = -0.668$; $p = 0.000$). This means that the higher the PLR value, the lower the CD4 level.

Although no studies have directly examined the relationship between PLR and CD4, previous study has discussed the prognostic role of PLR in HIV. The cohort study conducted by Raffetti et al.[9] demonstrated that an increasing PLR was linked with the mortality risk among HIV patients.[9] Using the Cox proportional hazard model, it was found that PLR <100 and PLR >200 compared to PLR 100-200 are linked with a higher risk of death.[9]

In HIV infection, increased PLR can occur due to increased platelets and decreased lymphocytes. Increased platelets occur due to dysregulation of various cytokines and coagulation biomarkers such as fibrinogen, fibrin, thrombin, D-dimer, and VWF.[45] Platelet activation levels can also increase due to the presence of viral antigen-antibody complexes and anti-platelet antibodies produced by B lymphocyte cells in response to viruses.[46] This was demonstrated in research conducted by Nkambule et al.[47] which showed higher platelet activation in HIV patients compared to the participants of the control group.[47] Meanwhile, advanced HIV infection can also have a cytopathic effect and induce increased apoptosis of CD4 T lymphocyte cells, causing lymphopenia.[48] Therefore, the increase in PLR in HIV infection occurs linearly with the decrease in CD4 count.

The Roles of NLR and PLR as Predictor of CD4 Count

The linear regression analyses concluded that NLR and PLR significantly influenced the CD4 count ($p = 0.020$; $p = 0.016$) as shown in Table 5. *Nagelkerke R Square* was 0.282 which means that the tested variable had a 28.2% influence on the dependent variable (CD4 count), while other variables outside this research analysis influenced the additional 71.8%.

Table 5. Linear Regression Test.

Variables	B	p-value	*Nagelkerke R Square*
NLR	-25.549	0.020	
PLR	-0.486	0.016	0.282
Constant	436.740	0.000	

The regression model in this multivariate analysis is as follows:

$$Y = 436.740 – 25.549\ X_1 – 0.486\ X_2$$

Y = CD4 count
X_1 = NLR
X_2 = PLR

Our finding in multivariate analysis showed that NLR and PLR had a prognostic role in determining the CD4 count. This result is strengthened by previous research which reported that NLR and PLR could be markers of the progressivity of HIV infection.[9,49] The cohort study conducted by Raffetti et al.[9] regarding the relationship between NLR and PLR with the mortality risk of 8230 HIV patients showed that patients with NLR 2-4 and >4 had a higher mortality risk compared to patients with NLR <2.[9] Also, patients with PLR <100 and PLR >200 had a higher mortality risk than those who had PLR 100-200.[9] Another cohort study also found that HIV patients with Non-AIDS-Defining Cancers (NADCs) who had increased NLR and PLR had a higher risk of death.[50]

A research conducted by Merriman et al.[51] involving 259 HIV patients, proved that increased NLR and PLR could arise among patients who were receiving ARV treatment or patients who were newly diagnosed with uncontrolled infections.[51] This study revealed that increased NLR was associated with patient mortality ($p = 0.0405$).[51] This corresponds with the study by Hanberg et al.[49] which demonstrated a strong relationship between NLR and PLR with patient mortality ($p < 0.0001$).[49]

An increase in NLR and PLR indicates systemic inflammation, which has been shown to increase the risk of mortality in various diseases.[9] Meanwhile, in HIV infection, CD4 count reflects the patient's immunological status and decreased levels of this marker is a factor that can increase the risk of mortality and morbidity.[52] This study identified a significantly strong negative correlation between NLR and PLR on CD4. This is corroborated by the result of the linear regression test, revealing that NLR and PLR contributed to a 28.2% influence on CD4 count. Thus, this study could validate that high NLR and PLR reflect the immunological status and the progressivity of HIV infection as indicated by low CD4 count.

STRENGTH AND LIMITATION

Our study highlights the impact of NLR and PLR in CD4 count and expands previous results about the prognostic role of these two markers. As inflammatory markers, they are cheap and widely available from routine hematology test in limited healthcare settings. This can provide a simple and easy way to determine the immune status of HIV patients as reflected by the CD4 count. There are several limitations such as we have not carried out serial monitoring of the hematological variables throughout the disease course and the data we collected consisted of patients who had varying durations of ARV treatment. Thus, we suggest a further study to investigate the predictive role of NLR and PLR in each disease stage with the larger sample size of HIV patients, which may provide more specific results.

CONCLUSIONS

This study found a significantly strong negative correlation between NLR and PLR to CD4 count in HIV patients, showing that high NLR and PLR could predict decreased immunity in HIV patients as indicated by low CD4 count. In health facilities where access to CD4 count testing is limited, NLR and PLR could serve as alternative prognostic parameters for monitoring treatment outcomes in PLHIV. This could possibly assist clinicians in monitoring HIV patients' immune status, thus contributing to a reduction in HIV-related morbidity and mortality.

ETHICAL CLEARANCE

This research was approved by the Health Research Ethics Committee of Dr. Moewardi Hospital with number 102/II/HREC/2023.

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CONFLICT OF INTEREST

We affirm that there are no conflicts of interest.

AUTHOR CONTRIBUTION

We affirm that all authors have contributed to this work. Each author has been involved in drafting and critically revising the content. All authors have given approval and agree to be accountable for this work.

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