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Original Research Paper

Hematological alteration in HIV patients

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Abstract
HIV is a global health problem still challenging in almost all parts of the world, including Indonesia. HIV AIDS cases in Indonesia continue to increase from year to year. HIV is characterized by a progressive decline in the immune system that contributes to the clinical progression of the disease. Hematological alterations can result from the consequences of HIV. This study aimed to determine hematologic alteration in HIV patients as a predictor of disease severity. The study design was descriptive observational with a cross-sectional approach to see hematological abnormalities in HIV patients at PKU Muhammadiyah Surakarta Hospital. This study produced data that hematological alterations found include anemia in 60% of HIV patients, with the most cases being mild anemia. A small percentage of HIV patients experience leukopenia and thrombocytopenia, which are as much as 8% and 12%. HIV-positive patients have at least one or more cytopenia. Thus, hematologic alteration can independently predict morbidity and mortality and is associated with disease progression and even death.

Keywords: anemia; hematologic alteration; HIV; leukopenia; thrombocytopenia

1. Introduction
HIV is generally known as a global public health issue that remains a health challenge in almost all parts of the world. Based on WHO estimates, there are 38.4 million people with HIV, with a mortality of 650,000 people in 2021 (World Health Organization, 2021).

Even though it is purposed to fluctuate, data toward case of HIV AIDS found in Indonesia keep increasing yearly. In the last 11 years, the amount case of HIV is tended to its peak in 2019, which was 50,282 (Kemenkes RI, 2020). Human immunodeficiency virus (HIV) has the characteristic progressive immune system decline. HIV improves rapid intracellular results and also replication in activation of the host system of immune differentiated by releasing pro-inflammatory chemokines and also cytokines, activation of polyclonal B cell, and also progressive decline in CD4+T cells. This kind of activation and inflammation elp the clinical progression of the disease found in people. The virus can also attach to CD4+ negative cells of blood, for example erythrocytes, in complement receptor type 1 (CR1) presence, or called as c3b/c4b or CD35 receptors (Bhardwaj et al., 2020). CD4 levels in advanced HIV patients are found in very low numbers, so that they can interfere with the immune system response of DTH and CMI. It will also affect the disruption of infection control (Bell & Noursadeghi, 2018).

Hematological and/or cytopenic abnormalities are the most general consequences of HIV AIDS and a major predictor of infection of HIV in people with HIV/AIDS, related to cronical risk of disease and also death (Tilahun et al., 2022). The causes of cytopenia in infection of HIV are multifactorial, such as direct consequences of infection of HIV, effects of drug, co-infection of hepatitis B virus, opportunistic infections and also virus of hepatitis C and others. The pathophysiology of cytopenia can be broadly classified as abnormalities in production of bone marrow and making destruction of peripheral blood cells (Gebreweld et al., 2020).

Anemia has been associated with various consequences that reduce patients' quality of life. Anemia can cause fatigue, congestive heart failure, and increase the risk of HIV-related dementia. HIV has been shown to induce anemia by directly infecting hematopoietic progenitor cells or inducing autoantibodies against erythropoietin (Deressa et al., 2018). Leukopenia is also general, but it can become partly due to lymphocytopenia related to infection of HIV (Ciccacci et al., 2020). Thrombocytopenia is a decrease in platelet survival due to the increased destruction of peripheral platelets mediated by the presence of antiplatelet antibodies or immune complexes bound to platelets, and also impaired platelet production due to bone marrow suppression by myelosuppressive drugs. Thrombocytopenia is also associated with increased morbidity and HIV patients mortality relating to the bleeding risk (Deressa et al., 2018). However, according to research conducted by Parinitha & Kulkani (2012), thrombocytopenia is not very significantly seen along with the progression of the disease (Parinitha &; Kulkarni, 2012).

The frequency and severity of hematologic manifestations can affect CD4 cell counts related to disease progression and patient survival. So it is important to carry out HIV treatment simultaneously with the emerging hematological manifestations to reduce morbidity. However, until now, not much research has been done on this matter. Thus, this research was done on purpose to help determine the presence of hematological alterations in HIV patients as a predictor of disease severity.

2. Research Methods

This study applied kind of analytical observational hrough a cross-sectional approach at PKU Muhammadiyah Surakarta Hospital. The samples in this study were all HIV patients undergoing treatment, both men and women aged 18 years or older, at PKU Muhammadiyah Surakarta Hospital. HIV patients who had hematology examination data were also included in this study. HIV patients with comorbidities such as pulmonary tuberculosis or a history of lung malignancy were excluded to avoid research bias. The sampling technique is carried out using non-probability techniques by purposive sampling. This study used a research instrument in the form of secondary data obtained from patient medical records. This research has received a letter of ethics from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Universitas Muhammadiyah Surakarta, with number 4358A/B.1/KEPK-FKUMS/VIII/2022.

3. Results and Discussion

3.1.Result

The study was conducted on HIV patients undergoing treatment at PKU Muhammadiyah Surakarta Hospital by taking secondary data from medical records of HIV patients at PKU Muhammadiyah Surakarta Hospital. The results of data analysis showed that the sample in this study amounted to 25 patients who fit the criteria for inclusion and exclusion of the study as follows:

Table 1. Research Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion Criteria
Male and Female gender Age ≥18 years Have hematology examination data	Have comorbid diseases such as pulmonary tuberculosis and pulmonary malignancies

Source: Secondary data, 2022

It was found that HIV patients were more found in the male sex with 16 people (64%) than the female sex, which was 9 people (36%).

Table 2. Frequency Distribution of Subjects by Gender

HIV patients	Total	Percentage (%)
Male	16	64
Female	9	36
	25	**100**

Source: Secondary data, 2022

HIV patients without anemia counted 10 people (40%), mild anemia reported are 9 people (36%), moderate anemia reported are 5 people (20%), and severe anemia as many as 1 person (4%) with a mean deviation (mean SD) 11.564±2.04.

Table 3. Frequency Distribution of Subjects by Degree of Anemia

HIV patients	Total	Percentage (%)
No anemia	10	40
Mild anemia	9	36
Moderate anemia	5	20
Severe anemia	1	4
	25	**100**

Source: Secondary data, 2022

HIV patients with leukopenia numbered 2 people (8%) and without leukopenia numbered 23 people (92%) with a mean SD of 6,985 ± 2.30.

Table 4. Distribution of Subject Frequency by Leukopenia Condition

HIV Patients	Total	Percentage (%)
Leukopenia	2	8
Normal	23	92
	25	**100**

Source: Secondary data, 2022

HIV patients with thrombocytopenia numbered 3 people (12%) while 88% did not experience thrombocytopenia.

Table 5. Distribution of Subject Frequency by Thrombocytopenia Conditions

HIV patients	Total	Percentage (%)
Thrombocytopenia	3	12
Normal	22	88
	25	**100**

Source: Secondary data, 2022

3.2.Discussion

In this study, the highest percentage for the gender category was 64% men, while women were 36%. A similar percentage of comparison was obtained in Bhardwaj et al. (2020) research with men at 57.5% and women at 42.5%, most other studies have a greater percentage of women than men (Bhardwaj et al., 2020). These findings are supported with Sajadipour et al. (2022) study which states that men suffer more HIV than women. This can occur due to several factors, including employment, drug abuse, a imprisonment history, unsafe sex, heterosexuality, and making a sex partner who has HIV (Sajadipour et al., 2022).

Hematologic disorders for example anemia, thrombocytopenia, leukopenia, coagulopathy, neutropenia, and vascular malignancy are common in people live while having HIV AIDS (Durandt et al., 2019). Balogun et al. (2020) research anemia was found in 72 (29.2%), leukopenia in 20 (8%) and thrombocytopenia in 6 (2.4%) patients (Balogun et al., 2020). Mild and moderate anemia was observed in 14 people (56%) covering more than half of the patients while severe anemia was observed in only 1 patient (4%) and another 40% did not have anemia. Ciccacci et al. (2020) research he observed that 66.1% of the study participants were anemic. In a study involving 22,657 participants, the study explained that severe and moderate anemia was found in 8.2% and 21.9% and stated that the risk of early mortality increased as the severity of anemia increased (Ciccacci et al., 2020). It is supported by Fiseha et al. (2017) and Ageru et al. (2019) study which states that mild anemia is more common in HIV patients than moderate to severe anemia (Ageru et al., 2019; Fiseha et al., 2017).

Leukopenia is observed in only 12% of patients. Research conducted by Gebreweld et al. (2020) stated that as many as 13.8% of participants experienced leukopenia. Then the participants had been on HAART therapy for at least 6 months (Gebreweld et al., 2020). Few patients with leukopenia in HIV

can be affected by the consumption of ART. Talargia et al. (2021) research states that the leukopenia, neutropenia, and lymphopenia prevalence is 7.0%, 20.9%, and also 6.6% before starting ART and also 15.4%, 1.1, and 4.4% after starting ART (Talargia et al., 2021).

There was a decrease in the incidence of leukemia from 22.19% to 13.58% in study participants at baseline before starting ARV with patients who had undergone ARV therapy for 6 months (Vaswani et al., 2022). Meanwhile, another study observed an increased incidence of leukopenia after starting antiretroviral therapy (Damtie et al., 2021; Duguma et al., 2021; Tilahun et al., 2022). This difference can occur due to differences in the immune status of samples, differences in the nature of research samples, and the clinical stage of HIV AIDS (Bisetegn & Ebrahim, 2021; Gunda et al., 2017).

Thrombocytopenia is observed in 12% of patients. Ciccacci et al. (2020) research found 2.9% of study participants who had thrombocytopenia in baseline (Ciccacci et al., 2020). Administration of antiretroviral drugs seems to reduce thrombocytopenia rates in HIV patients compared to before starting therapy (Damtie et al., 2021; Duguma et al., 2021; Tilahun et al., 2022; Vaswani et al., 2022). In line with Tan et al. (2023) research which stated that the entire platelet count at the time after the treatment given was higher than before ($Z = -5{,}662$, $P < .001$) (So et al., 2023). A research in Uganda stated that the thrombocytopenia prevalence was 17.8% in patients of HIV who had never used antiretrovirals and HAART was 13.0% in patients taking ART for up to 6 months (Taremwa et al., 2015).

Infection of human immunodeficiency virus (HIV) is often related to obvious abnormalities of hematologic (Deressa et al., 2018). Over time, haematological abnormalities had been reported as independent morbidity and mortality predictors in HIV-infected patients and are associated with disease progression and even death (Katemba et al., 2018; Tilahun et al., 2022). According to Vaughan et al. (2017) research of the 307 patients of HIV-positive, 63.2% had one or more cytopenia (Vaughan et al., 2017).

Anemia is one of the hematologic problems often observed in patients with HIV infection. Anemia has an incidence varying from 30% to 95%, with the greatest burden in patients with advanced disease (Deressa et al., 2018). The factor caused of anemia in infection of HIV can be multifactorial and are found according to stage of HIV disease, age, sex, pregnancy status, and incidence of potential infections (Duguma et al., 2021). Normochromic normocytic anemia is the most commonly observed anemia type as an example in a study conducted in Ethiopia (Berhane et al., 2020; Turner et al., 2022). So, it is important to monitor the degree and relevant factors of anemia in vulnerable groups, especially in inadequate settings to improve disease treatment options (Deressa et al., 2018).

Leukopenia is known general, but it can be caused by lymphocytopenia related to infection of HIV (Ciccacci et al., 2020). Neutropenia can be such as general leukopenia that is found in 5-30% of patients with early symptoms of HIV case and up to 70% of the patients in advanced stages of AIDS (Shi et al., 2014). Like other cytopenia, the causes of HIV-related neutropenia are multifactorial, such as direct consequences of infection of HIV, opportunistic infections, disorders of autoimmune, HIV therapeutic malignancies, drugs such as antiretroviral therapy (especially regiman containing AZT), and opportunistic infections (Gebreweld et al., 2020).

A research in Ghana resulted that the neutropenia, leukopenia, and lymphopenia prevalence was 13%, 72.5%, and 6.5% in patients before ART and also for about 6.5%, 85%, and 18% in patients of post-ART (Samuel Kwadwo & Emmanuel Awusah, 2018). leukopenia and lymphopenia prevalence that has decreased CD4 counts was combined before starting ART, but not significantly after starting ART. It can be made by ART leading to a statistical increase in leukocyte counts (Ako et al., 2018).

Leukopenia is common in HIV patients who are already in an advanced stage. An absolute decrease in CD4 T lymphocyte count is the main factor of the development of opportunistic infections and also is the earliest immunological abnormality of HIV infection (Wan Mohamad et al., 2018). There is a decrease in the granulocyte progenitor cells production and the formation of granulocyte-monocyte colony units in the spinal cord in HIV patients (Hanif et al., 2020).

Thrombocytopenia is a decrease in platelets caused by increased destruction of peripheral platelets mediated by antiplatelet antibodies or immune complexes bound to platelets, and also impaired platelet production because the suppression of bone marrow by myelosuppressive drugs (Duguma et al., 2021). The causes of changes in platelet levels in people with HIV AIDS (ODHA) are multifactorial and can result from peripheral platelet damage or decreased platelet production (Vishnu & Aboulafia, 2015).

Thrombocytopenia was detected in 6.3% of the study participants. All thrombocytopenia subjects were on ART, and 60% were in the age group over 40 years (Deressa et al., 2018). The occurrence of

thrombocytopenia and anemia in HIV patients is exacerbated by an increased CD4+ CD4+ T lymphocyte count of <200 cells/uL, viral load, and co-infection or opportunistic infections (Marchionatti & Parisi, 2021). Another research in Ethiopia resulted that, thrombocytopenia prevalence was 4.1% in some patients with HAART and also 9% in patients who had never used HAART (Enawgaw et al., 2014). Thrombocytopenia tends to improve with the use of HAART (O'Bryan et al., 2015).

Asia, studies cross sectional run in India indicated an 18% thrombocytopenia prevalence. A study cross sectional in China, haf such a large sample of recently diagnosed PLHIV, resulted a prevalence of thrombocytopenia for about 15.6% (Shen et al., 2015), while another research in the same country on PLHIV who had never used ART found the prevalence of thrombocytopenia was only 4.5% (Fan et al., 2015).

The main target of HIV infection is immune cells, especially those that express CD4 molecules, so they can suppress and cause a progressive decline in function in CD4 cells and macrophages (Tjokropawiro, 2015). A normal CD4 cell count is 410-1,590 cells/mL of blood. The lower the CD4 level in the body, the human immunity decreases, so it is easy to get sick or can experience opportunistic infections. Low CD4 levels are found in people with immunosuppressed diseases, such as HIV. The more severe the condition of the HIV patient, the lower the CD4 cell count (Ladyani & Kiristianingsih, 2019).

Studies done in Uganda and Nigeria reported 65% and 59.8% of participants had at least one form of respectively blood cytopenia (Denue et al., 2013; Kyeyune et al., 2014). The incidence of hematologic abnormalities increases with a downgrade in the CD4+ T cell count. Patients who showed CD4+ T cell counts of <200 cells/µL had a greater risk of leukopenia, anemia, and also neutropenia before starting ART treatment, whereas these abnormalities decreased significantly after starting ART (Duguma et al., 2021). The findings of several research indicate that patients of HIV with CD4+ T cells <200 cells/ul and naïve HAART have a higher risk of developing anemia, this may occur due to erythropoiesis dysfunction due to increased viral load in line with decreased immunity (Deressa et al., 2018). HIV patients before starting HAART therapy with CD4+ T cells <200 cells/ul 4.2 and 3.2 times more prone to anemia and also leukopenia than patients with CD4+ T cells <500 cells/ul (Duguma et al., 2021). In line with Turzillo et al. (2018) research states that ARV treatment can increase CD4 lymphocyte count in HIV AIDS patients (Turzillo et al., 2018). Studies conducted by Tilahun et al. (2022) states that decreased CD4+ T cells are not related to anemia but are associated with leukopenia and thrombocytopenia (Tamir et al., 2019; Wondimeneh et al., 2014). The observed incidence of anemia and thrombocytopenia is not associated with the clinical stage of HIV sufferers, but patients with clinical stage 4 are more likely to develop leukopenia (Tilahun et al., 2022). Like Duguma et al. (2021) research which states that there is an association of CD4+ T cell count <200 cells/ul with hematologic abnormalities in patients before initiation of HAART therapy, but no significant relation is observed of hematologic abnormalities and also CD4+ T cell count category in patients with HAART (Duguma et al., 2021).

Patients with naïve HAART have a significant association with anemia, showing the role of HAART in reducing the risk of anemia (Deressa et al., 2018; Fent et al., 2020; Woldeamanuel & Wondimu, 2018). A decrease in anemia after initiation of HAART shows the HAART efficacy in lowering viral load which further contributes to the differentiation and also blood cells survival (Damtie et al., 2021). The formulation of antiretroviral drugs used can have a positive and negative effect on hematological parameters, although some medications used as therapy for HIV-related diseases are myelosuppressive, the use of zidovudine is the most common cause of severe cytopenia (Damtie et al., 2021). Several studies have reported that HAART therapy has reduced the prevalence of thrombocytopenia However, there are also a large number of reports indicating the occurrence of these hematologic abnormalities occurs even in patients receiving ART (Deressa et al., 2018).

Hematological parameters for HIV can also be applied to pregnant women. Pregnant women with HIV have significantly lower hematocrit and leukocytes and higher ESR than pregnant women without HIV (P<0.000). There was no statistically significant difference between the two groups in terms of platelets and reticulocytes (P>0.05). However, among HIV-positive pregnant women, women with CD4 counts of <350/µL had statistically lower leukocyte and lymphocyte counts than women with CD4 counts of ≥350/µL (P<0.05), while women taking zidovudine (AZT) treatment had lower hematocrit values and statistically higher cell volume averages compared to women without AZT (P< 0.05),

however, there was no statistically significant difference in hematologic parameters (P>0.050) between HIV-positive pregnant women with first- and second-line ARVs (Abdulqadir et al., 2018).

4. Conclusion

Based on the results of studies that have been conducted, it can be concluded that anemia is observed in 60% of patients and most have mild anemia. The causes of anemia in HIV infection are multifactorial and are found depending on the stage of HIV disease, age, sex, pregnancy status, and incidence of opportunistic infections. Only a small percentage of patients develop leukopenia and thrombocytopenia, which are 8% and 12%. This can occur due to multifactorial, including direct consequences of HIV infection, autoimmune disorders, opportunistic infections, malignancies, HIV therapeutic drugs such as antiretroviral therapy (especially regiman containing zidovudine) and opportunistic infections. Thus, it is hoped that this study can be the basis for future research on the relationship of hematological alteration in HIV patients as a predictor of disease severity.

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