CORRELATIONS BETWEEN CLUSTER DIFFERENTIATION 4 COUNTS, HUMAN IMMUNODEFICIENCY VIRUS CLINICAL STAGES, AND HEMOGLOBIN LEVEL AMONG HUMAN IMMUNODEFICIENCY VIRUS PATIENTS WITH ANEMIA IN MERPATI CLINIC, WANGAYA HOSPITAL, DENPASAR, BALI, INDONESIA: A CROSS-SECTIONAL STUDY

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ABSTRACT

Objective: The objective of this study was to determine the correlation between cluster of differentiation 4 (CD4) counts, human immunodeficiency virus (HIV) clinical stages, and hemoglobin (Hb) level among HIV-infected patients with anemia.

Methods: A cross-sectional study was conducted in November 2017 at Merpati Clinic of Wangaya Hospital, Denpasar, Bali, Indonesia. We selected 79 HIV patients with anemia to participate in our study. We grouped CD4 counts into two categories: <200 cells/μL and ≥200 cells/μL, and we classified the HIV clinical stages into HIV and acquired immunodeficiency syndrome (AIDS).

Results: About 55.7% (44) of men and 44.3% (35) of women were participated in this study. As many as, 91.1% (72) of participants were AIDS patients. The mean Hb was 8.77 g/dl with SD 1.79 g/dl. 81% (64) of study participants were suffered from anemia on chronic disease or inflammatory anemia, and 19% (15) of study participants were suffered from iron deficiency anemia. The median for CD4 counts was 94 cells/μL (3–309 cells/μL) with as many as 78.5% (62) of participants were found to have low CD4 counts (<200 cells/μL). Spearman analysis revealed a positive correlation between CD4 counts and Hb level (r=0.427, p<0.001). Independent sample t-test analysis found a correlation between the HIV clinical stages and Hb level. There was a difference between the mean of Hb level in each stage with the average difference of 0.8 g/dl (95% confidence interval 0.04–1.6; p<0.04).

Conclusions: There is a correlation between CD4 counts, HIV clinical stages, and Hb level among HIV patients with anemia.

Keywords: Human immunodeficiency virus clinical stages, Cluster differentiation 4 counts, Anemia.

INTRODUCTION

Anemia is the most common hematologic disorder associated with human immunodeficiency virus (HIV) infection affecting 60–80% of patients in the late stages of HIV at various cluster of differentiation 4 (CD4) levels and with various causes [1-3].

The pathophysiology of HIV-related anemia involves three basic mechanisms, which are decreased red blood cell production, increased red blood cell destruction, and ineffective production of red blood cells. Anemia can also be a result of nutritional deficiency, most commonly iron, folic acid, and Vitamin B12. Vitamin B12 deficiency is associated with malabsorption in the ileum or due to gastric pathological processes caused by infections affecting the gastric mucosa in patients with HIV [4-6].

Although anemia can occur in any stages of HIV infection, its severity positively correlates with progression of the disease and mortality [7].

Owiredu *et al*. reported that highly active antiretroviral therapy can increase B12 serum level; however, they do not describe symptoms associated with B12 deficiency such as macroscopic anemia and neuropathy. Anemia independently decreases the survival of the patient (HR 2.6, 95% confidence interval [CI] 1.9–3.4), improves disease progression, and increases mortality in HIV-infected individuals [6,8-29].

The incidence of anemia increases annually with the progression of the disease, affecting 3% of all asymptomatic HIV infection patients, 12% of asymptomatic patients with CD4<200/μL, and 37% of patients with acquired immunodeficiency syndrome (AIDS). The risk of anemia increases in African-American race, older age, low body mass index, history of pneumonia, oral candidiasis, history of fever, use of zidovudine (ZDV), low CD4 cell counts, and high HIV-1 RNA levels in plasma. ZDV was reported as a cause of hematological disorders, especially, anemia at weeks 4–12 of ZDV initiation [11-21,30-47].

The causes of anemia in HIV patients are multifactorial, such as the HIV itself, opportunistic infection, immune mechanisms, malignancies, and drugs. Nutritional anemia in HIV patients due to an inadequate diet intake and malabsorption. High viremia, decreased CD4 counts, and severity of anemia (lower hemoglobin [Hb] levels) are associated with increased morbidity and mortality in HIV-infected patients [3,7,8,11,14].

This study was to evaluate the correlation of anemia to CD4 counts and HIV clinical stages in HIV patients were visited to Merpati Clinic, Wangaya hospital, Denpasar, Bali, Indonesia.

METHODS

A cross-sectional study was conducted in November 2017 at Merpati Clinic of Wangaya Hospital, Denpasar, Bali. Ethical clearance was

obtained No: 05/RSUDW/Litbang/2017 from the local ethical committees. We collected data from a patient who visited Merpati Clinic and completed at least 1 year follow-up from the ethical clearance granted date.

Research purposes
This study aimed to determine the correlations between CD4 counts, HIV clinical stages, and Hb level among HIV patients with anemia.

Research design
A cross-sectional study was conducted at Merpati Clinic, Wangaya Hospital, Denpasar, Bali-Indonesia. We recruited 79 HIV patients with various stages of anemia.

Population and duration of the study
The study participants were HIV patient with various stages of anemia visiting the outpatient services of Merpati Clinic, Wangaya Hospital, Denpasar, Bali, Indonesia. The participants were aged between 18 and 65 years old. The study was conducted in November 2017.

Sample size
Using a consecutive sampling technique, we included a total of 79 patients. Every patient who met the criteria was selected until we reached the desired sample size. The inclusion criteria included HIV patients with anemia, aged over 18 years old. We excluded pregnant and lactating women, patients with chronic renal impairment, and patients with thalassemia.

Variables and data sources
Our study variables included CD4 counts, HIV clinical stages, and Hb levels. We also collected data on social demographic characteristics such as age, sex, and other laboratory parameters.

Data analysis
We used a structured questionnaire to obtain data on sociodemographic characteristics. The HIV clinical stages of all participants were determined using the World Health Organization (WHO) guideline and were grouped as clinical HIV and advanced clinical form of AIDS.

CD4 parameters were measured following the recommended guideline and were grouped into two categories: CD4 ≥200 cells/µL and <200 cells/µL. Hb level was obtained from routine hematology test and was grouped into four groups: Mild anemia (Hb: 10–11.9 g/dl), moderate anemia (Hb: 9.9–7 g/dl), severe anemia (Hb: 6.9–4 g/dl), and very severe anemia (Hb: 4 g/dl).

We displayed the average and standard deviation for all numerical or continuous variables. However, we used median and interquartile range for all data that were not normally distributed. Categorical data were presented in relative frequency (number and percent). We performed the non-parametric analysis to determine correlations of each independent variable with Hb level. We used the precision value of 95% (p<0.05). All data analysis was performed using SPSS software for Windows version 24.0.

RESULTS

A total of 79 individuals with HIV infection in various stages of anemia were participated in this study. The sociodemographic characteristics are presented in Table 2.

The WHO defines anemia as Hb level under 13 g/dl for men and under 12 g/dl for women. For the purpose of this study, we used the classification as depicted in Table 1 [6].

The age data were not normally distributed when tested using the Kolmogorov–Smirnov test. The median of age data for all participants was 37 years old, with the youngest of 20 years old and the oldest of 75 years old. The body mass index was normally distributed with a mean of 18.65 kg/m² (SD±2.86 kg/m²). The overall CD4 counts of the

participants were not normally distributed. The median of CD4 counts of all participants was 94 cells/µL with the lowest of 3 cells/µL and the

Table 1: Staging of anemia severity [6]

Anemia severity	Hb (g/dl)
Mild	10–11.9
Moderate	9.9–7
Severe	6.9–4
Very severe	<4

Table 2: The sociodemographic characteristics of participants (sex, education, marital status, anemia morphology, anemia severity, HIV severity, and opportunistic infection)

Variables	n (%)
Sex	
Male	44 (55.7)
Female	35 (44.3)
Education	
Non-formal education	2 (2.5)
Elementary school	6 (7.6)
Junior high school	19 (24.1)
High school	45 (57.0)
University	7 (8.9)
Marital status	
Marriage	60 (75.9)
Single	11 (13.9)
Widow/widower	8 (10.1)
Anemia morphology	
ACD	64 (81.0)
IDA	15 (19.0)
Anemia severity	
Mild	20 (25.3)
Moderate	47 (59.5)
Severe	10 (12.7)
Very severe	2 (2.5)
CD4 lymphocyte count (Cells/µL)	
<200	62 (78.5)
≥200	17 (21.5)
Chest X-ray	
Normal	19 (24.1)
Tuberculosis and/or pneumonia	60 (75.9)
Stage of HIV	
HIV	7 (8.9)
AIDS	72 (91.1)
Opportunistic infection	
Without opportunistic infection	8 (10.1)
With opportunistic infection	71 (89.9)

n=79, Values are numbers or numbers (%). CD4: Cluster of differentiation 4, HIV: Human immunodeficieny virus, AIDS: Acquired immunodeficieny syndrome, ACD: Anemia of chronic disease, IDA: Iron deficiency anemia

Table 3: Participants' characteristic (age, height, weight, BMI, and hematologic data)

Characteristic	Mean±SD/median (minimum–maximum)
Age (year)	37 (20–75)
Height (cm)	160 (148–185)
Weight (kg)	50 (30–78)
BMI (kg/m²)	18.65±2.86
Hematologic data	
Hb (g/dl)	8.77±1.79
SI (mg/L)	42 (7–187)
TIBC (mg/mL)	104 (37–602)
Ferritin (µg/ml)	425 (16–678)
Lymphocyte (%)	14.1 (1.7–41.4)
CD4 counts (cells/µL)	94 (3–309)

n=79, Values are numbers or numbers (range). Data are expressed as mean±SD. SD: Standard deviation, Hb: Hemoglobin, BMI: Body mass index, CD4: Cluster of differentiation 4, SI: Serum iron, TIBC: Total iron binding capacity

highest of 309 cells/µL. The Hb levels of all participants were normally distributed with mean values of 8.77 g/dl (SD±1.79 g/dl (Table 3).

Correlation between CD4 counts and Hb levels
Due to the CD4 counts, data were not normally distributed, and we performed a non-parametric correlation (Spearman) analysis to determine the correlation between CD4 counts and Hb level (Table 4).

The relationship between clinical stage and Hb levels
Independent sample t-test was performed to assess the relationship between HIV clinical stages and Hb levels (Table 5).

DISCUSSION

Correlation between CD4 counts and Hb levels
Anemia is one of the most common abnormalities seen in HIV. The severity of anemia correlates with the late clinical HIV stage and low CD4 counts. An increased number of viruses along with the development of HIV was followed by the release of inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1, and interferon gamma. The cytokines have been shown to inhibit red cell production (erythropoiesis) and myelosuppression. TNF levels were found to be consistently elevated in HIV infection, and this condition is correlated with viral load. As HIV disease progresses, the severity of anemia also increases [12,17,23,27,31-41].

This study found a moderate positive correlation between CD4 counts and Hb level (r=0.427; p<0.001).

Obirikorang and Yeboah, 2009, in a prospective case–control study involving 228 individuals with HIV in Ghana, also found a positive correlation between Hb levels and CD4 counts (r=0.1755; p<0.0001) [22].

Hb is an easy and cheap parameter that can be used to predict morbidity and mortality of a progression of HIV infection. Hb monitoring can alert clinicians regarding anemia conditions of HIV patients and to determine anemia treatments required or not.

Similar studies by Paras *et al.*, 2017, found that low CD4 counts were significantly associated with anemia (p=0.0001) [23,29,30,42].

Moore *et al.*, 1998, found that anemia therapy using erythropoietin was associated with improved prognosis allowing a long-term administration of ZDV.

Table 4: Correlation between CD4 counts and Hb levels

Variables	Mean±SD (minimum–maximum)	r	p-value
CD4 counts	94 (3–309) cell/µL	0.427	<0.001**
Hb levels	8.8±1.8 g/dl		

n=79, Values are numbers or numbers (range). Data are expressed as mean±SD. SD: Standard deviation, p<0.05 is statistically significant, CD4: Cluster of differentiation 4. In the data analysis, there was a significant moderate positive correlation (r=0.472) between CD4 counts and Hb level (p<0.001), Hb: Hemoglobin

Table 5: The relationship between HIV clinical stages and Hb levels

Variable	HIV clinical stages	
	HIV (n=7)	AIDS (n=72)
Hb	9.5±0.8	8.7±1.8

n=79, Data are expressed as mean±SD. SD: Standard deviation, HIV: Human immunodeficieny virus, AIDS: Acquired immunodeficieny syndrome, Mean of Hb levels among participants with HIV was 9.5±0.8 and in participants with AIDS 8.7±1.8. The data analysis found a statistically significant mean difference of Hb level among HIV and AIDS patients (95% CI 0.04–1.64; p<0.04), Hb: Hemoglobin

A cross-sectional study of Hb measurements has consistently shown to play an important role in the basic management of HIV disease in West Africa [24,25,28,43].

However, Alavi *et al.*, 2009, found that there was no correlation between CD4 counts and Hb levels (r=0.451; p=0.056). This finding might be confounded by malnutrition and various socioeconomic factors, including a history living in prison and the use of injecting narcotics resulting in chronic anemia and low Hb levels. Moreover, three-quarters of the participants in their study were injecting drug users that misappropriately represent the true HIV situation [26,44,45].

The clinical staging of HIV infection with Hb levels
HIV infection is caused a gradual loss of CD4 counts. Loss of CD4 counts and systemic immune activation are the major hallmarks of HIV infection. Systemic immune activation is characterized by massive production of pro-inflammatory cytokines [14,17,19,23].

This study revealed a significant relationship between HIV clinical stages and Hb levels. The mean Hb level among HIV stage was 9.5±0.8 g/dl and the mean Hb among AIDS stage was lower: 8.7±1.8 g/dl. An average difference between HIV and AIDS patients was 0.8 g/dl (95% CI 0.04–1.64; p<0.04). This finding indicates that the severity of anemia increases with the progression of the HIV clinical stages.

Similar studies in India by Mathews *et al.*, 2013, with 187 participants found a higher proportion of anemia among patients in AIDS than pre-AIDS clinical stages [27].

Alavi *et al.*, 2009, in a cross-sectional study conducted in India with 306 participants, aimed to examine the incidence of anemia and its association with the WHO-based clinical staging and found that the proportion of anemia was higher among patients with HIV stage 4 (33.3%) when compared with stage 1 (1.2%). They also found that the severity of anemia increases with HIV clinical stages (p=0.0001) [23].

CONCLUSIONS

Anemia is a common problem among HIV-infected patients, as a result of chronic inflammation or antiretroviral therapy. This study shows that the CD4 counts and HIV clinical stages correlate with Hb level among HIV patients with anemia. The severity of anemia correlates with low CD4 counts and advance HIV clinical stage.

AUTHORS' CONTRIBUTIONS

Ketut Suryana constructing an idea or hypothesis for research and manuscript, planning methodology to reach the conclusion, organizing and supervising the course of the project or the article, financial support, responsibility in data management, reporting, logical interpretation of the results, literature review, and construction of the whole format of the manuscript, and reviewing the article before submission (about spelling, grammar and its scientific aspects). Hamong Suharsono responsibility in logical interpretation and literature review. Gede Budiasa responsibility in the laboratory. Jarwa Antara responsibility in prepare and follow-up the participants, data management and reporting, literature review. Puji Astuti, Ida ayu Indah and Putri Stuti data collecting and reporting.

CONFLICTS OF INTEREST

There were no conflicts of interest among the authors.

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