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# Correlation of CD4/CD8 Ratio with Carotid Intima-Media Layer Thickness in HIV/AIDS Patients at Sanglah General Hospital, Bali, Indonesia

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**Abstract**

**BACKGROUND:** The discovery of antiretroviral (ARV) drugs in 1996 led to a shift in the causes of mortality and morbidity of patients with HIV/AIDS. Initially, the cause of mortality and morbidity was associated with opportunistic infection HIV/AIDS-related complication, but now are more associated with non-AIDS complication such as cardiovascular disease. Atherosclerosis is a major cause of cardiovascular disease. The atherosclerosis was assessed by measuring carotid intima-media thickness (CIMT) using B mode ultrasound (USG), which is one of the diagnostic tools in indicating the presence of atherosclerotic plaque.

**AIM:** This study aims to evaluate the ratio of CD4 / CD8 towards carotid intima-media thickness.

**METHODS:** Design of study was analytic cross-sectional. This study was conducted in May – July 2017 in HIV patients who taken consecutively came to the VCT polyclinic of Sanglah hospital. Statistical analysis used Spearman correlation test to evaluate the correlation between the CD4/CD8 ratio and carotid intima-media thickness and multiple linear regression to predict carotid intima-media thickness through CD4/CD8 ratio.

**RESULTS:** Total from 50 samples, data characteristic were 33 males (66%) and 17 females (34%), mean of age 30.60 ± 5.58 years, median of CD4/CD8 ratio 0.275 (0.02-1.39) and median of CIMT 0.75 (0.4-1.5) mm. There is a strong negative correlation (r = -0.85; p = 0.001) CD4/CD8 ratio with CIMT. The calculation of the prediction of carotid intima media thickness can be calculated through the equation Y = 0.727 -0.791 (X1) + 0.012 (X2), where X1 is CD4/CD8 ratio and X2 is the age of the patient.

**CONCLUSION:** there is a significantly strong negative correlation between the CD4/CD8 ratio and CIMT in HIV patient who comes to VCT polyclinic of Sanglah Hospital. The smaller CD4/CD8 ratio, the value of CIMT will be thicker, and vice versa.

## Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the human immune system. This loss of function causes a progressive immune system response disorder, which then develops into Acquired Immunodeficiency Syndrome (AIDS). Characteristics of this disease in the form of a decline in the immune system that causes opportunistic infections, secondary neoplasm, and other neurological manifestations

The discovery of antiretroviral drugs (ARVs) in 1996 is considered one of the successes in medicine in controlling HIV infection. The presence of antiretroviral drugs causes a shift in the causes of morbidity and mortality of patients with HIV/AIDS infection. Initially, the causes of morbidity and mortality were associated with opportunistic infections associated with HIV, but now more morbidity and mortality are associated with non-AIDS complications such as cardiovascular disease, renal impairment, liver disease, neurocognitive disorders, osteoporosis, muscle atrophy, and frailty [1]. Pacheco et al., (2009) conducted a cohort study in 1538 HIV-infected patients and had taken ARVs from 1997-2006, found that 226 (14.7%) died during the study, 43.4% had non-AIDS-related complications, 37.6% had complications of opportunistic infections. Deaths associated with HIV/AIDS infection experienced a significant decrease over time (p < 0.01). In the 2005-

2006 period, it was found that non-AIDS-related deaths were higher than AIDS-related deaths [2].

Cardiovascular disease is an important cause of morbidity and mortality in HIV/AIDS patients. Patients with HIV/AIDS have a higher risk of having myocardial infarction and death due to cardiovascular disorders. The mortality rate of cardiovascular events in HIV/AIDS patients in Europe and North America reached 6.5%-15% [1]. Rates of hospitalization for coronary heart disease and acute myocardial infarction in HIV positive are higher than HIV negative person (6.5% versus 3.8%, p = 0.003, 4.3% versus 2.9%, p = 0.07) [3].

Atherosclerosis is a major cause of cardiovascular disease. Atherosclerosis in HIV patients occurs younger than the general population, beginning at < 30 years with an average age of 48 years. Although HIV infection itself also facilitates atherosclerosis. Atherosclerosis associated with ageing and its major pathogenesis is the occurrence of inflammatory processes. While in HIV patients, there is a chronic inflammatory process that affects the presence of premature ageing syndrome. Therefore, in HIV patients, more easily, the occurrence of atherosclerosis than with no HIV infection [4], [5], [6].

The diagnosis of early atherosclerosis is made by measuring the thickness of the carotid arteries intima tunica and the presence of atherosclerotic plaque. Measurement of Carotid intima-media thickness (CIMT) with B-mode ultrasonography (USG) is a sensitive and non-invasive technique for identifying and quantifying subclinical vascular disease and evaluating the risk of cardiovascular disease. CIMT is significantly correlated with the risk of myocardial infarction, stroke, death from coronary heart disease, or a combination of these. Carotid plaque is defined as a focal region in which a CIMT of more than 1.5 mm protrudes into the lumen [7].

Over the past three decades, the number of Cluster Differentiation (CD) 4 was used as an evaluation of HIV clinical management. In a study conducted by Villar et al., (2014), the CD4/CD8 ratio could be used as a marker of inflammation and immunosenescence and as a predictor of mortality in patients with HIV infection. This CD4/CD8 ratio indicates immune activation in people with HIV infection. The smaller the CD4/CD8 ratio, the higher the immune activation. In HIV infection, there will be CD4 cell damage that will cause the CD4 value to drop dramatically. CD4 cell decline will be compensated by continuous CD8 increases. Even with the provision of ARVs, slow CD4 cell recovery is not necessarily followed by a direct decrease in CD8 cells so that immune activation occurs continuously. This will lead to a smaller CD4/CD8 ratio that indicates high chronic inflammatory activity. This process of chronic immune activation is associated with increased atherosclerosis. The study concluded that the ratio of CD4/CD8 inversion determines carotid intima-media thickness in patients with HIV infection (OR 2.9, CI 95%: 1.2-7.1) [4].

Atherosclerosis, which is one of the non-AIDS complications, has a major influence on the incidence of morbidity and mortality in patients with HIV/AIDS [8]. Research on the CD4/CD8 ratio associated with atherosclerosis in HIV patients is rare. This research aims to role out the association of atherosclerosis events and to determine the role of CD4/CD8 ratio in the occurrence of atherosclerosis (in this case measured by CIMT using USG) in HIV outpatients at tropical disease and infection polyclinic Sanglah General Hospital, Bali-Indonesia.

## Methods

This study was an observational study with cross-sectional analytic design to determine the correlation between CD4/CD8 ratio with carotid intima-media thickness as a marker of atherosclerosis in HIV patients. The research was conducted in tropical disease and infection outpatient clinic Sanglah General Hospital, Bali-Indonesia in May 2017 until July 2017. The subjects of this study were recruited through consecutive sampling to be fulfilled the desired number of samples. The inclusion criteria in this study were HIV outpatient care in tropical disease and infection polyclinic and patients aged between 18-40 years. Exclusion criteria in this study are HIV patient with diabetes mellitus, hypertension, hypercholesterolemia, hypertriglyceridemia, malignancy, coronary heart disease, chronic renal failure, obesity, pregnancy, and cocaine users. The thickness of the Intima-Media (CIMT) of the carotid artery is the value of CIMT as measured by USG B-mode Ultrasound Logic-5 aircraft with a linear transducer frequency of 7.5 Mhz. The examination includes the thickness of the tunica intima-media of the carotid artery and the presence of atherosclerotic plaque. Measurements of CMT are performed at one point on both sides of the carotid artery, expressed in millimetres. The point is in the communist carotid artery (10 mm before the carotid bulb). The measurements of CIMT in all samples will be performed by one consultant radiology specialist. The CD4/CD8 ratio was a comparison of CD4 lymphocyte count cell count, and CD8 T lymphocyte counts examined using flow cytometry (Becton Dickinson (BD) FASCount System.

The data were analysed using Spearman correlation test to evaluate the correlation between CIMT with CD4/CD8 ratio and linear regression analysis to assess the effect and pure relationship of CD4/CD8 ratio to CIMT after controlling confounding variables by analysis.

## Results

The study involved as many as 50 HIV patients who came to the tropical disease and infection polyclinic at Sanglah General Hospital, Bali-Indonesia. The complete subject characteristics can be seen in Table 1.

**Table 1: Subject characteristics**

| Subject Characteristics | Frequency |
|---|---|
| Gender | |
| Male | 33 (66%) |
| Female | 17 (34%) |
| Age (Mean ± SD) | 30.60 ± 5.58 |
| BMI (kg/m2) (Mean ± SD) | 20.52 ± 2.40 |
| Smoking status | |
| No | 34 (68%) |
| Yes | 16 (32%) |
| Smoking duration (years), median (min-max) | 0 (0-20) |
| HBsAg Status | |
| Negatif | 50 (100%) |
| Reactif | 0 (0%) |
| Anti HCV Status | |
| Negatif | 49 (98%) |
| Reactif | 1 ( 2%) |
| TBC status | |
| Negatif | 42 (84%) |
| On treatment | 5 (10%) |
| End of treatment | 3 (6%) |
| Combination therapy | |
| TDF/3TC/EFV | 26 (52%) |
| AZT/3TC/NEV | 7 (14%) |
| TDF/3TC/NEV | 2 (4%) |
| AZT/3TC/EFV | 2 (4%) |
| AZT/3TC/aluvia | 1 (2%) |
| TDF/3TC/aluvia | 3 (6%) |
| Naif | 9 (18%) |
| ARV therapy duration (month), median (min-max) | 12 (0-120) |
| CD4/CD8 ratio | 0.275 (0.02- 1.39) |
| CD4/CD8 < 1 | 47 (94%) |
| CD4/CD8 ≥ 1 | 3 (6%) |
| CIMT (mm), median (min-max) | 0.75 (0.4-1.5) |

Based on Table 1, the most gender in the study subjects were men as many as 33 people (66%), the mean age in the study subjects was 30.60 ± 5.58 years, the mean body mass index in the study subjects was 20.52 ± 2.40 kg/m$^2$, all patient without comorbidity of Hepatitis B, only one patient with hepatitis C comorbidity, based on TB status 42 (84%) of study subjects had negative TB status, based on antiretroviral therapy a combination of TDF/3TC/EFV is the most commonly used regimen as mucg as 26 people (52%), based on the duration of antiretroviral treatment there was a range of ARVs in patients ranging from 0 to 120 months, based on CD4/CD8 ratios, the most is < 1 as much as 47 people (94%), CIMT thickness ranges from 0.4 to 1.5 mm. The correlation between CD4/CD8 ratio and CIMT can be seen in Table 2.

**Table 2: Correlation between CD4/CD8 ratio with CIMT**

| Variable | Median (interquartil range) | r | p-value |
|---|---|---|---|
| CD4/CD8 ratio | 0.275 (0.32) | | |
| CIMT | 0.755 (0.4) | -0.85 | 0.001* |

*significant (p < 0.05).

Based on Table 2, the correlation between CD4/CD8 ratio and carotid artery intima-media thickness, with correlation coefficient of r = -0.850 and p-value = 0.001. This indicates that the CD4/CD8 ratio has a strong negative correlation that is significant against carotid artery intima-media thickness. So, it can be interpreted that any increase in CD4/CD8 ratio will be followed by decreased CIMT. Multiple linear regression analysis of CD4/CD8 ratio with CIMT and control of confounding factors can be seen in Table 3.

**Table 3: Multiple linear regression on CD4/CD8 ratio with CIMT and confounding factors**

| Variable | β | R-square | CI 95% | p-value |
|---|---|---|---|---|
| CD4/CD8 ratio | -0.791 | 0.561 | -0.99 – (-0.592) | < 0.001 |
| Age | 0.012 | | 0.002 – 0.022 | 0.022 |
| Combination of ARV | 0.011 | | -0.013 – 0.035 | 0.356 |
| Duration of smoking | 0.005 | | -0.007 – 0.017 | 0.401 |
| Gender | 0.019 | | -0.118 – 0.156 | 0.781 |
| BMI | 0.000 | | -0.025 – 0.026 | 0.972 |
| Constant | 0.727 | | 0.411 – 1.042 | < 0.001 |

Based on Table 3, after multivariate analysis with multiple linear regression on independent variables, the effect of CD4 / CD8 ratio and other confounding variables on CIMT, the variable that proved to influence CIMT is the ratio of CD4 / CD8 and patient age.

The coefficient β ratio of CD4 / CD8 ratio (β1)-0,791 means that every 1 point increase of CD4 / CD8 ratio followed by a decrease of CIMT equal to 0,791 mm, coefficient β of age (β2) 0,012 meaning that every 1-year-old growth will be followed by CIMT increase equal to 0,012 mm. From the result of multivariate analysis with multiple linear regression with the value of β 0 that is 0,727 could be interpreted as an equation formula as follows:

Y = 0.727 - 0.791 (X1) + 0.012 (X2)

Y: Carotid intima-media thickness

X1: CD4/CD8 ratio

X2: patient age.

The value of discrimination through R-square result is 0.561, which means that the formula obtained can explain CIMT influenced by CD4 / CD8 ratio and age is 56,1% while the rest 43,9% is explained by another variable outside the research studied variable.

## Discussion

The result of this study found a strong negative correlation between the CD4/CD8 ratio with CIMT. These findings are supported by research by Villar et al., (2013) that the CD4/CD8 ratio is correlated with CIMTwith r = -0.2, p = 0.037 [8]. Another interesting point with different methods obtained from Morrel et al. (2016) research found that the progression of carotid artery intima-media thickness was inversely related to CD4/CD8 ratio with OR = 0.283; CI 95% (0.099-0.809), p = 0.019 [9]. Another research conducted by Lo et al. (2010) found that the CD4/CD8 ratio was negatively correlated with the volume of atherosclerotic plaque. Also, Lo and colleagues concluded that the CD4/CD8 ratio was

stronger than either CD4 cell count or viral load versus plaque volume [10]. Studies conducted in New York concluded that low CD4 cell count was a major risk factor for atherosclerosis in HIV-infected patients. Compared with non-HIV-infected patients, the prevalence risk ratio of atherosclerosis in HIV patients with CD4 cell count < 200 cells / mm3 was 2 (95% CI: 1.22-3.28) in women and 1.74 (CI 95%; 1.04-2.93) in men [11]. A low CD4 value will result in a low CD4/CD8 ratio value, and this is by our study, which will lead to increased carotid intima-media thickness in HIV-infected patients. In contrast, higher CD4 values will result in a higher CD4/CD8 ratio. A high CD4/CD8 ratio indicates a low inflammatory factor and is associated with a decrease in the incidence of atherosclerosis in HIV-infected patients.

The CD4/CD8 ratio shows the level of strength of the immune system. A lower CD4/CD8 ratio indicates a higher rate of chronic inflammatory activation. Most patients with HIV infection have a low CD4/CD8 ratio, even patients who have received ARVs often fail to achieve normal CD4/CD8 ratios, despite achieving normal CD4 cell counts. This is due to immunological abnormalities in the same HIV patients encountered in elderly patients, including skewed T cell phenotype, CD8 cell activation (CD38 +), CD8 cell senescence (CD28- and CD 57 + CD28-). This immune activation considered a major factor in premature ageing in HIV patients, results in an immunocultural phenotype. CD8 increases are continuous, regardless of whether or not there is a CD4 increase. However, CD8, which has increased and activated, is CD8, which has lost its full function [9], [12]. CD8 cell activation contributes to vascular damage will mediate the occurrence of apoptosis of macrophages, smooth muscle cells, endothelial cells which subsequently lead to the formation of necrotic nuclei which is the forerunner to the formation of atherosclerotic plaque [13]. HIV-infected patients with higher CRP levels, high CD8 cell activation, high T-cell response to CMV was independently associated with a carotid increase in carotid intima-media thickness of HIV patients [11].

In this study, multivariate analysis of CD4/CD8 ratio and confounding variables were age, sex, BMI, duration of smoking and combination of ARV. After gradual multivariate analysis, it was found that CD4/CD8 ratio and age influenced carotid artery intima-media thickness in this study subjects. From the equation formula obtained is: Y = 0.727 -0.791 (X1) + 0.012 (X2), that the increase of CIMT in HIV-infected patients is influenced by the smaller ratio of CD4/CD8 and increasing age. This is by previous research results stating the role of CD4/CD8 ratio affects the occurrence of carotid artery intima-media thickening [8], [9]. In this study, age also affects the thickness of the carotid artery intima-media layer. Age can independently contribute to the development of cardiovascular disease. Every decade of age is associated with about twice the increased risk of cardiovascular disease (OR per decade of age, i.e., 2.14, 1.80, and 2.33 for atherosclerosis, carotid stenosis, and abdominal aortic aneurysm) [15]. This is also supported by Morell's et al., (2016) study with 96 HIV-infected patients it was found that CIMTwas significantly associated with age (r = 0.497; p < 0.001) [9].

Another study conducted by Bakar et al. (2010) concluded that HIV patients with ARV treatment compared with no treatment had a lower risk of cardiovascular disease. The earlier the treatment, the risk of cardiovascular disease will be smaller. Early ARV treatment may increase CD4 cell counts faster to improve CD4/CD8 ratios. An increase in CD4/CD8 ratio will decrease the inflammatory rate that has implications for the small incidence of atherosclerosis [14].

The limitation of this study is the data taken at a time, so it is difficult to determine the cause and effect relationship. Furthermore, this study was unable to monitor how much the effect of CD4/CD8 ratio changes on carotid artery CIMT plaque changes.

In conclusion, there is a negative correlation between CD4/CD8 ratio with carotid intima-media thickness in HIV/AIDS infected patients in tropical disease and infection polyclinic at Sanglah General Hospital, Bali-Indonesia. The ratio of CD4/CD8 and age is the most important factor in the occurrence of non-AIDS complications, specifically the occurrence of atherosclerotic plaque.

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