



Cluster of Differentiation 4 Count and Left Ventricular Diastolic Function in Patients with Hiv - Aids

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Abstract: Background: People with Acquired Immunodeficiency Syndrome (AIDS) are at risk of developing structural and functional cardiac abnormalities that are unrelated to common cardiac risk factors (e.g. Hypertension, Diabetes Mellitus, Smoking habit). AIDS may be associated with chronic inflammation related to multiple factors related to the Human Immunodeficiency Virus (HIV) infection and its complications. Cardiac abnormality with AIDS may be subclinical and may present long before the onset of clinical heart failure symptoms. Objectives: To anticipate the risk of cardiovascular morbidity in people with AIDS. Methods: The researchers studied 52 people with AIDS in this observational cross-sectional study, which were further categorized into those with cluster of differentiation 4 (CD4) count of less than 200/mm³ and those with CD4 count of more than 200/mm³. Echocardiographic examinations were done to evaluate cardiac structural and functional values. Results: Mean age was 33 years old, predominantly male (71.2%). The group with a CD4 count of less than 200/mm³ showed higher Left Ventricular Mass Index (LVMI) values (113.08 vs. 39.99, p=0.012), a higher risk of developing diastolic dysfunction (OR 9.35, CI 95%, p=0.018) and pericardial effusion (OR 3.83, CI 95%, p=0.048). Conclusion: A CD4 count of less than 200/mm³ is associated with a higher risk of developing cardiac diastolic dysfunction and structural abnormalities.

Keywords: HIV, AIDS, Echocardiography, Diastolic Dysfunction

1. Introduction

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) remain a worldwide pandemic, with an estimation of 36.7 million cases worldwide up until 2015; with five million cases found in Asia-Pacific region, including Indonesia.[1]

HIV infection has been well known to be associated with cardiovascular morbidity, represented by a higher risk of cardiovascular disease even in the absence of major conventional cardiovascular risk factors (i.e. dyslipidemia, hypertension, diabetes mellitus, and smoking habit). Various manifestations can be found, including myocarditis, Dilated Cardiomyopathy, pericardial effusion, endocarditis, pulmonary hypertension, and cardiac neoplasm.[2,3] In the

era of antiretroviral usage, multiple multicenter studies have shown that diastolic dysfunction, rather than systolic dysfunction is the most common cardiac abnormality found in people with AIDS (43.4% vs. 8.3% respectively).[2] Basic pathology of this phenomenon has yet been completely explained, with some theories suggesting chronic infection and inflammation of the left ventricle (LV) as the main cause. [4-7] It is commonly associated with viral replication, non-specific inflammatory process, antiretroviral use, micronutrient deficiency, and various indirect etiologies. [8,9] In addition, structural abnormality and dysfunction of the LV may be subclinical; it can be found even before the clinical heart failure signs and symptoms appeared. [10] A

study about these subclinical findings may be useful in order to anticipate the risk of cardiovascular morbidity people with AIDS.

2. Methods

2.1. Study Design

The study design is an observational cross-sectional study of people with AIDS that were evaluated as they were admitted as outpatients or those who were admitted in the general ward of Wahidin Sudirohusodo General Hospital Makassar, Indonesia. The basic characteristics, clinical and treatment histories, risk factors, and laboratory values were abstracted from medical charts and entered into an electronic database. These data were then reviewed and double-checked for validity by trained staff. Additional data were collected through physical examination and echocardiography measurements. The local hospital ethical committee was approved the study protocol.

2.2. Laboratory Evaluation

The basic cluster of differentiation 4 (CD4) cell count was done in the Wahidin Sudirohusodo General Hospital's central laboratory. Other clinical laboratory tests that were performed were basic hematology panel, high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol (TC), and triglyceride (Tg), glucose, C-reactive protein (CRP), D dimer, ureum and creatinine; all were done in the same laboratory.

2.3. Echocardiographic Measurements

In this study, experienced echocardiographers who were blinded to the study performed the echocardiography examinations. The examination results were recorded digitally and then interpreted by one experienced reader blinded to the study. The Left Ventricular End Systolic and End Diastolic volumes were determined using the biplane modified Simpsons method to obtain the left ventricular ejection fraction.⁸ Other measurements, including left ventricular mass index, Left Atrium and Right Atrium volume, Tricuspid Annular Plane Systolic Excursion (TAPSE), early (E) and late diastolic (A) mitral inflow velocity, deceleration time, and Tissue Doppler Imaging were also obtained.

2.4. Echocardiographic Outcomes

Various echocardiographic outcomes were being studied: the LV diastolic function, the LV systolic function, LV systolic function, LV chamber quantification, and the rest of cardiac chamber size. LV diastolic function was represented by the Doppler peak early (E) and late diastolic (A) mitral inflow velocity, E/A ratio, mitral inflow deceleration time, and lateral mitral annular velocity (E') on tissue Doppler. LV diastolic dysfunction was further classified into three categories [11], the first degree of diastolic dysfunction was

defined as E/A ratio of less than 0.8, with deceleration time of more than 200ms [12]; the second degree was defined as E/A ratio of 0.8 – 1.5 with deceleration time of 160-200 ms (or with the founding of E/A ratio change during valsalva maneuver equals 0.5) [13], and the third degree was defined as E/A ratio of more than two, with deceleration time of less than 160 of ms. [11, 13] LV systolic function was represented by the Ejection Fraction (EF) which was determined using Simpson biplane method, where the normal category is defined as EF of more than 55 %.[6], [14] LV chamber quantification was represented by the LV mass index (LVMI) and Relative Wall thickness (RWT). [14, 15] LVMI was calculated using the standard validated formula recommended by the American Society of Echocardiography (ASE). Values of LV mass were each normalized to the body surface area (BSA). RWT was calculated by the standard validated formula and then used in conjunction with the LVMI to define the LV geometry. Normal LV geometry was defined as LVMI of less than 115g/m² in men (Male) and less than 95 g/m² in women with the RWT value of less than 0.42. [16] Concentric LV remodeling was defined as LVMI of less than 115 g/m² (men) and less than 95 g/m² (women) with the RWT value of less than 0.42. Concentric LV Hypertrophy (LVH) was defined as LVMI of more than 115 g/m² (men) and more than 95 g/m² (women) with the RWT value of more than 0.42. Eccentric LVH was defined as LVMI of more than 115 g/m² (men) and more than 95 g/m² (women) with the RWT value of less than 0.42. [16]

2.5. Statistical Analysis

Computed analyzing was performed for all the data analysis. Bivariate spearman correlation was used to determine the correlation between various numerical variables and CD4 count with the diastolic echocardiographic outcomes. Multivariate logistic regression analysis between the CD4 count categories was then performed as a comparison of the echocardiographic diastolic dysfunction outcomes. Statistical testing was conducted at the Confidence Interval (CI) of 95%. Data were analyzed using SPSS software version 23 (IBM corporation).

3. Results

3.1. Baseline Characteristics

Among 52 patients, the mean age was 33 years old, 71.2% were male, and 28.8% were female. 75% were underweight with mean BMI of 16.5 kg/m² (12.8 – 22.4 kg/m²). Mean heart rate was 96.7 beats/minute. The mean CD4 level was 205.7/mm³ with 25 (48.1%) patients having a CD4 count of less than 200/mm³ and 27 (51.9%) patients having a CD4 count of more than 200/mm³. The mean troponin level was 0.062 ng/dl, with 32.7% of patients having elevated troponin levels. An elevated CPR was found among 67.3% of patients (mean values 205.7 mg/l). The mean leukocyte count was 7057.6/uL. Additional characteristics are shown in Table 1.

Table 1. Baseline Characteristics of HIV/AIDS Patients Based on the CD4 Count.

	CD4 < 200/mm ³	CD4 > 200/mm ³
	(n = 25)	(n = 27)
Age (years)	32.6 ± 5.9	33.9 ± 6.9
Male (%)	76	66.7
Body Mass Index (kg/m ²)	16.1 ± 2.1	16.8 ± 2.1
Heart Rate (bpm)	100 ± 12.8	93 ± 15.7
Systolic BP (mmHg)	112 ± 10	112 ± 8
Diastolic BP (mmHg)	72 ± 6.4	71 ± 5.7
<i>Laboratory Values</i>		
CD4 count (/mm ³)	66.1 ± 58.2	335.0 ± 105.8
Troponin I (ng/dL)	0.07 ± 0.11	0.04 ± 0.09
CRP (mg/dL)	29.7 ± 40.2	42.1 ± 53.6
D-dimer (ng/dL)	1.3 ± 1.5	0.79 ± 1.4
WBC(/uL)	7952 ± 7265	6229.6 ± 5429.8
Hb (g/dL)	9.1 ± 2.7	10.2 ± 2.2
PLT(/uL)	252,520 ± 133635	221,025 ± 103,097
Ureum (mg/dL)	24.6 ± 9.7	22.7 ± 9.0
Creatinine (mg/dL)	0.7 ± 0.26	0.70 ± 0.22
RBG(mg/dL)	100.6 ± 19.9	107.2 ± 30.6
Total Cholesterol(mg/dL)	143.0 ± 61.8	167.2 ± 61.8
HDL Cholesterol (mg/dL)	24.1 ± 16.5	28.5 ± 12.0
LDL Cholesterol (mg/dL)	93.5 ± 58.2	110.0 ± 48.7
Triglyceride (mg/dL)	189.4 ± 79.2	188.3 ± 83.5

CD4, Cluster of differentiation 4; BP, Blood Pressure; CRP, C-Reactive Protein; WBC, White Blood Cell; Hb, Haemoglobin; PLT, Platelet; RBG, Random Blood Glucose; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein

3.2. Baseline Echocardiography Findings

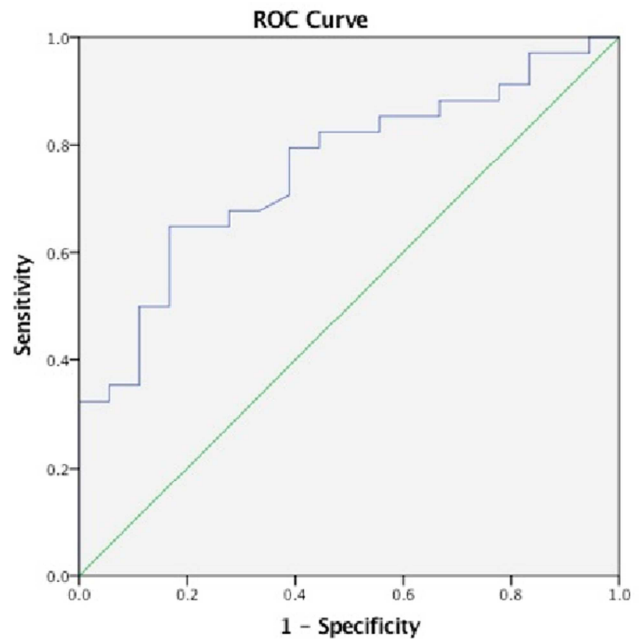
Table 2. Echocardiography Parameters in HIV/AIDS Patients Based On Their CD4 Count.

Echocardiography Parameters	CD4		P
	< 200/mm ³	> 200mm ³	
E (m/s)	0.67	0.71	0.418
A (m/s)	0.78	0.15	0.057
E/A ratio	0.87	1.07	0.026
Deceleration Time (ms)	211.6	185.2	0.015
LVEF (%)	61.6	64.8	0.138
LVIDd (mm)	44.8	42.3	0.097
IVSD (mm)	9.16	8.63	0.365
LVPWd (mm)	10.0	9.2	0.053
LVMI (g/m ²)	113.08	39.99	0.012
RWT	0.45	0.44	0.501
LA diameter (cm)	2.85	2.75	0.459
TAPSE (cm)	2.01	2.01	0.913
Right Atrial Pressure (mmHg)	4.20	3.74	0.411
RV Free Wall Thickness (cm)	0.61	0.53	0.027
PVAccT (ms)	97.76	110.13	0.123
mPAP (mmHg)	35.01	29.44	0.123

CD4, Cluster of differentiation 4; E, early diastolic mitral inflow velocity; A, late diastolic mitral inflow velocity; LVEF, Left Ventricular Ejection Fraction; LVIDd, Left Ventricular Internal Diameter End Diastole; IVSD, Interventricular septal end diastole, LVPWd, Left Ventricular Posterior Wall End Diastole; LVMI, Left Ventricular Mass Index; RWT, Relative Wall Thickness; LA, Left Atrium; TAPSE, Tricuspid Annular Plane Systolic Excursion; RV, Right Ventricle; PVAccT, Pulmonary Vein Acceleration Time; mPAP, Mean Pulmonary Artery Pressure

The Ejection Fraction ranges from 41.0 – 74.1% (Mean 63.2%); 5.8% patients had a depressed Ejection Fraction (of less than 50%). Thirty four (65.4%) of the patients had an abnormal diastolic dysfunction, 31 (59.6%) had a grade one diastolic dysfunction, while 3 (5.8%) had a grade two diastolic dysfunction. Mean E velocity was 0.69 ± 0.17 m/s, A velocity was 0.747 ± 0.16m/s, and Deceleration time was 197.8 ± 39.5 ms. The mean E/A ratio was 0.98 ± 0.32. The mean LVMI was 100.1 ± 36.6 gr/m² with a mean of RWT of 0.44 ± 0.07. Among 52 patients, 38.5% had a concentric remodeling, 32.7% had a normal LV geometry, 23.1% had a concentric hypertrophy and only 5.8% had an eccentric hypertrophy. Most patients (90.4%) had a normal regional wall motion and no pericardial effusion (73.1%). Other echocardiography findings are listed in Table 2. Patients with a CD4 count of less than 200/mm³ had higher LVMI than those with a CD4 count of more than 200/mm³ (113.08 vs. 39.99, $p = 0.012$).

3.3. CD4 Count Correlation to the Echocardiographic Findings

**Figure 1.** Area Under the Curve for CD4 count <200/mm³.

There was no significant difference in the E velocity and A velocity between patients with a CD4 count of less than 200/mm³ and those with a CD4 count more than 200/mm³ (0.679 ± 0.18 vs. 0.718 ± 0.16, $p = 0.418$ and 0.786 ± 0.15 vs. 0.700 ± 0.15, $p = 0.057$, respectively). Patients with a CD4 count of less than 200/mm³ had a significant higher deceleration time than those with CD4 count of more than 200/mm³ (211.6 ± 29.4 vs. 185.2 ± 43.8, $p = 0.01$). Bivariate Spearman correlation showed a significant moderate correlation between CD4 count and the diastolic dysfunction grade ($r = -0.427$, $p = 0.002$). The lower CD4 count was associated with the higher grade of diastolic dysfunction. We found no significant correlation between CD4 count and

other functional echocardiographic findings such as LV ejection fraction ($p = 0.329$), regional wall motion ($p = 0.480$), and LVH types ($p = 0.535$). Multivariate regression analysis showed a CD4 count of less than $200/\text{mm}^3$ significantly predicts diastolic dysfunction (Odds Ratio [OR], 9.35, CI 95%; $p = 0.018$)

4. Discussion

Structural and functional cardiovascular abnormalities are not uncommon in people with AIDS. Common findings include LV systolic and diastolic dysfunction, pericardial effusion, infective endocarditis, cardiac malignancy, pulmonary hypertension, atherosclerosis, vasculitis, arrhythmia and lipodistrophy.[3] Our study found various abnormalities on echocardiography examination, which included systolic dysfunction (9.6%), diastolic dysfunction (65.4%), pericardial effusion (26.9%) and pulmonary hypertension (67.3%). In a cohort study of AIDS contribution to de novo presentations of heart disease, cardiomyopathy, pericardial effusion, and pulmonary hypertension were commonly found. [17] Moreover, chronic inflammation, frequent pericardial effusion, and probable myocardial edema were found to be associated in HIV infections. [18]

In the HIV-HEART study, the dominant sex was male, with a mean age of 44.2 years old and mean BMI of 24.1 kg/m^2 .¹⁹ In our study, the group was also predominately male (71.2%), but with a younger age and lower BMI (33.3 years old and 16.5 g/m^2 respectively). These findings might be useful in minimizing the age-related and BMI-related effect on the pathological echocardiography findings, since both have been related to various abnormality findings in echocardiography. Older age is well known to increase the risk of diastolic dysfunction, while other cardiovascular risk factors such as hypertension, diabetes mellitus, and peripheral artery disease frequently comorbid in obese populations.[2, 6, 20]

The researchers found a larger number of diastolic dysfunction in our study than systolic dysfunction (31 samples with diastolic dysfunction, 3 samples with systolic dysfunction) This result was similar with a meta-analysis study that was done by Remick et al. in 2014 that found a higher rate of diastolic dysfunction among HIV/AIDS patients.¹⁰ Schuster et al. also found a high prevalence of LV diastolic dysfunction (64%) in people with AIDS receiving an antiretroviral therapy. [22]

Cerrato et al. did a meta-analysis on 11 studies of HIV patients and found 31.8% had first grade diastolic dysfunction, 8.53% had second grade and 3.02% had third grade dysfunction. [23] Our study found a similar result in which a large percentage of patients with diastolic dysfunction had a first grade diastolic dysfunction (59.6%), followed by second grade diastolic dysfunction (5.8%).

As the increase of LVMI may reflect cardiac structural abnormality; it may also be related to the development or progression of diastolic dysfunction on HIV patients.[24] In

the HIV-HEART study, they found that the LVMI values in HIV-infected patients were both significantly above the normal range in both sexes.[25] Our study found that the mean LVMI for both sexes were between normal ranges (male: 108.9, female 78.1). However, the researcher found that LVMI values were significantly higher in the sample group with CD4 counts of less than $200/\text{mm}^3$ than those with CD4 cell counts of more than $200/\text{mm}^3$ (113.08 vs. 87.9 respectively, $p = 0.012$). These findings were consistent with a study done by Hsue et al. in 2010 that found higher LVMI values on HIV patients.[26] Ntusi et al. in their study using Cardiac Magnetic Resonance also found a similar result, which was proven unrelated to the BMI.[18]

Using logistic regression analysis, our study found that a CD4 count less than $200/\text{mm}^3$ stands as an independent predictor of diastolic dysfunction (OR: 9.35, CI 95%, $p = 0.018$) (see Table 3). The area under the curve (AUC) was significant for 0.756, indicating CD4 as a good predictor of LV diastolic dysfunction with a cutoff point of 236.5 (Figure 1). A previous study of CD4 count as a predictor of cardiovascular morbidity found that a nadir CD4 count of less than $50/\text{mm}^3$ was an independent predictor of hypertension.²⁷ As hypertension and other conventional cardiovascular risks were excluded, the researchers did not evaluate their association in our study. However, the researchers found no significant difference in systolic and diastolic blood pressure between those with a CD4 count less than $200/\text{mm}^3$ and those with a CD4 count more than $200/\text{mm}^3$.

Our study also found that a CD4 count less than $200/\text{mm}^3$ was associated with a higher occurrence of pericardial effusion (10 vs. 4 findings of pericardial effusion in sample group with a CD4 count of less than $200/\text{mm}^3$ versus more than $200/\text{mm}^3$ respectively, $p=0.041$). In a logistic regression analysis, the researchers found that a CD4 count of less than $200/\text{mm}^3$ was a significant independent predictor of pericardial effusion (OR: 3.83, CI 95%, $p=0.048$). In a prospective multicenter cohort study of HIV-infected patient, Lind et al found that the incidence of pericardial effusion was low in the presence of CD4 counts of less than $200/\text{mm}^3$. [28]

Table 3. Logistic Regression Analysis on Predictors of Echocardiographic Abnormalities.

Variables	OR	p
<i>LV Diastolic Dysfunction</i>		
CD4 count < $200/\text{mm}^3$	9.35	0.018
<i>Pericardial Effusion</i>		
CD4 count < $200/\text{mm}^3$	3.83	0.048

OR, Odds Ratio; LV, Left Ventricular; CD4, Cluster of Differentiation 4

Chronic inflammation process plays an important role in the development of pericardial effusion in people with AIDS, which also might be triggered by opportunistic infection, e.g. tuberculosis. In a study of 50 tuberculosis patients, it was found that 4% has diastolic dysfunction associated with the tuberculosis infection. [2] This study

didn't found any specific infection that correlates significantly with the development of pericardial effusion nor diastolic dysfunction.

5. Conclusion

People with AIDS with low CD4 count had a higher risk of developing cardiac functional and structural abnormalities. Those with a CD4 count of less than 200/mm³ tend to have a higher LVMI, a higher risk of diastolic dysfunction and pericardial effusion.

Conflict of Interest

The authors declare that they have no competing interests.

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