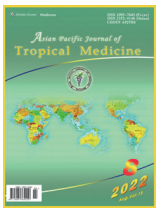

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Interleukin-15 is a significant predictor of sarcopenia in human immunodeficiency virus infected patients on antiretroviral therapy: A cross-sectional study

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ABSTRACT

Objective: To identify the relationship between interleukin (IL)-15 levels and sarcopenia in human immunodeficiency virus (HIV)-infected patients who have received antiretroviral therapy.

Methods: This study was a cross-sectional design with 70 participants conducted from January to March 2021. All the participants were assessed for sarcopenia and the IL-15 levels. Sarcopenia was established based on the the Asian Working Group for Sarcopenia (AWGS) 2019 criteria. Plasma IL-15 was determined. This analysis was carried out by means of 2×2 tabulation and the statistical test used is *Chi*-square.

Results: Seventy patients received antiretroviral therapy >6 months and showed a good clinical response. Among them, 36 (51.4%) took zidovudine-based antiretroviral therapy with a median duration of illness of 5 years. The proportion of sarcopenia in patients with HIV infection was 32.9%. The median CD4 cell count was 395.5 cells/L (range: 203-937 cells/L). Logistic regression analysis revealed that age>50 years (a*OR* 8.3, 95% *CI* 1.6-44.5), underweight (a*OR* 7.7, 95% *CI* 1.5-40.5), IL-15≥150.5 ng/L (a*OR* 4.9, 95% *CI* 1.3-19.0) and female (a*OR* 4.8, 95% *CI* 1.2-18.3 were significant and independent adverse predictors of sarcopenia in subjects with HIV infection.

Conclusions: There is an association between high levels of IL-15 and sarcopenia in HIV-infected patients on antiretroviral therapy for more than 6 months with good clinical response.

KEYWORDS: Antiretroviral therapy; HIV; IL-15; Inflammatory; Sarcopenia; Underweight

1. Introduction

Antiretroviral therapy (ART) is effective in the early treatment for human immunodeficiency virus (HIV), however, patients with HIV still have a shorter life expectancy compared to people without HIV infection[1]. One of the evidences of the aging process in HIV infection is the occurrence of geriatric syndromes which include sarcopenia, frailty and falls whose prevalence is almost twice that of the non-HIV population[2]. The effect of long-term ART treatment is a significant contributor to this condition. In the first generation of antiretroviral drugs, nucleoside reverse transcriptase inhibitorssuch as zidovudine, zalcitabine, didanosine, and stavudine cause myopathy, reduced activity tolerance, and severe lactic acidosis resulting in more rapid decline in muscle function and mass[3].

Sarcopenia is a syndrome characterized by progressive and

Significance

High level of IL-15 is associated with sarcopenia in HIV-infected patient on antiretroviral therapy. Increased physical activity shows an improvement in physical stamina, body composition, and inflammatory markers in sarcopenia.

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comprehensive loss of mass accompanied by skeletal muscle strength or function, which is at risk of causing physical disability, low quality of life, and even death[4]. Sarcopenia arises due to the disruption of the complex balance between anabolic and catabolic factors of muscle protein with age, thus affecting the tropism and efficiency of skeletal muscle[5].

Skeletal muscle is capable of producing and secreting myokines that play a role in the incidence of sarcopenia. Interleukin (IL)-15 is one of the myokines with complex biological effects and can be pro-inflammatory or anti-inflammatory depending on the targets[6,7]. In geriatric patients, low serum IL-15 levels are associated with sarcopenia[6]. The relationship between IL-15 levels and sarcopenia in HIV-infected patients who have received antiretroviral therapy has not been done. Thus, this study aims to identify the relationship between IL-15 levels and sarcopenia in HIV-infected patients who have received antiretroviral therapy.

2. Subjects and methods

2.1. Informed consent and ethical approval

Subjects have been informed about this study and have signed an informed consent to participate. This study has cleared ethical clearance issued by the ethical committee with number LB.02.01/XIV.2.2.1/1848/2021.

2.2. Study design

This study is a cross-sectional design conducted at the voluntary counselling and testing (VCT) polyclinic in Sanglah General Hospital, Bali, Indonesia, from January to March 2021. The participants were all HIV-infected patients who were obtained by consecutive sampling. With inclusion criteria aged ⩾18 years who have received ART >6 months with good clinical outcomes. Exclusion criteria were patients with acute infection and a history of using non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids for at least 2 weeks before the study.

2.3. Participants

A total of 108 patients were examined during the period, but only 70 were included in the study. Twenty-two were excluded because they had used steroid in the last 2 weeks, 12 refused to participate, and 4 were lost to monitoring.

2.4. Sarcopenia assessment

Sarcopenia was established based on the Asian Working Group for Sarcopenia (AWGS) 2019 criteria. The components of sarcopenia consist of muscle mass, strength, and walking speed. Sarcopenia was defined when 2 of the 3 criteria were met, namely:

1. Muscle mass was measured using bio-electrical impedance analysis, and then skeletal muscle index was calculated. It is considered to be low if the value for men is <7.0 kg/m^2 or women <5.7 kg/m^2.

2. Examination of muscle strength is done with a handgrip dynamometer. It is considered to be low if the strength of men <28 kg or women <18 kg.

3. Physical performance is determined by walking speed (m/s) (calculated by a 6-meter walking test). Low physical performance when walking speed <1 m/s.

Table 1. Characteristics of patients who had received antiretroviral therapy for more than 6 months with good clinical responses (n=70).

Variables	n (%)
Age[&], years	42.1±9.4
>50	11 (15.7)
⩽50	59 (84.3)
Sex	
Female	27 (38.6)
Male	43 (61.4)
Comorbidity(s)	
No	67 (95.7)
Yes	3 (4.3)
HIV stage	
1	17 (24.3)
2	5 (7.1)
3	7 (10.0)
4	41 (58.6)
BMI[&], kg/m^2	22.7±3.8
Underweight	13 (18.6)
Normal	19 (27.1)
Overweight	16 (22.9)
Obese	22 (31.4)
Skeletal muscle index[#], kg/m^2	6.0 (2.6-8.6)
Grip strength[#], kg	32.2 (15.9-57.5)
Walking speed[&], m/s	0.8±0.2
CD4 count[#], cells/L	395.5 (203-937)
ART regimen	
Zidovudine based	36 (51.4)
Tenofovir based	34 (48.6)
Illness duration[#], year	5 (1-20)
>5	34 (48.6)
⩽5	36 (51.4)
Sarcopenia	
Yes	23 (32.9)
No	47 (67.1)

ART: antiretroviral therapy; BMI: body mass index. Data was expressed as [&]mean±SD, or [#]median (interquartile range).

2.5. IL–15 levels

The blood serum IL-15 level was examined using the human IL-15 ELISA kit by the Bioassay Technology Laboratory (Catalogue Number E0097Hu) from Bioassay Technology, China, and measured by the ELISA method.

2.6. Statistical analysis

The descriptive statistical analysis aims to describe the characteristics of research subjects and calculate the proportion of sarcopenia incidence. If normally distributed, variables with a numerical data scale are displayed using the mean±SD. If not normally distributed, it is displayed using the median and interquartile range. Variables that scale categorical data are displayed using relative frequency or number and percentage. Receiver operating characteristic analysis was used to determine the cut-off point of IL-15. The bivariate analysis aimed to show the incidence of sarcopenia based on the IL-15 category. This analysis was carried out by means of 2×2 tabulation. The statistical test used *Chi*-square aim is to show the incidence of sarcopenia based on the IL-15 levels. $P<0.05$ was considered as statistically significant.

3. Results

There were 70 patients included in this study who had received ART>6 months with good clinical outcomes, consisting of 43 men (61.4%) and 27 women (38.6%) with a mean age of (42.2±9.4) years. A total of 59 patients infected with HIV (59/70, 84.3%) aged ⩽50 years, and 11 patients >50 years (11/70, 15.7%); 55 (55/70, 78.6%) based on clinical characteristics; 3 (3/70, 4.3%) had comorbidities (2 with Diabetes Mellitus (DM) and 1 with chronic kidney disease (CKD); 41 (41/70, 58.6%) suffering from stage 4 HIV infection as per the WHO instructions. The average body mass index (BMI) of the research subjects was 22.7 kg/m^2, and walking speed was 0.86 m/s with a median skeletal muscle index (SMI) of 6.05 kg/m^2 and grip strength of 32.25 kg. The median CD4 cell count of the subjects was 395.5 cells/L (range: 203-937 cells/L). A total of 36 people (36/70, 51.4%) took zidovudine-based ART with a median duration of illness of 5 years. The proportion of sarcopenia in patients with HIV infection was (23/70, 32.9%) (Table 1).

The analysis of serum IL-15 levels obtained the lowest level of 95 ng/L and the highest level of 342 ng/L with a median of 151.5 ng/L. In the analysis with the receiver operating characteristic curve, the area under the curve is 0.649 with a *P*-value of 0.043. The cut-off point for optimal IL-15 levels to predict the risk of sarcopenia was

Table 2. Relationshiop between serum IL-15 and sarcopenia, and bivariate analysis of independent variables with sarcopenia

Variables	Sarcopenia, *n* (%)		Prevalence ratios (95% *CI*)	*P*-value
	Yes	No		
IL-15 level, ng/L				
⩾150.5	18 (48.6)	19 (51.4)	3.2 (1.3-7.7)	0.003*
<150.5	5 (15.2)	28 (84.8)	1	
Age, years				
>50	7 (63.6)	4 (36.4)	2.4 (1.3-4.3)	0.032*
⩽50	16 (27.1)	43 (72.9)	1	
Sex				
Female	14 (51.9)	13 (48.1)	2.5 (1.3-4.9)	0.007*
Male	9 (20.9)	34 (79.1)	1	
Education status				
Lower education	5 (33.3)	10 (66.7)	1.0 (0.5-2.3)	1.000
Higher education	18 (32.7)	37 (67.3)	1	
Comorbidity(s)				
No	1 (33.3)	2 (66.7)	1.0 (0.2-5.2)	1.000
Yes	22 (32.8)	45 (67.2)		
BMI				
Underweight	9 (69.2)	4 (30.8)	2.6 (1.4-5.0)	0.009*
Normal	4 (21.1)	15 (78.9)	0.8 (0.3-2.2)	0.754
Overweight/obese	10 (26.3)	28 (73.7)	1	
CD4 count, cells/L				
⩽500	17 (35.4)	31 (64.6)	1.5 (0.5-4.4)	0.501
>500	6 (27.3)	16 (72.7)	1	
Illness duration, years				
>5	13 (38.2)	21 (61.8)	1.4 (0.7-2.7)	0.352
⩽5	10 (27.8)	26 (72.2)	1	
ART regimen				
Zidovudine based	12 (33.3)	24 (66.7)	1.0 (0.5-2.0)	0.930
Tenofovir based	11 (32.4)	23 (67.6)	1	

ART: antiretroviral therapy; BMI: body mass index. *$P<0.05$.

150.5 ng/L (sensitivity 78.3% and specificity 59.6%) (Figure 1).

Bivariate analysis of independent variables obtained IL-15 ⩾150.5 ng/L, age >50 years, female and underweight had a significant effect on sarcopenia (Table 2). In logistic regression analysis, age >50 years old, underweight, IL-15 ⩾150.5 ng/L and female remained as significant and independent variables associated with sarcopenia (Table 3).

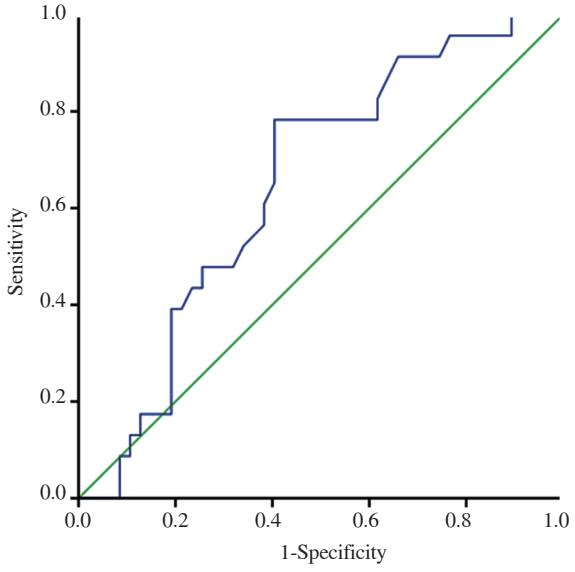

Figure 1. Receiver operating characteristic curve of IL-15's ability and the best cut-off point in predicting sarcopenia.

Table 3. Multivariate analysis of the relationship of age, BMI, IL-15 levels, and sex with sarcopenia.

Variables	a*OR*	95% *CI*	*P*
Age, years			
⩽50	1		
>50	8.3	1.6-44.5	0.013*
BMI			
Normal	1		
Underweight	7.7	1.5-40.5	0.015*
IL-15 level, ng/L			
<150.5	1		
⩾150.5	4.9	1.3-19.0	0.021*
Sex			
Male	1		
Female	4.8	1.2-18.3	0.023*

BMI: body mass index. *P<0.05.

4. Discussion

The incidence of sarcopenia in HIV patients who have received antiretroviral therapy is more common in those aged >50 years. This is consistent with the research by Abdul Aziz *et al.*, and Echeverria *et al*[8,9]. Aging is the primary cause of sarcopenia among healthy people and people with HIV infection. Sex differences in muscle tone and decreased strength in people with HIV infection are still a topic of debate. One mechanism under consideration is that women have more body fat than men. Sarcopenic obesity (reduced lean body mass in the context of excess adipocytes) can increase fat infiltration into muscle, decrease physical function, worsen sarcopenia and increase mortality[10]. Sarcopenia found in HIV patients <50 years in this study was higher than that of HIV-positive people[9]. Factors that increase susceptibility to sarcopenia in HIV-infected patients are persistent chronic immune activation and inflammation, despite viral suppression, so early screening and appropriate intervention can prevent the worsening of the condition[11,12].

In this study, there was a relationship between BMI (underweight category) and the occurrence of sarcopenia. This is supported by the results of four studies showing that the higher the BMI, the lower the odds of sarcopenia[11,13]. The relationship between BMI and sarcopenia is related to lipoatrophy. Lipoatrophy can be augmented by metabolic changes and fat redistribution due to ART toxicity that varies in intensity depending on the type of ART used[14].

In this study, high levels of IL-15 were significantly and independently associated with sarcopenia. One of the special characteristics of chronic HIV infection is the activation of $CD8^+$ memory cell phenotypes with low levels of CD-122 (the chain of IL-2 and IL-15 receptors) and poor response to cytokines, hence the $CD8^+$ requires a high amount of IL-15 to maintain proper function[15]. Production of IL-15 is also regulated by involving IL-15R. IL-15/IL-15Rα protein is not produced by skeletal muscle cells under stable conditions but needs to be induced by TNF-α and IFN-γ and presented on the cell surface. Dysregulation of this control can result in excessive secretion and overexpression of IL-15, which can even lead to autoimmune or inflammatory diseases. Muscle atrophy may occur in skeletal muscle that carries the IL-15 transgene or receives systemic exogenous IL-15. Thus, chronic IL-15 overexpression can cause a U-shaped effect on mitochondrial oxidative function and turn into a pro-inflammatory catabolic effect for concomitant muscles with TNF-α, which remains high in chronic HIV infection[16,17].

Echeverria *et al.* and the AIDS Clinical Trials Group found a significant association between the decreased muscle mass with disease duration >5 years[8]. Longer exposure to thymidine analogue/D-drugs ART is associated with sarcopenia. D-drugs can inhibit gamma-DNA polymerase, an enzyme that plays a role in mitochondrial DNA replication so that it can cause mDNA depletion

and mutations that result in cellular respiration dysfunction. These drugs can also induce oxidative stress and reduce L-carnitine in skeletal muscle[18]. However, three studies have shown that antiretroviral therapy tends to result in increased muscle mass even with more extended treatment regimens (particularly zidovudine/stavudine) despite the potential of thymidine analogue ART to induce muscle mitochondrial toxicity. The association of D-drugs with sarcopenia should be further explored as they are still widely used as standard therapy in many low- and middle-income countries[19].

A sedentary lifestyle is one of the main causes of loss of strength and muscle mass. Several factors that influence the incidence of sarcopenia in HIV patients are caused changes in metabolism and increased activation of the immune system, especially as a result of combination ART treatment. Persistent inflammatory processes alter muscle tissue, resulting in muscle protein catabolism and muscle fat accumulation. Increased physical activity is essential in managing sarcopenia in the general population and people living with HIV/AIDS (PLWH) patient groups. The role of physical activity in PLWH patients with sarcopenia shows an improvement in physical stamina, body composition, and inflammatory markers[20].

The limitations of this study were using control data of PLWHA at the VCT polyclinic where the subject's medical record data was incomplete, especially viral load data and $CD4^+/CD8^+$ ratio, causing limitations in calculating these variables for relationship analysis. One of the efforts made to minimize these limitations is to select a sample that has used ART for more than 6 months with a good clinical response so that with a homogeneous sample, it is hoped that the variation in data can be reduced.

There is an association between high levels of IL-15 and sarcopenia in HIV-infected patients on ART for more than 6 months with good clinical response. It is necessary to consider regular screening for sarcopenia and more comprehensive management through optimal nutrition, physical exercise and ART approaches to prevent sarcopenia. Increased physical activity shows an improvement in physical stamina, body composition, and inflammatory markers in sarcopenia.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

A.A develepod the theoretical formalism, performed the analytic calculations and performed the numerical stimulations. Both A.S and S.A contributed to the final versions of the manuscript. S.A supervised the project.

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