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Association Between Soluble Cluster of Differentiation 14 Levels and Active Tuberculosis Infection in Human Immunodeficiency Virus Patients

Y. A. A. Gayatri[1]*, Putu Juni Wulandari[2]

[1]Department of Internal Medicine, Tropical and Infectious Disease Division, Udayana University, Sanglah Hospital, Bali, Indonesia; [2]Internal Medicine Education Program, Faculty of Medicine, Udayana University, Sanglah Hospital, Bali, Indonesia

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***Correspondence:** Y. A. A. Gayatri, Department of Internal Medicine, Tropical and Infectious Disease Division, Udayana University, Sanglah Hospital, Bali, Indonesia. E-mail: yuli_gayatri@unud.ac.id
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Abstract

BACKGROUND: Tuberculosis is the major opportunistic infection and the leading cause of death among the HIV population worldwide. Indonesia is included among the countries seriously affected by both TB and HIV. HIV increases the lifetime risk of TB infection. One of the parameters related to TB infection in HIV patients is the level of sCD14, which is part of monocytes and macrophages and can bind to lipoarabinomannan in Mycobacterium tuberculosis.

METHODS: This study uses cross-sectional analysis. The research subjects were determined by the purposive consecutive method at the Sanglah Hospital, Bali, in 2021–2022. The sCD14 level was measured by the ELISA method. The diagnosis of active tuberculosis was confirmed by examining patient specimens using the molecular rapid test method RT-PCR GeneXpert MTB/RIF.

RESULTS: There were 60 subjects with HIV infection, consisting of 42 (70%) men and 18 (30%) women. The mean age was 39.13 ± 11.734 years. The median body mass index was 18.8 (16.3–23.4), clinical stage 1–2 was 17 (28.3%), and stage 3–4 was 43 (71.7%). A total of 46 (76.7%) people had other opportunistic infections besides TB. The cut-off point for sCD14 levels was 2900 ng/mL. Subjects with active TB infection were 18 (30%) people and 42 (70%) people without TB. The results of bivariate analysis using the Chi-Square test found a significant relationship between sCD14 levels and active tuberculosis infection in HIV patients ($p < 0.001$). Multivariate analysis with logistic regression showed that high sCD14 levels were independently associated with active tuberculosis infection in HIV patients (AOR 13.64; 95% CI: 2.89–64.42; $p = 0.001$), while other confounding factors were not significantly associated with active tuberculosis infection in HIV patients.

CONCLUSION: sCD14 levels are associated with active tuberculosis infection in HIV patients.

Introduction

The incidence and prevalence of TB among HIV individuals are higher than in the general population, although there is variation in different areas. In 2018, there were approximately 10 million people affected by TB. Indonesia is included in the eight countries that contribute the most TB cases. The WHO noted that the number of TB incidents in Indonesia was 316 per 100,000 people, and in people with HIV infection, the incidence was 7.9 per 100,000 people [1]. CD14 is a receptor for bacterial lipopolysaccharide complexes [2]. This role of CD14 makes sCD14 levels often used as a good indicator to detect monocyte cell activation [3]. However, a significant increase occurred in infectious conditions, including TB infection. This is because monocytes play a role when TB bacteria enter the lungs. sCD14 can also bind to lipoarabinomannan, which is part of Mycobacterium tuberculosis [4]. The highest increase in sCD14 levels was found in TB patients with HIV. This is due to the co-stimulation of these two conditions, resulting in systemic macrophage activation [5].

Methods

This study was a cross-sectional observational-analytical study designed to determine the association between sCD14 levels and active tuberculosis in HIV patients. This research was conducted in the inpatient ward and polyclinic of Sanglah Hospital, Bali, from August 2021 to January 2022. The study sample consisted of all HIV patients aged more than or equal to 18 years undergoing treatment in an inpatient room or polyclinic at Sanglah Hospital Denpasar after meeting the inclusion and exclusion criteria. The sampling method used was the Consecutive Sampling technique, which took samples from HIV patients who met the inclusion and exclusion criteria during the study period and were taken until the number of samples was reached.

Inclusion criteria were patients with HIV infection aged more than or equal to 18 years undergoing treatment at Sanglah Hospital and patients who were examined by GeneXpert TCM to determine the presence of active TB infection. The exclusion

criteria are patients who have received previous TB drugs within the last 3 months, sepsis, Systemic Lupus Erythematosus patients, Rheumatoid Arthritis patients, Hepatitis B and/or hepatitis C patients, and patients who refuse to participate in this study. Patients who agreed to be sampled in the study were then checked for active TB infection using GeneXpert RT-PCR, and blood samples were taken to check sCD14 levels using the Quantikine® ELISA Human CD14 Immunoassay (R&D Systems) reagent. The collected data were then analyzed for Receiver Operating Characteristics (ROC) aimed at assessing the best cut-off point of sCD14 to be categorized into high and low in association with active tuberculosis. The Chi-square test was used for bivariate analysis between variable sCD14 levels and active tuberculosis infection. A logistic regression test was performed for multivariate analysis of independent and confounding variables with active tuberculosis infection. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) Statistical IBM version 24.0 program.

Results

This study involved 60 research subjects. There were 18 (30%) people with TB infections and 42 (70%) without TB. The overall basic characteristics of research subjects are presented in Table 1.

Table 1: Characteristics of the research subject

Variable	n=60
Gender, n (%)	
Male	42 (70%)
Female	18 (30%)
Age (years) mean ± SD	39.13 (11.734)
Age, n (%)	
<50 years	46 (76.7%)
≥50 years	14 (23.3%)
BMI (kg/m^2), median (min-maks)	18.8 (16.3–23.4)
BMI, n (%)	
Underweight	28 (46.7%)
Normal	32 (53.3%)
Clinical stage HIV, n (%)	
Stage 1–2	17 (28.3%)
Stage 3–4	43 (71.7%)
Other opportunistic infection, n (%)	46 (76.7%)
TB status, n (%)	
TB	18 (30%)
Pulmonary TB	17 (94.4%)
Extra pulmonary TB	3 (16.6%)
Without TB	42 (70%)

In this study, the median sCD14 levels were higher in patients with active TB infection than in patients without TB. The median sCD14 level in active TB patients was 3549 ng/mL, with a range between 1805 and 6147 ng/mL. The median sCD14 level in patients without TB infection was 2285.50 ng/mL, with a range between 963.30 and 3582 ng/mL. The limit value of the sCD14 level is more than or equal to 2900 ng/mL, which has a sensitivity of 83.33% and a specificity of 73.81% for the occurrence of TB infection. The ROC curve for sCD14 and active TB infection can be seen in Figure 1.

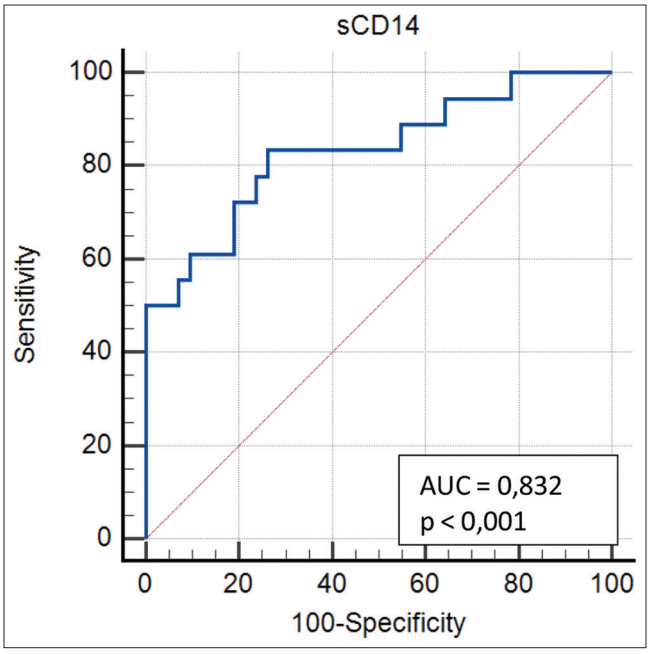

Figure 1: ROC curve of sCD14 and TB infection (AUC = 0.83; 95% CI: 0.71–0.92; p < 0.001)

Bivariate analysis using the Chi-square test showed a significant relationship between sCD14 and active TB infection (Table 2).

Table 2: Bivariate analysis between sCD14 levels and TB infection in HIV patients

sCD14	TB n (%)	No TB n (%)	OR CI (95%)	p
High	15 (53.6%)	13 (46.4%)	11,15	0.001
Low	3 (9.4%)	29 (90.6%)	(2.75–45.30)	
Total	18 (30%)	42 (70%)		

Multivariate analysis with logistic regression showed that the variable associated with TB infection in HIV patients was only sCD14, with the strength of the relationship seen from the adjusted OR of 13.64, while the confounding variables did not have a significant relationship to TB infection in HIV patients (Table 3).

Table 3: Logistic regression analysis of independent and confounding variables on TB infection in HIV

Variable	Adjusted OR	CI 95%	p
sCD14			
High	13.64	2.89–64.42	0.001
Low			
Gender			
Male	0.44	0.09–2.02	0.289
Female			
Age			
≥50 years	1.10	0.19–6.20	0.908
<50 years			
BMI			
Underweight	0.40	0.08–1.95	0.261
Normal weight			
HIV stage			
3–4	1.49	0.02–92.99	0.850
1–2			
Opportunistic infection			
Yes	1.78	0.02–144.71	0.796
No			

Discussion

The subjects of this study were 60 patients with HIV infection, consisting of 42 (70%) men and

18 (30%) women. The mean age of the subjects was 39.13 ± 11.734 years, with 46 (76.7%) people younger than 50 years and 14 (23.3%) people older than 50 years. These results are in accordance with the data on the Situation Report on the Development of HIV/AIDS in Indonesia by the Ministry of Health of the Republic of Indonesia in 2021, where it was found that the prevalence of HIV in men (69%) was higher than women (31%), and by age group, the highest age was at the age group of 25–49 years (71.3%), followed by the age group of 20–24 years (16.3%), and the age group of 50 years (7.9%) [6]. Nutritional status in this study had a median BMI of 18.8 (16.3–23.4) kg/m^2, with 28 (46.7%) underweight and 32 (53.3%) normal weight. This is in accordance with a study conducted by Song *et al*., where the prevalence of HIV patients with normal weight (71.64%) was higher than that of underweight patients (23.68%) [7]. The clinical stage of HIV in this study was found in stage 1–2 in as many as 17 (28.3%) people and stage 3–4 in as many as 43 (71.7%) people; this is in accordance with research conducted by Assemie *et al*., where the percentage of stage 3 HIV–4 (62.3%) is higher than stage 1–2 (37.7%) [8]. A total of 46 (76.7%) people had opportunistic infections, with the most common symptoms of opportunistic infections being wasting syndrome (50%) and chronic diarrhea (43.48%). This is consistent with a study conducted in Kenya, which showed that 78.8% of HIV patients who came to the hospital had opportunistic infections [9]. Lumsden *et al*. found that the most common symptoms in advanced HIV patients were chronic diarrhea and wasting syndrome [10].

This study showed that the median sCD14 level was higher in HIV patients with active TB infection, which was 3549 ng/mL with a range between 1805 and 6147 ng/mL, compared to HIV patients without TB, which was 2285.50 ng/mL with a range between 963.30 and 3582 ng/mL. The cut-off point for sCD14, based on ROC analysis, for active TB infection was more than equal to 2900 ng/mL. Statistical analysis found a significant relationship between sCD14 levels and active tuberculosis infection in HIV patients ($p < 0.001$). High sCD14 levels have a chance of having a TB infection as much as 11.15 times (OR 11.15; 95% CI: 2.75–45.30). Based on multivariate analysis, it was found that sCD14 levels were independently associated with active tuberculosis infection in HIV patients (AOR 13.64; 95% CI: 2.89–64.42; $p = 0.001$). This could be linked to the role of sCD14 in signaling various defensive factors in TB infection. Monocytes and macrophages, which are the main producers of sCD14, migrate to infected tissues as part of the innate immune system. sCD14 then binds to lipoarabinomannan in Mycobacterium tuberculosis, which then induces activation and secretion of proinflammatory cytokines. Increased activation of macrophages and other inflammatory factors in the combined conditions of TB and HIV infection results in higher sCD14 levels in TB-infected HIV patients [11], [12].

This is consistent with previous studies, which showed that the highest sCD14 levels were found in HIV patients with active TB compared to patients without TB infection. Previous studies have also shown that sCD14 levels have the highest sensitivity and specificity values compared to other markers [12], [13], and [14]. Similar results were obtained in Liu's study, where the highest sCD14 results were found in culture-positive HIV patients, who had a median sCD14 value of 2199 ng/mL, compared with culture-negative HIV patients, who had a median sCD14 of 1148 ng/mL [12]. Another study conducted by Druszczynska *et al*. showed that the highest sCD14 levels were found in patients with active TB, which was more than 2000 ng/mL, and the results of the analysis showed that serum sCD14 levels were significantly increased in patients with active TB infection compared to patients without TB infection ($p< 0.001$) [13]. The study by López-Ramos *et al*. compared several biomarkers to differentiate TB and non-TB infections. It was found that sCD14 had the best AUC value of 0.90 ($p = 0.00$), with 100% sensitivity and 58.8% specificity [14]. Other confounding variables in this study, such as gender, age, nutritional status, clinical stage of HIV, and other opportunistic infections, were not significantly associated with tuberculosis infection in HIV patients. This is in accordance with the findings of several previous studies, which also did not find a significant relationship between these factors and tuberculosis [15], [16], [17], [18], [19].

The limitation of this study was that most of the active TB diagnoses in this study were obtained based on sputum specimens, where the quality of the sputum produced also affected the results of the TCM GeneXpert MTB/RIF. However, clinical and radiological symptoms pointed to TB infection, the results of TCM did not detect the presence of Mycobacterium tuberculosis. Confounding factors in this study, such as autoimmune diseases (Systemic Lupus Erythematosus and Rheumatoid Arthritis), which can also affect sCD14 levels, and TB infection, were obtained based on anamnesis, physical examination, and medical history, and no further investigation was performed.

Conclusion

This study proves that sCD14 is an adjunct biomarker in the pathogenesis of TB in HIV infection. This shows that the median sCD14 level in HIV patients with active tuberculosis infection was higher than in patients without tuberculosis infection. The cutoff point for sCD14 levels of more than 2900 ng/mL can be used to determine active tuberculosis infection in HIV patients with a sensitivity of 83.33% and a specificity of 73.81%.

Consent and Ethical Approval

With a well-detailed research proposal and a letter of introduction from the Head of Department, an informed consent form and an application letter were submitted to the Head, Health Research and Ethics Committee of the Institution. After their meetings and thorough perusal of the protocols of the research, ethical approval was given for the study. Participants' written consent has been collected and preserved by the author(s).

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