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Prospective use of soluble urokinase plasminogen activator receptor to screen TB co-infected with HIV patient among TB patient

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ABSTRACT

Background: Tuberculosis patient who co infected with the human immunodeficiency virus (HIV) belong to the patient group at high risk for multi-drug resistant TB (TB-MDR). Early recognition is very important to reduce the number of TB/HIV co-infection cases. Soluble urokinase plasminogen activator receptor (suPAR) is considered to be a strong biomarker in HIV as well as TB patients.
Aim: This study was carried out to evaluate whether suPAR could be used as a biomarker to identify the TB/HIV patients among pulmonary TB-patient.
Patients and methods: We used a cross-sectional study design, in which registered patients were grouped into 3 categories: TB/HIV (n = 15), pulmonary TB-AFB(+) (n = 15), and healthy controls (n = 10). Plasma suPAR levels were measured using ELISA kit. A sputum culture and drug susceptibility test were performed for each patient.
Results: suPAR levels in the TB/HIV group (15.26 ng/mL) were significantly higher ($p < 0.05$) than those in the TB-AFB (+) group (7.75 ng/mL) and the healthy control group (1.76 ng/mL).
Conclusion: Plasma suPAR level of TB patients co-infected with HIV showed significantly difference from that of TB-AFB(+) patients suggested its potential to screen the TB/HIV among pulmonary TB-AFB(+) patients.
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Introduction

Human immunodeficiency virus (HIV) infection accelerates the progression of pulmonary tuberculosis (TB) infection to the advanced stage of the disease and is associated with the reactivation of TB infection [1]. Immunosuppression-induced HIV infection alters the normal immune response toward TB infection, resulting in atypical signs and symptoms, decreased cavitation, and transfer of bacilli into respiratory secretions. Since the progress is slow and sometimes without clear symptoms, HIV co-infection among pulmonary TB patients is hardly recognized in the early phase and hence makes the diagnosis of TB/HIV more complicated [2,3]. In Indonesia, TB/HIV co-infection belongs to one of the 9 TB groups at high risk for multi-drug resistant TB (MDR-TB) [4,5]. In the last decade, the increase of TB/HIV co-infection cases has contributed to the re-emergence of MDR-TB. This is partly due to the late diagnosis of TB/HIV; hence, a reliable assessment method to identify TB/HIV is urgently required, particularly in resource-limited countries.

Soluble urokinase plasminogen activator receptor (suPAR) plays an important physiologic role in the cell, particularly during cell migration, adhesion, angiogenesis, fibrinolysis, and cell proliferation [6]. These molecules are released into several body fluids such as blood, urine, and cerebrospinal fluid. The suPAR level may reflect the presence of inflammation in response to an infection by a microorganism [6,7]. suPAR has been shown to be a strong prognostic biomarker in immunocompromised patients because it is negatively associated with $CD4^+$ cell count, especially in HIV patients [8]. Furthermore, elevated levels of plasma suPAR are associated with high mortality among individuals with a variety of infectious diseases, including active TB, HIV-1 infection, pneumococcus pneumonia, sepsis, and malaria [6,7]. In Indonesia only a few studies have observed the role of suPAR levels as a biomarker [9,10], particularly in related with TB/HIV co-infection. This study aims to investigate whether suPAR could be used to differentiate the immunological condition of TB co-infected with HIV from the

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pulmonary TB patient with positive Acid Fast Bacillus Testing (AFB). This is a preliminary study to assess the potential of suPAR to screen the incidence of TB/HIV among TB patients.

Patients and methods

Patients

This study population was designed using cross sectional observational study. The research subjects consisted of TB/HIV patients (n = 15) and TB-AFB (+) patients (n = 15) who visited Department of Pulmonary, Saiful Anwar Hospital, Malang, Indonesia from August–December 2011. An additional 10 healthy people who served as negative controls were recruited from medical students from Faculty of Medicine, Brawijaya University, Malang. The TB/HIV patients, fulfilled the following inclusion criteria: TB patient but newly diagnosed for HIV by pulmonogist without a history of antituberculosis drugs, testing positive for acid-fast bacilli (AFB), $CD4^+$ cell count <200, age between 15 and 65 years, and agreeing to be a subject of the research by signing informed consent. TB patients with comorbid diseases, such as severe infection (pneumonia or malaria), heart disease, diabetes mellitus, malignancy, or extra pulmonary TB without pulmonary TB and pregnant patients were excluded from the study. The inclusion criteria for TB patients including newly diagnosed TB, age between 15 and 65 years, AFB(+).

Routine examination

TB and HIV diagnosis were performed through several clinical and laboratory investigations in accordance with standard procedures conducted in Indonesian hospitals [11]. These included patient complaints (i.e., clinical history), chest radiography, body mass index, erythrocyte sedimentation rate (ESR), examination of sputum for AFB and mycobacterial culture. For suspected TB who co-infected with HIV, $CD4^+$ cell count and viral load measurement were also conducted.

Microbiological research method

Sputum samples were collected from patients in each group to observe the viability of *Mycobacterium tuberculosis* using Lowenstein–Jensen medium culture [11].

Sample handling

A 3-mL blood sample was obtained from each patient by vena puncture. Sera were centrifuged (6000×*g*) at 4 °C for 10 min, in 0.5-mL aliquots, and subsequently stored at −80 °C.

Enzyme-Linked Immunosorbent assay

Measurement of plasma suPAR levels were performed in duplicate using commercially available enzyme-linked immunoassay kits according to the manufacture's protocol (suPARnostic, ViroGates A/S, Copenhagen, Denmark) [13]. A microplate reader (Biotech) was used to read the optical density of the samples at 450 nm, with the wavelength correction set at 650 nm.

Statistical analysis

Differences between the groups and controls were analyzed using T-test and one-way analysis of variance. All statistical analyses were conducted using SPSS version 16 (IBM Corporation, USA).

Ethics

The present study was approved by the Ethics Committee of Saiful Anwar Public Hospital, Brawijaya University, Indonesia. All patients provided written informed consent.

Results

Characteristics of TB/HIV patients

Among the 30 TB patients who were recruited in this study, there were more male patients (66.7%) than female patients (33.3%) in both groups (i.e. TB/HIV and TB). The majority of patients in both groups had a body mass index of <18.5 kg/m^2 (Table 1). Coughing dominated the clinical symptom that were often found in both groups (TB/HIV and TB). Besides that in the TB HIV patients complaint to loss weight (93,3%), followed by weakness (73,3%), fever (73,3%), and shortness in breath (60%). On the other hand the TB patients showed slightly different symptoms i.e. weight loss (53,3%), chest pain (40%), night sweat (40%) and blood in cough blood (33,3%). For X-ray examination was dominated by far advance lesion on TB groups. However in TB HIV patients milliary lesion (26,7%) and middle lesion (13,3%) were also observed.

Based on the lymphocyte count test, the TB HIV group showed low value (<1200). The measurement of $CD4^+$ cell count demonstrated that from 15 TB HIV patient only 10 patient showed $CD4^+$ cell count with average of 47,7 (<2 0 0),

Sputum examination revealed that the majority of TB/HIV patients (60%) tested negative for AFB; in contrast, all TB were positive for AFB. Surprisingly, when the sputum of TB/HIV patients was cultured, only 60% showed growth (positive culture). Conversely, all of the sputum samples obtained from patients with TB showed a positive culture (Table 2).

Comparison of suPAR levels in TB/HIV and TB patients

The level of plasma suPAR in the TB/HIV group was significantly higher than that in the TB group (15.26 vs. 7.75 ng/mL; $p < 0.001$).

Table 1
Characteristics of TB/HIV and TB patient.

Parameter		TB/HIV	TB
		(n = 15)	(n = 15)
Sex	Male	10(66.7%)	10(66.7%)
	Female	5(33.3%)	5(33.3%)
Age	≤20th	1(6.7%)	0
	21–30th	6(40%)	5(33.3%)
	31–40th	6(40%)	2(13.3%)
	41–50th	2(13.3%)	6(40%)
	51–60th	0	1(6.7%)
	>60th	0	1(6.7%)
BMI (Body Mass Index)	<18,5	10(66.7%)	11(73.3%)
	18,5–23	5(33.3%)	4(26.7%)
	>23	0	0
Clinical symptoms	Cough	14(93,3%)	15(100%)
	Blood in cough	1(6.7%)	5(33.3%)
	Shortness breath	9(60%)	5(33.3%)
	Chest pain	1(6.7%)	6(40%)
	Fever	11(73.3%)	4(26.7%)
	Night sweat	4(26.7%)	6(40%)
	Weakness	11(73.3%)	1(6.7%)
	Loss weight	14(93.3%)	8(53.3%)
Lesion	Normal	0	0
	Minimal	0	0
	Median	2(13.3%)	0
	Far advance	9(60%)	15(100%)
	Miliar	4(26.7%)	0

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