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Original Research Article

Relationship between C-reactive protein, ferritin serum and cluster of differentiation 4 cell count with pulmonary tuberculosis in naive HIV patient in Bali

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ABSTRACT

Background: Diagnostic of Pulmonary tuberculosis (PTB) in patients with Human immunodeficiency virus (HIV) infection remain challenging. Evaluation based on clinical symptoms, inflammation biomarkers, and immunodeficiency status, can provide a feature of PTB disease in HIV patient. The aim of the study was to analyze the relationship between acute phase reactant and immunodeficiency status with PTB in patients with naïve HIV infection.
Methods: A cross sectional study was conducted in Sanglah General Hospital and Kuta Selatan Public Health Service on February-June 2021. C-reactive protein (CRP), Ferritin serum levels, and CD-4 cell count were obtained from patient's serum. Data were collected by questionnaire. Bivariate analysis using Chi square test or Kolmogorov Smirnov test, and multivariate analysis using logistic regression.
Results: A total of 60 participants were included in this study, and 58.3% had pulmonary tuberculosis (38.3% bacteriologically confirmed, 20% clinically confirmed). Fifty five percent participants had CRP level ≥10 mg/l, 83% had ferritin serum level ≥260 ng/ml, and 83% had CD4 cell count<200 cell/ml. Multivariate analysis showed that the most influential factor for PTB in HIV patients was CRP level≥10 mg/l (adjusted prevalence ratio/APR=4.9; 95%CI=7.81-2327,04, p=0.001) and ferritin serum level ≥260 ng/ml (APR=3.32, 95%CI=1.752-433.65, p=0.018).
Conclusions: High CRP and ferritin serum levels were significantly related with PTB in naive HIV patients. No relationship was found between low CD4 cell count and PTB in naive HIV patients.

Keywords: C-reactive protein, Ferritin serum, CD4 cell count, Pulmonary tuberculosis, Naive HIV infection

INTRODUCTION

Pulmonary tuberculosis (PTB) in individuals with Human immunodeficiency virus (HIV) infection is a global problem with a high prevalence and incidence to date. TB-HIV coinfection was mentioned to be associated with increased morbidity and mortality of infected individuals.[1] Indonesia was included in the 8 countries contributing to two-thirds of the total cases globally with a percentage of 8.5%. In 2019, the total incidence of TB cases in Indonesia was 845.000 cases, the incidence of TB-HIV was 19,000 cases, and TB-HIV mortality was 4,700 cases. The prevalence of TB-HIV cases among the total TB cases was estimated at 2.2% (0.95%-4.1%) with TB-HIV mortality

of 1.7%.[1,2]

The estimated annual risk of TB disease reactivation among individuals with latent TB infection and untreated HIV globally ranges from 3%-16%.[3] Enforcement of PTB cases in patients with HIV is a challenge to date. This is caused by the clinical symptoms of PTB are not typical in individuals with HIV. Systemic inflammatory response and micronutrient deficiency in Mycobacterium tuberculosis (MTB) infection can be identified from the assessment of acute phase reactants such as CRP and serum ferritin.[4]

Immunosuppression in HIV patients is associated with CD-4 cell count. TB-HIV coinfection can occur at any CD-4 cell count, although the risk is said to increase with the progression of the immunodeficiency condition and CD-4 lymphocyte depletion.[3,5] The rapid molecular test of sputum is an examination with high sensitivity and specificity for the diagnosis of PTB with higher level of diagnostic accuracy than microscopic examination.[5,6]

Evaluation of clinical symptoms, inflammatory biomarkers, and CD-4 cell counts could help in the initial assessment of PTB manifestations in individuals with HIV, before confirmation by rapid molecular test is performed, especially in health care facilities that do not have these diagnostic tools. The aim of the study was to find out the relationship between CRP, serum ferritin, and CD-4 cell count with pulmonary tuberculosis based on clinical symptoms and signs, and the results of the sputum rapid molecular test in patients with naïve HIV infection.

METHODS

A cross sectional study was conducted in Sanglah General Hospital, Denpasar, Bali and Kuta Selatan Public Health Service started from February 2021 until June 2021. A total of 60 participants were included in this study. All participants were patients diagnosed with naïve HIV infection who underwent treatment at Sanglah Hospital and Kuta Selatan Public Health Service, and recruited by consecutive sampling.

Inclusion criteria were all patient diagnosed with naïve HIV infection in Sanglah General Hospital and Kuta Selatan Public Health Service, more than 18 years old, and willing to participate in this study. Patients with HIV infection on Highly active antiretroviral therapy (HAART), patient with malignancy, patient with type 2 diabetes mellitus, history of others immunosuppression disease, others acute infection, acute physically trauma, and patients in pregnancy were excluded.

PTB in patient with HIV infection were diagnosed based on clinical sign and symptoms, and also from the result of sputum rapid molecular test. The confirmation of diagnosis was divided by bacteriologically and clinically. CRP and ferritin serum level were measured by photometry method and the value based on cut of point. CD-4 cell count were measured by flow cytometry method and the value result divided into <200 cell/ml and ≥200 cell/ml. Inpatients blood samples were obtained on fifth to seventh day of admission, after clinical symptoms improved and or when the patient discharge from the hospital in order to reduced diagnostic bias. Outpatients blood samples were obtained during a visit to pulmonary polyclinic and or Voluntary counselling and testing (VCT) clinic. Patients with naïve HIV infection who came to the polyclinic or admitted at Sanglah Hospital and Kuta Selatan Public Health Service were interviewed. After physical examinations, chest X-ray examination, and sputum rapid molecular test were performed, then venous blood was taken to measure the levels of CRP, ferritin serum, and CD-4 cell count. All data result was completely record and filled out on the questionnaire. Naive HIV patients with clinically confirmed of PTB were followed up 2 weeks to 1 month after Antitubercular drugs (ATD) administration to assess clinical improvement of PTB, thereby strengthening the diagnosis of clinical PTB and reducing the possibility of diagnostic bias. Informed consent was obtained from all study participants. Ethics and licensing are completed according to the provisions. The collected data was then processed using IBM SPSS Statistics 26.0. Bivariate analysis using Chi square test or Kolmogorov Smirnov test, and multivariate analysis using logistic regression.

RESULTS

Sixty naive HIV infection patients met inclusion criteria, and 41 patients (68.3%) were male. Median age was 35.5 years old with interval range 22-59 years old, and the median of Body mass index (BMI) was 18.95 kg/m^2 with a BMI range 13.6-24.4 kg/m^2. Only 28 participants (46.7%) had a history of smoking.

Clinical symptoms of PTB were found in 34 samples (56.7%). Chest X-rays supporting TB were found in 34 samples (56.7%) with a feature of pulmonary infiltrates at the apices in 16 samples (47.1%), hilar lymphadenopathy in 4 samples (11.7%), and miliary appearances in 14 samples (41.2%). The median CRP level was 11.48 mg/l with a range of values between 1.04-81.13. The median ferritin level was 554.04 ng/ml with a range between 27.42-7368.51. The median CD-4 cell count was 100 cell/ml with values ranging from 3-580. The results of rapid molecular test examination showed that MTB detected low in 6 samples (10%), MTB detected medium in 13 samples (21.7%), MTB detected high in 4 samples (6.7%), and MTB not detected obtained in 37 samples (61.7%). Twenty-three samples were bacteriologically confirmed, 12 samples were clinically confirmed, and 25 samples were non PTB (Table 1).

Clinical improvement of TB symptoms were found in all patients with clinically confirmed PTB after 2 weeks ATD treatment. Based on the Receiver operating characteristic (ROC) analysis, the Area under the curve (AUC) value for CRP was 97.7% and AUC value for ferritin was 87%. In

this study, the optimal cut-off point for CRP was 10 mg/l with a sensitivity of 88.6% and a specificity of 92%. Meanwhile, the optimal cut-off point of ferritin is 260 ng/ml with a sensitivity of 94.3% and specificity of 68% (Figure 1). Bivariate analysis showed that CRP value≥10 mg/l had clinically and statistically significant relationship with PTB [prevalence ratio (PR)] 6.341; 95%CI=2.556-15.731, p<0.0001), ferritin serum value≥260 ng/ml had clinically and statistically significant relationship with PTB (PR=7.646; 95%CI=2.043-28.661, p<0.0001), CD-4 cell count<200 cell/ml had clinically and statistically significant relationship with PTB (PR=7.646; 95%CI 2.043-28.611, p<0.0001), and nutritional status also had clinically and statistically significant relationship with PTB (PR=2.21, 95%CI=1.34-3.49, p<0.0001) (Table 2).

Table 1: Participant's characteristics (N=60).

Characteristics	N (%)	Median (min-max)
Gender		
Male	41 (68.3)	
Female	19 (31.7)	
Age (years)		35.5 (22-59)
Body mass index (kg/m^2)		18.9 (13.6-24.4)
Smoking history		
Smoker	28 (46.7)	
Non-smoker	32 (53.3)	
Clinical sign of PTB		
Yes	34 (56.7)	
No	26 (43.3)	
Chest X-ray		
Supporting PTB	34 (56.7)	
Within normal limit	26 (43.3)	
CRP (mg/l)		11.48 (1.04-81.13)
Ferritin (ng/ml)		554.04 (27.42-7368.51)
CD4 (sel/ml)		100 (3-580)
Rapid molecular test		
Not detected	37 (61.7)	
Detected low	6 (10.0)	
Detected medium	13 (21.7)	
Detected high	4 (6.7)	
Confirmation of PTB		
Non-PTB	25 (41.7)	
Clinically PTB	12 (20.0)	
Bacteriological PTB	23 (38.3)	

Table 2: Bivariate analysis of CRP, ferritin, CD-4 cell count, gender, age, nutritional status and smoking status to PTB.

Variables	N (%)	PTB	Non-PTB	Prevalence ratio (PR)	95% CI	P value
CRP (mg/l)						
High (≥10)	33 (55)	31	2	6.341	2.556-15.731	<0.0001
Low (<10)	27 (45)	4	23			
Feritin (ng/ml)						
High (≥260)	41 (83)	33	8	7.646	2.043-28.611	<0.0001
Low (<260)	19 (17)	2	17			
CD-4 (cells/ml)						
<200	41 (83)	33	8	7.646	2.043-28.611	<0.0001
≥200	19 (17)	2	17			
Gender						
Male	41 (68)	27	14	1.56	0.88-2.77	0.083
Female	19 (32)	8	11			
Age (years)						
<35.5	29 (48)	16	13	0.90	0.59-1.39	0.631
≥35.5	31 (52)	19	12			

Continued.

Variables	N (%)	PTB	Non-PTB	Prevalence ratio (PR)	95% CI	P value
Nutritional status (BMI in kg/m^2)						
<18.5	26 (43)	22	4	2.21	1.40-3.49	<0.0001
≥18.5	34 (57)	13	21			
Smoking status						
Smokers	28 (47)	17	11	1.08	0.71-1.65	0.726
Non-smokers	32 (53)	18	14			

Table 3: Multivariate analysis of CRP, ferritin, CD-4 cell count and nutritional status to PTB

Variables	Initial model			Final model		
	APR	95%CI	P value	APR	95%CI	P value
CRP ≥10	4.99	4.64-4735.10	0.005	4.90	7.81-2327.04	0.001
Ferritin ≥260	2.78	0.86-301.86	0.063	3.32	1.752-433.65	0.018
CD4<200	1.397	0.12-132.65	0.433	1.41	0.12-137.05	0.429
Nutritional status	1.32	0.197-70.45	0.380	1.41	0.49-33.79	0.193

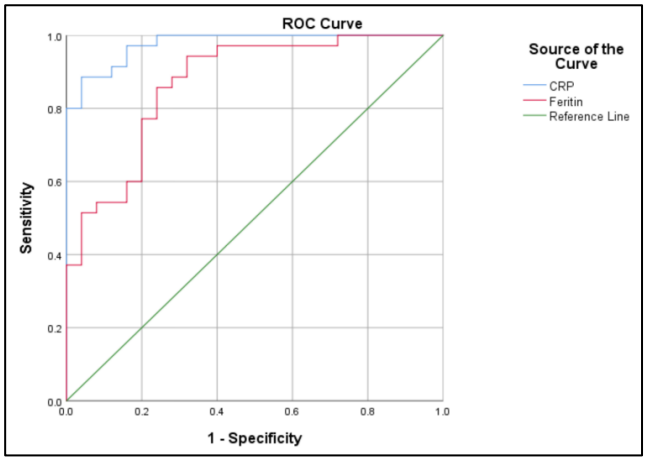

Figure 1: Receiver operating characteristic (ROC) analysis and Area under the curve (AUC) value for CRP and ferritin.

Multivariate analysis with logistic regression on the variables that in the bivariate analysis had a significant p value, including nutritional status (p=0.238), CRP≥10 mg/l (p=0.005), ferritin serum≥260 ng/ml (p=0.063), and CD-4 cell count<200 cell/ml (p=0.243). Based on the results of the analysis showed that the most influential variable in relationship with PTB was CRP≥10 mg/l with an adjusted PR of 4.9 (95%CI=7.81-2327.04, p=0.001) and ferritin serum≥260 ng/ml with an adjusted PR=3.32 (95%CI=1.752-433.65, p=0.018) (Table 3).

DISCUSSION

This study found more male participants, with a median age of 35.5 years. Shapiro et al in 2018 reported HIV patients were more common in men (58%), with a median age of 32 years.[6] The median BMI in this study was 18,9 kg/m^2 with a range of 13.6-24.4 kg/m^2. This is similar with the prospective study conducted by Yoon et al in 2017, in which stated that the median BMI of patients with naïve HIV infection who have just started Antiretroviral (ARV) therapy was 21.2 kg/m^2.[7] In our study, PTB symptoms mostly was weight loss and cough for more than 2-3 weeks. A prospective study in Uganda showed that patients with TB-HIV co-infection presented with the most symptoms of weight loss and subacute and chronic cough.[8] Thirty-four patients in our study showed typical radiographic features of PTB, with a predominant infiltrate at the lung apex. Nakiyingi et al in 2021 in a retrospective study obtained a characteristic chest X-ray of patients with TB-HIV coinfection with 39.1% superior lobe infiltrates and 41% inferior lobe infiltrates.[8] Diagnosis of PTB in our study was based on clinical signs and symptoms of PTB, chest X-ray images and the results of the sputum rapid molecular test. Kakoma et al through a retrospective observation in Namibia found that from 400 sputum samples of HIV patients who underwent evaluation of active TB, 253 samples with positive results through rapid molecular test while 133 samples with positive microscopic examination, this showed that rapid molecular test examination can significantly reduce false-negative results, delay initiation of antitubercular treatment, reduce TB-related mortality, and transmission rates in the population.[9]

In our study, the optimal cut-off point of the CRP value was 10 mg/l. Yoon et al conducted a diagnostic accuracy study to assess CRP as a TB screening method in HIV patients were found the optimal cut off point for CRP was 9 mg/l, with a sensitivity value of 90% and specificity 70%.[7] Meca et al in a meta-analysis involving 9 studies to assess diagnostic accuracy of CRP in HIV patients with PTB found a reference value of CRP 8 mg/l can be used as a screening biomarker for active TB in HIV patients and also to evaluate the response to antitubercular therapy.[10]

In our study, the optimal cut-off point of ferritin was 260 ng/ml. Hyperferritinemia in patients with HIV infection and severe immunosuppression was associated with TB disease. Mishra et al found the optimal cut-off point value of ferritin was 380 ng/ml in HIV patients with TB compared with controls, this study also showed iron redistribution was associated with the presence of new

infection or reactivation of MTB. In positive smear results, the increase in ferritin levels corresponds to the level of positivity of smear sputum.[11] Opolot et al in a prospective study obtained a cut-off point of ferritin levels of 300 ng/ml to differentiate the incidence of TB disease in individuals with a history of HIV infection who had not started ARV therapy compared to the control group.[12] Akpan et al in case-control study reported that the optimal cut-off point for ferritin levels of 360 ng/ml to distinguish the presence of active TB and associated with the presence of anemia.[13]

In our study, analysis through Chi square test between CRP and PTB with a reference value of CRP≥10 mg/l was found a statistically significant difference with a prevalence ratio of 6.34 (p value<0.0001). Wilson et al in South Africa found an odds ratio of 6.37 in the bacteriologically and clinically confirmed TB group compared to the control group without TB in the sample with HIV infection.[14] Foromera et al in a retrospective study involving 90 patients with HIV infection found that the combined CRP value 10 mg/l and Erythrocyte sedimentation rate (ESR) 100 was significantly associated with TB disease.[15] A prospective study conducted in South Africa with a sample of 93 HIV patients who were evaluated for the presence of TB disease, showed the combination of increased CRP value (>8 mg/l) and clinical symptoms of TB could increase the accuracy of screening for active TB in individuals with HIV infection.[16]

In our study, analysis between the ferritin level and PTB with a ferritin reference value of ≥260 ng/ml found the prevalence ratio was 7.65 (p value≤0.0001). Study by Visser and Mostert stated hyperferritinemia was found in individuals with HIV infection with TB disease compared to individuals without HIV infection and significantly associated with the presence of active TB conditions in HIV patients.[17]

Bivariate analysis in our study regarding CD-4 cell count on the prevalence of PTB with a reference value of <200 cells/ml showed a prevalence ratio of 7.65 (p value<0.0001). Olsson et al through a prospective observation found CD-4 cells count <200 cells/ml was significantly associated with a higher incidence of PTB and CD-4 cells count in HIV with PTB group was negatively correlated with CRP levels.[18]

Based on the multivariate analysis in our study, the Adjusted prevalence ratio (APR) value for the CRP variable was 4.9. These results indicated an increase in the risk of PTB prevalence by 4.9 times in an individual with HIV infection at CRP levels≥10 mg/l after adjustment for variables considered to be confounding such as age, gender, nutritional status and smoking status. The ferritin variable obtained an APR value of 3.32 which indicates an increased risk of PTB prevalence by 3.32 times in an individual with HIV infection with a ferritin level of ≥260 ng/ml after adjustment for variables considered to be confounding such as age, gender, nutritional status and smoking status.

Lawn et al through a prospective study found that the AOR value of the CRP variable was 2,0 at the CRP reference value 10 mg/l after adjustment for confounding variables such as age, gender, nutritional status, baseline viral load, and CD-4 cell count.[19] Dermid et al conducted an 11-years retrospective study was found that ferritin is a independence biomarker risk factor of TB incidence in patients with HIV infection with an Incidence rate ratio (IRR) of 1.26 after adjusting for confounding variables such as age, gender, nutritional status and CD-4 cell count.[20] Meanwhile, based on multivariate analysis low CD-4 cell count in our study was not statistically significant with PTB after adjustment for confounding variables such as age, gender, nutritional status and smoking status. A retrospective study conducted by Negussie et al in patients with HIV infection also found that progressive decline in the CD-4 cell count is said to be associated with the incidence of extrapulmonary TB compared to PTB.[21]

Limitations of this study was the possibility of information bias when data collecting through questionnaires, especially in terms of smoking status of the research subjects. On the other hand, socioeconomic status and occupation from research subjects which is not evaluate in our study could be as confounding also.

CONCLUSION

In this study, most naive HIV patients with PTB had high CRP and ferritin serum level. CRP level ≥10 mg/l and ferritin serum level ≥260 ng/ml were significantly related with PTB in naïve HIV patients. No relationship was found between low CD-4 cell count with pulmonary tuberculosis in naïve HIV patient. CRP level was the most influential factors related to the pulmonary tuberculosis in patient with naïve HIV patient. In addition, it is also necessary to conduct further research with another prospective methods to assess the relationship CRP and ferritin level as prognostic and improvement factors during and after completing antitubercular treatment in HIV infection patient with pulmonary tuberculosis.

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