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THE ROLE OF CD4 LEVELS IN PREDICTING PENICILLIOSIS IN HIV/AIDS PATIENTS AT HAJI ADAM MALIK GENERAL HOSPITAL MEDAN

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Abstract
Introduction: Around 36.9 million people currently live with HIV with a high number of deaths, which can threaten the lives of HIV sufferers not only from the virus itself, but also opportunistic infections (OIs). *Penicillium marneffei* is one of the OIs that causes morbidity and mortality in patients infected with HIV. In areas with high endemicity, a CD4 level <100 cells/μL is predominantly at risk of infection with *P. Marneffei.*

Aim: To know the role of levels CD4 <100 cells/μL in predicting the occurrence of penicilliosis HIV/AIDS patients.

Methods: Diagnostic test study with cross-sectional design on 100 respondents, where research data uses secondary data within medical records of HIV/AIDS patients to get cut off value, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CD4 <100 cells /μL for diagnose the penicillosis. Data analysis using SPSS 20th.

Result: Based on the results of diagnostic tests CD4 levels <100 cells/μL with the incidence of penicilliosis in HIVAIDS patients, this study get a cutoff value: 14.5 cells/μL with [AUC: 0.5, p = 0.806; Sensitivity (63.1%); Specificity (42.9%); PPV (67.2%); NPV (38.5%); Accuracy (56%)].

Conclusion: In this study, CD4 <100cells/μL can not be used to predict penicilliosis in HIV/AIDS patients.

Introduction

HIV/AIDS infection is still a global health problem, including in Indonesia.[1] In Indonesia, since 1999, there has been an increase in the number of people living with HIV in higher-risk groups of people infected with HIV, such as sex workers and injection drug users, gay and women at low risk. Based on provincial reports, the highest number of cumulative cases of HIV infection reported from 1987 to September 2014 was DKI Jakarta Province (32,782 cases). The top ten cases of HIV are in the provinces of DKI Jakarta, East Java, Papua, West Java, Bali, North Sumatra, Central Java, West Kalimantan, Riau Islands and South Sulawesi.[2]

Nowadays HIV has a high number of deaths, which can threaten the lives of HIV sufferers not only from the virus itself, but opportunistic infections (OIs) and its complications can also cause death.[3] HIV-infected individuals with CD4 counts <100 cells/μL are at risk of being infected with the fungus *P. marneffei*, even in areas with high endemicity, being the majority infected.[4] HIV patients with CD4 <50 cells/μL, (80%) had penicillosis.[5] Fungal infection *P. marneffei* is an important cause of morbidity and mortality in HIV-infected patients in Southeast Asia.[6]

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Method

This research was diagnostic test study with cross-sectional study design.The data was taken within medical record patient at General Hospital Haji Adam Malik Medan. The data collection obtained from inpatients and outpatients with a diagnosis of HIV/AIDS in Haji Adam Malik Hospital that existed from August 2018-November 2019.

Data sample was collected with consecutive sampling technique in 100 patients which including the inclusion criteria as follows: HIV/AIDS patients with a CD4 level <100 cell/µL with skin lesions and get a touch biopsy examination and age >18 years old also the exclusion criteria as follows: data within medical records was incomplete and recurrent HIVAIDS patients. The samples were taken with minimum sample size calculation formula and processed using statistical software 20th.

Result

This study was attended by 100 respondents with HIV/AIDS which as inclusion and exclusion criteria.

Table 1. Distribution characteristics of respondent

Variable	N: 100 (%)
Sex	
Man	85 (85%)
Women	15 (15%)
Age(groups)	34 (19-63)
18-24	10 (10%)
25-34	42 (42%)
35-44	32 (32%)
45-54	12 (12%)
>55	4 (4%)
Occupation	
Trained	10 (10%)
Semi-trained	81 (81%)
Rude work	2 (2%)
Does not work	5 (5%)
Student	2 (2%)
Residence	
Urban	46 (46%)
Rural	54 (54%)
CD4 (cell/µL)	21 (1-99)
Penicilliosis	
Yes	65 (65%)
No	35 (35%)

This distribution characteristic study found dominantly men (85%) then women (15%) with most common age group was adult were (25-34) years, (35-44) years and (45-54) years. The top three types of occupations most respondents were semi-trained (81%) followed by trained (10%) and respondent who does not work (5%). Most of them live in rural areas (54%). Labolatorium result of level CD4 found that median and minimum-maximum

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was CD4 = 21 (1-99) cells/ µL. The percentage of respondents suffering from penicilliosis was (65%), most common then groups without penicilliosis. (Table 1)

Based on bivariate analysis there were no significant differences in characteristics distribution between respondent in both groups with and without penicillosis including sex (p = 0.660), age (p = 0.624), occupation (p = 0.157) and residence (p = 0.424). (Table 2)

Table 2. The relationship of the characteristics respondent to peniciliosis

Variable	Penicilliosis		p-value
	Ya (%)	No (%)	
Sex			0,660
Man	56%	29%	
Women	9%	6%	
Age(groups)			0,624
18-24	6%	4%	
25-34	24%	18%	
35-44	23%	9%	
45-54	9%	3%	
>55	3%	1%	
Occupation			0,157
Trained	5%	5%	
Semi-trained	57%	24%	
Rude work	1%	1%	
Does not work	1%	4%	
Student	1%	1%	
Residence			0,424
Urban	28%	18%	
Rural	37%	17%	

Table 3. CD4 levels in HIV / AIDS compared between group sufferes penicilliosis and without penicilliosis

Level CD4 (cells/µL)	HIV/AIDS Respondent		P-Value
	Penicilliosis (+)	Penicilliosis (-)	
Median	21	21	0,806
Minimum - Maximum	1-99	1-98	

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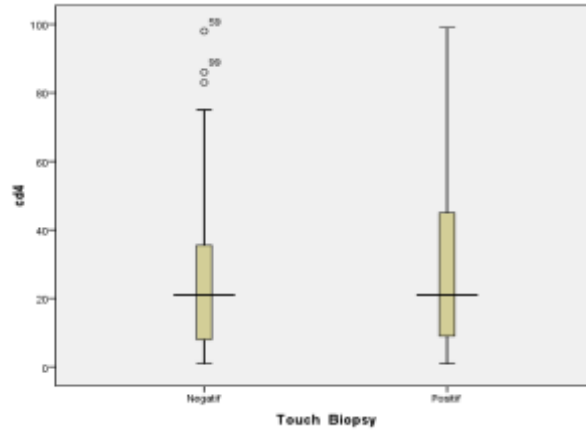

Figure 1. Box plots of Touch Biopsy to CD4

This study found the median, minimum and maximum CD4 levels both groups penicilliosis (+) and the penicilliosis (-) have almost the same value. The group of penicilliosis (+) had a median CD4 of 21 (1-99) cells/µL group penicilliosis (-) also had a median of CD4 21 (1-98) cells/µL. Based on the bivariate analysis, there were no significant differences in CD4 levels were found between both groups (p> 0.05). (Table 3)

Table 4 . Penicilliosis diagnostic test using cutoff values CD4 =14.50 cells/µL

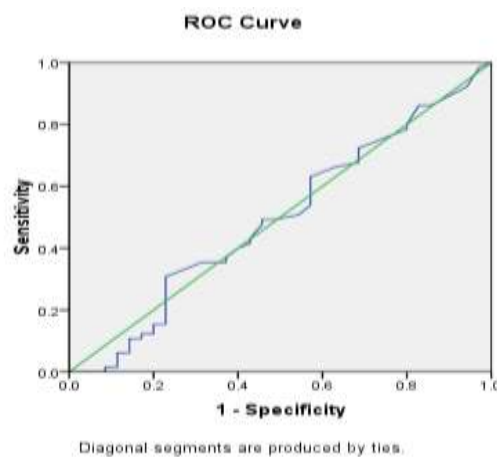| Diagnostic Test	Values
Sensitivity	63,1%
Spesicificity	42,9%
Positif predictive value (PPV)	67,2%
Negative predictive value (NPV)	38,5%
Area under the curve (AUC)	0,5
Accuracy	56%

Diagonal segments are produced by ties.

Figure 1. ROC curve level of CD4 to penicilliosis

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The diagnostic test in this study has two variables were CD4 as a predictor variable and the incidence of penicillosis in HIV patients as a gold standard variable. The sensitivity value of CD4 examination was (63.1%) where the ability of CD4 to give positive results of penicilliosis in HIV patients was (63.1%). The results of the study showed that the specificity (42.9%) means that the ability of CD4 cell <14.5 cells/µL to accuracy diagnose was true according to HIV patients who were not infected with penicillosis (42.9%). The results of this study indicate CD4 levels have a higher sensitivity value than specificity values, this means that CD4 levels have the ability to screen for or detect penicilliosis better than for diagnostics. This study also found the estimated CD4 positive value of (67.2%), which means that HIV patients with a CD4 test result <14.5 cells/µL, then (67.2%) chance of being penicilliosis positive. An estimated negative value (38.5%) has a meaning that subjects with a CD4 test result >14.5 cells/µL then (38.5%) chance of being negative for penicillosis.

Based on the ROC curve it was found that the CD4 AUC is (0.5), it can be concluded that statistically the CD4 level in this study had a very weak AUC interpretation value (0.5) and a weak accuracy value (56.0%). Based on the sensitivity, specificity, AUC and accuracy of the CD4 cell, it shows that the CD4 cell with a cutoff value 14.5 cells/µL cannot be used to diagnose penicilliosis in HIV.

Discussion
In a study in Thailand in 1997 in 80 HIV patients with penileillosis it turned out that the majority were male as many as (88.8%) and women only (11.3%) women. Similar to this study that was found the majority of research subjects were men (85%). The incidence of HIV/AIDS is experienced commonly in men because it is more involved in active transmission of the virus through sexual relations by changing partners, more exposure to the use of injection drug needles, and same-sex sexual activity. In previous studies it was known that this was related to the way HIV was transmitted, reported 45% in heterosexuals; 40% of injecting narcotics users; 15% in homosexuals.[7]

In previous studies of 513 HIV patients infected with penicilliosis, the average age was between 25-32 years.[8] Similar to this study where the majority were found, (42%) subjects were aged 25-24 years. But in other places obtained from 80 people of the study subjects, the average age of younger than this study who suffer from HIV with penicilliosis was between (16-30) years (66.3%). This may be related to where young people have greater opportunity to be exposed to the reservoir environment of the *P. marneffei* fungus, because they have more opportunities to work, or travel to areas endemic to penicilliosis.[9]

We found that all research subjects found 81 people (81%) had semi-trained jobs. Different things were found in other studies where the majority of HIV/AIDS patients with penicillosis were rude workers at 42.5%, followed by semi-trained workers (21.3%). A case report in Thailand shows that 56.3% of HIV patients infected with penicillosis live in rural areas because these patients often have close contact with the soil, which is the reservoir of *P. marneffei* fungus, even though there were also patients lived in urban areas (43.8%).[9] In this study the majority of research subjects have a residence in rural areas that is as much as (54%) and those who have positive touch biopsy results positif penicilliosis live in rural areas (37%), while 28% live in urban areas. The risk of penicillosis infection in HIV patients is not limited to patients who live in endemic areas, individuals who have visited endemic areas also have a risk of penicilliosis. Even in Thailand, a case report showed that *P. marneffei* fungi could be spread through dogs, where they found the fungus in a dog's nose swab.[10]

In this study found that all HIV patients with penicillosis had CD4 cell counts of less than 100 cells/µL. The same thing from the data presented in Thailand in HIV patients infected with penicilliosis had an average CD4 value of 63.8 cells/µL.[11] In another study conducted in Hong Kong the majority of HIV patients with penicilliosis had a CD4 <50 cells/µL (81%).[12] Study in 100 subjects, (65%) had positive touch biopsy results and 35% the study subjects did not find fungus growth on touch biopsy examination. Penicilliosis generally occurs in immunosuppressant patients where one of them is an HIV patient. This tendency is mainly in HIV patients with CD4 <100 cells/µL and even 80% of penicilliosis patients with HIV have CD4 <50 cells/µL.[5]

Research conducted in Vietnam by V.T. Son, et al. found that the majority of HIV patients with penicilliosis were men (89%).[13] In this study of all research subjects found (81%) had semi-trained jobs, compared to other

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studies found the majority of occupations of HIV patients infected with penileillosis were rude workers (42.5%), then followed by semi-trained workers (21.3%). A case report in Thailand shows that 56.3% of HIV patients infected with penile disease live in rural areas. Which also says that these patients have close contact with the soil, which is where the reservoir of penicilliosis.[9]

In this study, the average CD4 value in patients with positive penicilliosis was 29.5 mL, with a median value of 21 cells/µL. While HIV patients without penicillosis had an average CD4 cell count of 28.29 cells/µL. In a study conducted by Wong, et al found that the majority of HIV patients suffering from penileillosis had CD4 levels <50 cells/µL.[14] Likewise, a study conducted by Ghazali, et al in Malaysia in 2012, showed the majority of HIV patients suffering from penicilliosis had CD4 levels <50 cells/µL.[15] However, from this study it was found that CD4 had no significant differences on penicillosis in HIV/AIDS patients ($p = 0.806$). In addition, examinations to enforce penicilliosis in other studies have used serology, which is already routinely done in the endemic area of penileillosis in HIV patients with CD4 <50 cells/µL.[16]

In this study, a diagnostic test was performed to assess CD4 cell count as a predictor of the incidence of penicillosis in HIV/AIDS patients. The CD4 cutoff value for diagnosing penicillosis in HIV patients was 14.50 cells/µL. It was found that CD4 levels showed a higher sensitivity of (63.1)%, while the specificity of CD4 levels to diagnose penicillosis was (42.9%). This study also found positive predictive value of a CD4 (67.2%) which means that an HIV patient with a CD4 level test result <14.5 cells/µL, then (67.2%) chance of positive penicillosis. The negative predictive value (38.5%) has the meaning that subjects with CD4 test results >14.5 cells/µL then (38.5%) the possibility of negative penicillosis.

ROC curve found that AUC was (0.5) (very weak) and accuracy was weak (56.0%). Based on the sensitivity, specificity, AUC and accuracy of the CD4 level with a cutoff value 14.5 cells/µL cannot be used to predict penicillosis infection in HIV/AIDS at Haji Adam Malik General Hospital. Another study showed the results of CD4 levels in HIV patients infected with penicillosis with a median CD4 level of 14.5 cells/µL, where skin lesions had a manifestation after fever and anemia, apparently having high mortality rates and statistically significant.[17] Previous study at Haji Adam Malik General Hospital found that CD4 counts <100 cells/µL had an association with the incidence of penicillosis and were statistically significant.[18]

The results of this study differ from the results of research in Malaysia, where it is said that CD4 levels <50 cells/µL can be used as predictive values to diagnose penicillosis in patients with HIV/AIDS, and with clinical manifestations that support penicillosis then prophylactic administration can be considered in these patients.[15] A case report in H. Adam Malik General Hospital the incidence of penicillosis often appears in HIV patients with CD4 levels <100 cells/µL.[5]

These studies the majority of penicillosis will be found in HIV patients who have CD4 levels <100 cells/µL with skin manifestations. This might be because the examination to enforce penicillosis in this study is limited to touch biopsy, because other systemic mycoses can also be found with this examination, where in other studies to enforce penicillosis, blood culture, skin culture, then continued with bones marrow examination and body fluids. In addition, other studies assess clinical manifestations other than skin lesions found in HIV patients with CD4 levels <100 cells/µL suspected with penicillosis, and assess risk factors that patients tend to have penicilliosis infection.

Conclusion
In this study, CD4 <100cells/µL can not be used to predict the diagnose of penicilliosis in HIV/AIDS patients.

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