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The Role of Lactate Dehydrogenase (LDH) Compared to Arterial Blood Gases (ABG) in Diagnosing Pneumocystis Carinii Pneumonia (PCP) in HIV/AIDS Patients on Routine Antiretroviral Therapy

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ABSTRACT

Background: The lungs are one of the primary target organs for HIV disease and a major source of morbidity and mortality, among others, caused by *Pneumocystis carinii pneumonia* (PCP) or recurrent bacterial pneumonia. In developing countries, the incidence of PCP infection has soared, with high mortality rates ranging from 20% to 80%. The increase in serum LDH plays an important role in determining the severity of the disease. This study aims to determine the role of LDH examination as a diagnostic tool for PCP and Arterial Blood Gases (ABG) in HIV and AIDS patients.
Method: This research is an analytical study using an observational diagnostic test design, conducted from November 2020-January 2021 at the HIV Treatment Room at H. Adam Malik Hospital, Medan with 158 subjects. We calculate the value of sensitivity, specificity, positive predictive value, and negative predictive value.
Results: 75.3% of the total sample was male, with the highest age group being 30-39 years old (46.2%) 126 samples (79.7%) had CD4 levels 200 cells/mm3, 98 samples (62%) had LDH levels > 500 U/L. In this study, 113 samples (71.5%) fell into the ABG criteria [PaO2] <70 mmHg). LDH has superior sensitivity and specificity value compared to ABG examination. In this case PaO2 or A-A DO2 in diagnosing PCP in HIV-AIDS patients.
Conclusion: LDH examination combined with clinical and radiological examinations has good sensitivity and specificity in the diagnosis of PCP.

***Keywords*:** HIV, AIDS, *Lactate dehydrogenase, PCP*

INTRODUCTION

The lungs are one of the primary target organs for HIV disease and a major source of morbidity and mortality, among others, caused by *Pneumocystis carinii pneumonia* (PCP) or recurrent bacterial pneumonia.[1] PCP infection was one of the first signs that the HIV/AIDS epidemic was starting in the United States. PCP soon became one of the leading AIDS-related diseases in the United States. In the late 1980s, about 30-40% of people with HIV/AIDS were diagnosed with PCP.[2] In developing countries, the incidence of PCP infection has soared, with high mortality rates ranging from 20% to 80%.[3] The incidence of HIV-associated PCP is reported in varying amounts worldwide.

PCP is an important disease in HIV/AIDS patients in developing countries, with a high mortality rate. Before the widespread use of prophylactic antibiotics and antiretroviral therapy (ART), PCP

occurred in 70%-80% of patients with AIDS; and in the disease's course, PCP was associated with a 20%-40% mortality rate in immunosuppressive individuals. Approximately 90% of PCP cases occur in patients with CD4 T-lymphocytes (CD4 cells) of <200 cells/mm3. Other factors associated with a high risk of PCP include CD4+ cell percentage <14%, recurrent PCP, weight loss, and high plasma HIV RNA levels.[4]

LDH levels are often used as a marker of lung injury in PCP cases, and we associate their elevation with hypoxemia and have prognostic value. Serum lactate dehydrogenase (LDH) enzyme will be elevated in almost all cases of PCP over 250 IU/L.[5-7] Elevated serum LDH levels in samples of PCP patients are due to the release of LDH from host cells in response to cytoplasmic membrane damage and damage, lungs because of pathogens.[8] Elevated serum LDH is not specific enough to show lung parenchymal damage and in differentiating PCP from other types of pneumonia, but plays an important role in determining the severity of the disease. Decreased oxygen saturation as measured by pulse oximetry during exercise can diagnose PCP, especially in patients who have minimal symptoms, do not appear seriously ill, and have an atypical chest X-ray.[9]

Although the gold standard for diagnosing PCP is PCR examination of airway specimens such as BAL fluid, many have obstacles in terms of the availability of examinations and these diagnostic measures cannot be carried out, especially with the COVID-19 pandemic (coronavirus disease 2019).[10] However, early detection of PCP cases must still be done so that they can be treated immediately and prevent mortality. Therefore, researchers are interested in knowing the diagnostic accuracy of serum LDH compared to changes in Arterial Blood Gases (ABG) in diagnosing PCP in patients with HIV AIDS, especially at H. Adam Malik Hospital, Medan.

MATERIALS AND METHODS

This research is an analytic study using an observational diagnostic test design, carried out by collecting medical record data of HIV/AIDS patients diagnosed with and without PCP in the time interval of 2019. We plan data collection for 3 months, starting from November 2020-January 2021. We conducted this study at the Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/ RSUP H Adam Malik Medan after obtaining approval from the Research Ethics Commission of the Faculty of Medicine, Universitas Sumatera Utara. There were 560 HIV/AIDS patients treated at the Haji Adam Malik General Hospital in Medan for the 2019 period, of which 158 HIV/AIDS patients met the criteria.

Each patient with risk factors and clinical symptoms of HIV underwent a rapid test and ELISA 3 methods to confirm the diagnosis of HIV AIDS. We included patients with confirmed HIV AIDS as subjects in this study. Examination of clinical signs and symptoms of PCP infection both clinically and radiologically confirmed diagnostic by ABG examination. We performed arterial blood sampling on research subjects to determine ABG levels as a biomarker of PCP infection.

The research subjects were divided into 2 groups, namely the first group was HIV-AIDS patients who showed clinical signs and symptoms of PCP infection (change in ABG value, namely [PaO2] 70 mmHg or difference in [AA] DO2 ≤ 35mmHg) and the second group was HIV-AIDS patients who showed signs and symptoms of PCP infection, but changes in ABG values, namely [PaO2] <70 mmHg or differences in [AA] DO2 >35mmHg. All research subjects underwent serum LDH examination, namely by taking venous blood from research subjects to determine serum LDH levels as a biomarker of PCP infection.

Statistical Methods

Univariate and bivariate analyzes were performed. Univariate analysis was

performed to get the distribution of sample characteristics. We then tabulated the data in a 2x2 table to find the value of sensitivity, specificity, positive predictive value, and negative predictive value. We analyzed data using the computer program SPSS version 23 (Statistical Product and Service Solution) and a 95% confidence interval.

RESULTS

A total of 158 HIV/AIDS patients met the criteria in this study, we presented the characteristics of the subjects in this study in Table 1. The majority of the study subjects were male, 119 people (75.3%) with a median age of 35 years. The largest percentage of research subjects were 73 people (46.2%) aged 30-39 years, and the smallest was 2 people (1.3%) aged < 20 years. There were 106 HIV-AIDS patients diagnosed with PCP (67.1%) and 52 people (32.9%). The median CD4 level of HIV patients in this study was 27 cells/mm^3.

Table 1. Characteristics of the research sample.

Characteristics	n (%)
Gender	
Male	119 (75,3)
Female	39 (24,7)
Age	
< 20 year-old	2 (1,3)
20-29 year-old	37 (23,4)
30-39 year-old	73 (46,2)
40-49 year-old	35 (22,2)
≥ 50 year-old	11 (7,0)
Diagnosis	
PCP	106 (67,1%)
Non-PCP	52 (32,9%)
CD 4 levels	
CD 4 ≤ 200 cells/mm^3	126 (79,7%)
CD 4 > 200 cells/mm^3	32 (20,3%)
Median CD 4	27 cells/mm^3

Differences in LDH levels and ABG parameters between HIV patients with PCP and non-PCP are presented in Table 2. The median LDH levels of HIV-AIDS patients with PCP were higher than those without PCP, which were 526 (94-1072) U/L and 250 (7-2173) U/L, respectively.

Table 2. Median Minimum and Maximum LDH levels and Arterial Blood Gases (ABG) in HIV patients with PCP and non-PCP

Parameter	Unit	HIV patients		Total	p-value
		PCP	Non-PCP		
LDH	U/L	526 (94-1072)	250 (7-2173)	511 (7-2173)	0,0001
pH	-	7,47 (6,94-7,68)	7,45 (6,94-7,68)	7,47 (6,94-7,68)	0,645
PaCO2	mmHg	24 (12-40)	25 (12-40)	24 (12-40)	0,078
PaO2	mmHg	174,5 (81 – 211)	178,5 (81-222)	175 (81-222)	0,459
HCO3	mEq/L	17,4 (3,2-36,1)	19,3 (3,2-197)	18,4 (3,2-197)	0,007
TCO2	mmol/L	18,15 (3,7-28,7)	19,9 (2,05-28,7)	19,1 (2,05-28,7)	0,108
BE	mEg/L	-3,65 (-21,2-6)	-2,5 (-27 – 6)	-3,4 (-27 – 6)	0,123
SaO2	%	100 (93-100)	100 (97-100)	100 (93-100)	0,923

The median HCO3 levels of HIV-AIDS patients with PCP were lower than those of HIV-AIDS patients without PCP, which were 17.4 and 19.3, respectively. The median TCO2 levels of HIV-AIDS patients with PCP were lower than those of HIV-AIDS patients without PCP, which were 18.15 and 19.9, respectively. The median BE (base excess) levels of HIV-AIDS patients with PCP were higher than those of HIV-AIDS patients without PCP, which were -3.65 and -2.5, respectively. The median SaO2 levels of HIV-AIDS patients with PCP are the same as those of HIV-AIDS patients without PCP, which are 100% respectively.

The value of sensitivity, specificity, positive predictive value, the negative predictive value of LDH as a modality of PCP diagnosis in HIV and AIDS patients at H Adam Malik Hospital Medan is presented in Table 3. LDH has a sensitivity of 83.0%, specificity 80.7%, positive predictive value (positive predictive value) 89.7%, and negative predictive value (negative predictive value) 70.0%.

Table 3. Sensitivity value, specificity, positive predictive value, the negative predictive value of LDH as a modality of PCP diagnosis in HIV AIDS patients at H Adam Malik Hospital Medan

		Gold standard		Total
		PCP (+) Clinically (+) and CD4 <200 cells/mm^3	PCP (-) Clinically (-) and CD4 <200 cells/mm^3	
LDH	>500 U/L	88	10	98
LDH	≤500 U/L	18	42	60
	Total	106	52	158

The values of sensitivity, specificity, positive predictive value, the negative predictive value of ABG examination as a modality of PCP diagnosis in HIV and AIDS patients at H Adam Malik Hospital Medan are presented in Table 4. ABG examination has a sensitivity of 69.8%, specificity 25.0%, predictive value positive (positive predictive value) 65.4%, and negative predictive value (negative predictive value) 28,8%.

Table 4 The value of sensitivity, specificity, positive predictive value, the negative predictive value of ABG as a modality of PCP diagnosis in HIV AIDS patients at H Adam Malik Hospital Medan

		Gold standard		Total
		PCP (+) Clinically (+) and CD4 <200 cells/mm^3	**PCP (-) Clinically (-) and CD4 <200 cells/mm^3**	
ABG	[PaO2] <70 mmHg or differences of [(A-A)-DO2] >35mmHg)	74	39	113
ABG	[PaO2] ≥70 mmHg or differences of [(A-A)-DO2] ≤35mmHg)	32	13	45
	Total	106	52	158

Based on the analysis of the diagnostic test above, we can conclude statistically that LDH levels have superior sensitivity and specificity compared to the ABG examination as a diagnostic modality for PCP in HIV-AIDS patients at H Adam Malik General Hospital, Medan.

Table 5. P-value in univariate analysis of PCP with LDH levels > 500 U/L in HIV AIDS patients at H Adam Malik Hospital Medan

		PCP (+) Clinically (+) and CD4 <200 cells/mm^3	**PCP (-) Clinically (-) and CD4 <200 cells/mm^3**		**p-value**
LDH	>500 U/L	88	10	98	0,0001
LDH	≤500 U/L	18	42	60	
	Total	106	52	158	

In the univariate analysis, the p-value was 0.0001. The confidence interval used is 95%. Because the probability factor is less than 5% ($\alpha = 0.05$), then this result is significant if the value of $p < \alpha$ ($p = 0.0001$.) so there is a relationship between LDH > 500 U/L and the incidence of PCP in HIV and AIDS patients at H. Adam Malik Hospital Medan.

DISCUSSION

Based on this study, it is known that the incidence of HIV/AIDS patients diagnosed with Pneumocystis carinii pneumonia (PCP) infection at Haji Adam Malik General Hospital Medan is 106 (18.9%) out of 560 HIV/AIDS patients treated at Haji Adam Malik General Hospital Medan in 2019. This study aims to determine the role of LDH examination as a diagnostic tool for Pneumocystis carinii pneumonia (PCP) and compare it with Arterial Blood Gases (ABG) in HIV/AIDS patients suspected of having PCP. In the study, most research subjects were male 119 people (75.3%) with a median age of 35 years. Based on research data from patients who met the inclusion and exclusion criteria, 158 patients were studied and HIV-AIDS patients diagnosed with PCP were 106 (67.1%) and 52 people did not suffer from PCP (32, 9%).

We consider this percentage quite high when compared to the patients studied, but this figure is still below the incidence of PCP related to HIV/AIDS worldwide, where the percentage of reported figures varies. In developing countries, the incidence of PCP infection has soared, with high mortality rates ranging from 20% to 80%.[3] In Uganda, the frequency of PCP among HIV-infected patients with PCP ranges from 10 to 40%.[11] Between 2000 and 2013, a European study reported an increase in the age and proportion of patients who had an episode of *Pneumocystis jiroveci pneumonia* (PJP) preceded by an HIV diagnosis (ages 34–44 years, and from 48% to 67%).[12] PCP varies geographically, and some areas of the world have a low prevalence.[2]

Although PCP is rare in Africa and Asia, in India we found the number of PCP cases to vary from 6.1% to 60%, while the prevalence of PCP cases in Thailand is between 7-25%.[13,14] The prevalence of *Pneumocystis jirovecii* in 2017 in Indonesia was 14.5% among 55 AIDS patients with pneumonia (PCP). The prevalence data for the last 5 years based on sputum examination and bronchoalveolar lavage (BAL) is 28%.[15] Recent data show the prevalence of PCP in 2018 was 20%.[16] The median CD4 levels of HIV patients in this study were 27 cells/mm^3 were 126 (79.7%) HIV-AIDS patients with PCP in this study had CD4 levels of 200 cells/mm^3. Approximately 90% of PCP cases occur in patients with CD4 T-lymphocytes (CD4 cells) of <200 cells/mm^3. Other factors associated with a high risk of PCP include CD4+ cell percentage <14%, recurrent PCP, weight loss, and high plasma HIV RNA levels.[4] CD4+ T cells are also very important in infection, playing an important role in the function of memory cells to regulate the host inflammatory response by recruitment and activation of effector cells.[15]

Another study also by Stansel, et al, 1997 stated that low CD4+ levels had a strong correlation with the incidence of PCP ($p < 0.0001$); were from these data, 79% of the 145 PCP cases had CD4 levels < 100 cells/microliter and 95% had CD4 levels < 200 cells/microliter. The univariate analysis also showed unexplained recurrent fever, night sweats, oropharyngeal thrush, and involuntary weight loss were strongly associated with the incidence of PCP in those with CD4 cell count >200. Even after multivariate analysis, CD4 cell count remained a powerful predictor of PCP incidence ($p < 0.0001$).[16]

Initially, the researchers planned to diagnose PCP based on the gold standard for PCR examination of respiratory tract specimens such as BAL fluid, but this examination was constrained to be carried out due to the COVID-19 pandemic so that it had obstacles in terms of operator availability and limited availability of examinations.[17] Therefore, in this study, the diagnosis of PCP is based on clinical, radiological, and supportive conditions in patients with HIV/AIDS who have symptoms of PCP, such as recurrent fever, shortness of breath, CD4 < 200 cells/mm^3, and radiologically supports a PCP manifestation.

In daily clinical practice, the diagnosis of PCP in HIV/AIDS patients is mostly based on clinical conditions. Nearly over 50 percent of cases have at least two of the following symptoms: the classic triad of clinical signs of unexplained fever >37.7^{o}C (100°F) for over two weeks, dyspnea on exertion, and non-productive cough.[18] In other studies, the gold standard used to compare the accuracy of the diagnosis of LDH and ABG can be as radiological and clinician examinations or compared with other causes of pneumonia such as CAP and pulmonary TB through methenamine silver stain from respiratory mucosal samples, then the viral load was calculated.[19,20]

Therefore, in this study, LDH levels can be a sensitive and specific diagnostic modality for diagnosing PCP in HIV patients apart from clinical manifestations that support a presumptive diagnosis and faster and more effective therapy. Where there are complaints of shortness of breath on activity or non-productive cough within 3 months of being sick, chest radiological features as bilateral diffuse interstitial infiltrates or bilateral diffuse pulmonary disease on gallium scans but there are normal radiological features in 10% of cases (the role of CT scans can be determined) shows a ground glass or cystic lesion, PaO2 < 70 mmHg on examination Blood gas analysis, or low gas exchange capacity (<80% predictive value) or elevated AaDO2 and no evidence of bacterial pneumonia.[21]

CONCLUSIONS

We can use LDH examination as a diagnostic tool for *Pneumocystis carinii pneumonia* (PCP) in HIV AIDS patients because it has a sensitivity of 83.0%,

specificity of 80.7%, the positive predictive value of 89.7%, and negative predictive value of 70.0%, where LDH has superior sensitivity and specificity value compared to ABG examination, in this case, PaO2 or AA DO2 in diagnosing PCP in HIV-AIDS patients.

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