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ANEMIA, NUMBER OF T CD4 LYMPHOCYTE, OPPORTUNISTIC INFECTIONS AS MORTALITY PREDICTOR FACTORS IN PATIENTS INFECTED OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) IN HAJI ADAM MALIK GENERAL HOSPITAL MEDAN

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Abstract
Introduction: HIV (Human Immunodeficiency Virus) infection or commonly called AIDS (Acquired Immunodeficiency Syndrome) is currently one of the biggest health problem in the world. Anemia is one of the most frequent hematological complications in people with HIV infection which one of the anemia biomarker is Hb. HIV causes person's ability to figth infection decreases by decreasing levels of CD4 T lymphocytes that are responsible for one's immune response to fight infectious pathogens. A state of ongoing immunodeficiency will be related to the entry of various opportunistic infections that the risk of death will increase. The simple/economic examination of Hb level and examination of CD4 count are compulsory tests before starting ARV therapy and monitoring therapy that makes researchers are interested in examining anemia, CD4 T lymphocyte counts,opportunistic infections as predictors factor of mortality in HIV-infected patients in RSUP HAM Medan.
Aim: To determine anemia, CD4 T lymphocyte counts, opportunistic infections as predictors of mortality in patients infected with HIV (Human Immunodeficiency Virus) treated at RSUP HAM Medan.
Method: This retrospective cohort study was conducted on 100 adult patients diagnosed with HIV who were treated in the integrated ward of RSUP HAM Medan from January 2018 to December 2018. Patients were divided into two groups based on the status of the patient's outcome ie the living group (outpatients / outpatients / PBJ) and the group were edited (edited during their stay).
Result: Out of 100 HIV patients with 50 survivors and 50 receiving, 4 variables were associated with patient outcomes, namely: CD4 <200 (p: 0.001), anemia status (p: 0.006), PCP (p: 0.012) and TE (p: 0.046). TE is a dominant risk factor for mortality [p: 0.061 OR: 3.25: 95% IK (0.945-11.190).
Conclusion: The dominant risk factor for mortality was Toxoplasmosis Encephalopathy (TE) where HIV-infected patients with TE coinfection were at 3.25 times the risk of patient mortality [p: 0.061 OR: 3.25; 95% IK (0.945 - 11,190)].

Introduction
HIV (Human Immunodeficiency Virus)infection or commonly called AIDS (Acquired Immunodeficiency Syndrome) is currently one of the biggest health problems in the world. WHO (World Health Organization) reports that at the end of 2017 there were around 36.9 million people with HIV / AIDS (PLWHA), 940,000 deaths due to HIV, and 1.8 million people newly infected with HIV or around 5000 new HIV infections per day (WHO , 2018)

The number of HIV infections that occurred in North Sumatra in 2017 was 1,914 out of 48,300 total national HIV infections. In 2017, the percentage of HIV was in men (63.6%) and women (36.4%). According to the age group, there is a high incidence of HIV in the 25-49 year age group followed by the 20-24 and ≥50 year age groups. The district / city with the highest number of new HIV / AIDS sufferers in 2017 was Medan City with 1,333 HIV cases or around (60.29%) (Dinkes, 2018; Kemenkes, 2017).
Hematologic complications are strong independent predictors factor in determining morbidity and mortality in patients with HIV infection. Anemia is one of the most frequent hematological complications in people with HIV infection. The pathogenesis of anemia associated with HIV infection is complex and multifactorial (Dwiadnyana, 2018; Shen, 2013).

Research by Shen shows that anemia, specifically untreated anemia, is associated with shorter life expectancies in patients with HIV infection. Studies by Meidani et al and Eticha & Gemeda show that anemia and CD4 T lymphocyte counts are the strongest or independent predictors of determining mortality with poor response to HAART and there is a strong association with death in patients with HIV infection (Eticha, 2018 ; Meidani, 2012; Shen, 2013).

Other research conducted by Vanisri and Vadiraja, explained that HIV infection affects the parameters of the Red Blood Cell (RBC). In a study of inpatients at RSCM found that Hb levels <10 g / dL were predictors of mortality for HIV / AIDS patients. Anemia is a significant predictor of the progression of HIV into AIDS (Puspitasari, 2016; Vanisri, 2016).

HIV causes person's ability to fight infection decreases by decreasing levels of CD4 T lymphocytes that are responsible for one's immune response to fight infectious pathogens. CD4 is the best parameter to measure immunodeficiency (Tadege, 2018; Ministry of Health, 2014). The ongoing state of immunodeficiency is related to the cause of the entry of opportunistic infections so that the risk of death will increase (Eticha, 2018; Kemenkes, 2014).

The prevalence of opportunistic infections in patients with HIV infection in RSCM is oral candidiasis (40%), TB (37.1%), chronic diarrhea (27.1%), bacterial pneumonia (16.7%), cerebral toxoplasmosis (12%) and herpes zooster infection (6%). There is a correlation of a decrease in the number of CD4 T lymphocyte cells with the emergence of oral candidiasis because it affects the need for a systemic CD4 T lymphocyte threshold to protect the oral mucosa and local immune status (Putri, 2015).

The simple/economic examination of Hb level and examination of CD4 count are compulsory tests before starting ARV therapy and monitoring therapy that makes researchers are interested in examining anemia, CD4 T lymphocyte counts,opportunistic infections as predictors factor of mortality in HIV-infected patients in RSUP HAM Medan.

Methods

Study Population and Samples

The study population was all adult patients diagnosed with HIV who were treated in the integrated inpatient room of Haji Adam Malik Hospital Medan in the period January 2018 - December 2018. The study sample was part of the population that met the inclusion and exclusion criteria. Sampling with non-probability sampling is by means of consecutive sampling.

Study Design

This study is an analytic study with a retrospective cohort study in HIV-infected patients within a period of 1 year (January to December 2018). After obtaining Ethical Clearence and was approved by the Medical Research Ethics Commission of Faculty of Medicine University of Sumatera Utara/ RSUP Haji Adam Malik Medan.

All patients treated in the inpatient room with HIV diagnosis using the ELISA three methods or three methods rapid test that met the inclusion and exclusion criteria were sampled. Then the data is taken from the patient's medical records via SIRS (hospital information system) and recorded according to research needs. After the data is collected, data analysis is performed.

Statistical Analysis

Bivariate analysis with Chi-Square test was carried out to see the relationship between anemia, CD4 T lymphocyte counts, opportunistic infections and mortality in HIV-infected patients. Variables found to be significant from bivariate analysis are ($p < 0.25$) then these variables will be included in multivariate analysis. Multivariate analysis with multiple logistic regression methods to see which variables had the greatest effect on mortality in HIV-infected patients.

Result

This research was conducted at the Haji Adam Malik Hospital in Medan from 100 respondents who were infected with HIV. The characteristics of respondents infected with HIV in the table (4.1) have a median age of 35 (20-64) years with the most sex being male (78%) with the most high school education status (50%). Many respondents had a CD4 lymphocyte count <200 (87%) with a mean CD4 lymphocyte count (79.1 ± 112.12) and the three most opportunistic infections found sequentially were OK (78%), pulmonary TB and extra-pulmonary (62 %) and chronic diarrhea (51%). Based on anemia status, many respondents were anemic (92%) with an average Hb level (9.5 ± 2.42) with the most Hb levels with a Hb <8 ie in (72%) respondents.

Table 4.1Distribution of characteristics of HIV patients at RSUP HAM Medan

Variable	n (%)
Age (Median/Range)	35 (20-64)
Sex	
Men	78 %
Women	22 %
Education	
Elementary School	10 %
Junior High School	29 %
Senior High School	50 %
Diploma	5 %
Bachelor	6 %
CD4	79,1 ± 112,12
< 200	87 %
≥ 200	13 %
Opportunistic infections	
Oral Candidiasis	78 %
Lung TB and Extra Lung	62 %
Chronic Diarrhea	51 %
PCP	7 %
TE	21%
Wasting Syndrom	9 %
Etcetera	25 %
Anemia status	
Yes	92 %
No	8 %
Hb	9,5 ± 2,42
<8	72 %
≥ 8	28 %

Based on the table (4.2) the most common OIs characteristics based on the number of CD4 lymphocytes sequentially. The most frequent respondents experiencing opportunistic infections are Oral Candidiasis (78 people), pulmonary and extra-pulmonary TB (61 people), chronic diarrhea (51 people), TE (20 people), wasting syndrome (9 people), PCP (7 people) and others (25 people). All opportunistic infections were more commonly experienced by respondents with CD4 lymphocyte counts <200 compared to respondents with CD4 lymphocyte counts ≥ 200.

Table 4.2 Distribution of opportunistic infections based on CD4 lymphocyte counts in HIV-infected patients at RSUP HAM

Opportunistic infections	CD4 Lymphocyte Count		Total
	CD4 < 200	CD4 ≥200	
Oral Candidiasis	69 (88,5 %)	9 (11,5 %)	78
Lung TB and Extra Lung	54 (88,5 %)	7 (11,5 %)	61
Chronic Diarrhea	46 (90,2 %)	5 (9,8 %)	51

TE	18 (90,0 %)	2 (10,0 %)	20
Wasting Syndrom	9 (90,0 %)	0 (0 %)	9
PCP	7 (100,0 %)	0 (0 %)	7
Etcetera	23 (92,0 %)	2 (8,0 %)	25

In table 4.3, it can be seen the distribution of patient characteristics to the status of outcomes in HIV-infected patients at RSUP HAM Medan and found that there are 4 variables that have a significant relationship with the outcome status of patients, namely: 1. PCP, where patients infected with HIV with PCP all have death status where the percentage is 7 people (100%). The analysis showed that there was a significant relationship between PCP and the patient's outcome status (p = 0.012). 2. TE, Patients infected with HIV with more TE status who died have a status where the percentage is 15 people (30.0%) vs. 6 people (12.0%). The analysis showed that there was a significant relationship between TE and the status of patient outcomes (p = 0.046). 3. CD4 <200, mean respondent has a CD4 T lymphocyte value <200, that is 87 people with the percentage of respondents who died or were discharged (98% vs 76%). The analysis showed a significant relationship between the number of CD4 T lymphocytes with the patient's output status (p = 0.001). 4. Anemia status, The number of respondents with anemia status is more than those who are not anemic namely 92 people. Respondents with anemia were 50 people (100.0%) with death outcomes. The analysis showed a significant relationship between anemia status and patient outcome status (p = 0.006).

Table 4.3 Distribution of patient characteristics to outcome status in HIV-infected patients at RSUP HAM Medan

Variabel	**Died n =50 (%)**	**Sent home n= 50 (%)**	***P-Value***
Age (Median/Range)	36 (23-64)	34 (20-59)	-
Sex			0,629
Men	40 (80,0 %)	38 (76,0 %)	
Women	10 (20,0 %)	12 (24,0 %)	
Education			0,845
Elementary School	6 (12,0 %)	4 (8,0 %)	
Junior High School	15 (30,0 %)	14 (28,0 %)	
Senior High School	24 (48,0 %)	26 (52,0 %)	
Diploma	3 (6,0 %)	2 (4,0 %)	
Bachelor	2 (4,0 %)	4 (8,0 %)	
Opportunistic infections			
Oral Candidiasis	40 (80,0 %)	38 (76,0 %)	0,629
Lung TB and Extra Lung	29 (58,0 %)	32 (64,0 %)	0,539
Chronic Diarrhea	25 (50 %)	26 (52,0 %)	0,841
PCP	7 (14,0 %)	0 (0 %)	0,012*
TE	15 (30,0 %)	6 (12,0 %)	0,046*
Wasting Syndrom	7 (14,0 %)	2 (4,0 %)	0,160
Etcetera	11 (22,0 %)	14 (28,0 %)	0,488
CD4			0,001*
< 200	49 (98,0 %)	38 (76,0 %)	
≥ 200	1 (2,0 %)	12 (24,0 %)	
Anemia status			0,006*
Yes	50 (100 %)	42 (84,0 %)	
No	0 (0 %)	8 (16,0 %)	
Hb Level			0,656
<8	15 (30,0 %)	13 (26,0 %)	
≥ 8	35 (70,0 %)	37 (74,0 %)	

*(p < 0,05); Median (min-max); Average ± SB

Based on bivariate analysis the relationship between the main variables and other variables with a status of dead or repatriated outcomes having a value (p <0.25) was entered into a logistic regression test to find out which variable was the most dominant risk factor.

Table 4.4 Final model logistic regression test of risk factors for mortality of patients infected with HIV

Variable	OR (95 % CI)	*P*-Value
TE	3,25 (0,945 – 11,190)	0,061
CD4 ≤ 200	0,06 (.059 – 0,007)	0,010

OR (*Odds Ratio*); CI (*Confident Interval*)

Based on multivariate analysis, it was shown that the TE variables, CD4 T lymphocyte count and anemia status were included in the three dominant risk factors for outcome status of death in HIV-infected patients in HAM. The main variable that becomes the dominant risk factor is opportunistic infections from Toxoplasmosis Encephalopathy (TE), where HIV-infected patients with TE coinfection are at 3.25 times the risk of mortality.

Discussion

The results of this study showed the most opportunistic infections in HIV-infected patients treated with oral candidiasis showed data on patients who died compared to patients who were discharged (80% vs. 76%), followed by extra-pulmonary TB with more patients being discharged than those who were discharged. died (64.0% vs. 58%) and all three chronic diarrhea that occurred in half the patients either in patients who died or were discharged with a percentage (50% vs. 52%).

In line with other studies by Putri AJ et al, who reported opportunistic infections experienced by many HIV-infected patients, namely oral candidiasis (77.4%) and TB (29.0%) (Putri, 2015). The same findings reported the three most opportunistic infections in a sequence: wasting syndrome (62.1%), oral candidiasis (47.4%) and pulmonary TB (15.8%) (Dwiadnyana, 2018). Study by Shahrin (2014) with the highest percentage of three patients infected with HIV with death outcomes, namely TB (46%), esophageal candidiasis (9%) and PCP (8%). This shows that oral candidiasis and TB are opportunistic infections that are mostly experienced by HIV-infected patients included in this study. Other findings suggest that the pattern of opportunistic infections in Indonesia with co-infection often encountered is fungal, gastrointestinal and TB infections (Merati, 2015).

Another study on the analysis of mortality risk factors reported that deaths in HIV-infected patients in developing countries were associated with TB coinfection and found that patients with TB coinfection increased 2,872 times the risk of mortality. This can happen because patients have a low immune system and in Indonesia is the second country in the world with the most TB infections so that patients infected with HIV are vulnerable to TB infection (Pusdatin, 2018; Tadege, 2018).

Patients infected with HIV were more likely to have a CD4 <200 cells / µL (87%) ie with a death rate (98%) and a discharge outcome (76%). In line with other studies which found that many patients treated with CD4 <200 cells / µL were Assefa (79.4%) and Karima et al. (58.9%). Study by Puspitasari et al. (2016) with the proportion of patients who died with CD4 levels <200 cells / µL greater than those who died with CD4 levels> 200 cells / µL.

A cohort study at Gondar University found that CD4 levels were associated with patient mortality, whereas patients with CD4 levels <200 cells / µL compared patients with CD4> 200 cells / µL had 5 times the risk of mortality (P = 0,000). A state of advanced immunodeficiency is associated with an increased risk of opportunistic infections which will increase the risk of mortality (Eticha, 2018).

Another study reported that CD4 cell counts were significantly associated with mortality where high CD4 cell counts had a lower risk of mortality and lower CD4 cell counts were independent predictors of mortality that were significantly related to the significance value of the Tadege et al study (p = 0,000) and study of Shahrin et al (p <0.001) (Tadege, 2018; Shahrin, 2014).
All HIV-infected patients with anemia had an outcome of death (100.0%) which statistically had anemic relationship with a significant association with mortality (p = 0.001). The mean hemoglobin level in patients

infected with HIV with a death outcome was Hb <10 (9.2 ± 2.15). In line with other studies of HIV-infected patients who have HB levels <10 g / dL also obtained significant results on the incidence of mortality (p = 0.002) (Puspitasari, 2016). Anemia in HIV infection will be more severe the degree of anemia associated with micronutrient deficiencies, infections (viruses, bacteria and parasites), inducing drugs (AZT and cotrimoxazole) and neoplastic diseases (Haider, 2019).

Based on the highest Hb level with Hb <8 with more percentage of deaths compared to being discharged 15 people (30.0%) vs. 13 people (26.0%) while patients with Hb ≥ 8 percent more discharged outcomes compared with death outcomes, 37 people (74.0%) vs. 35 people (70.0%) although not showing a significant relationship (p = 0.656).

In this study found the three most opportunistic infections in respondents with a CD4 lymphocyte count <200 were oral candidiasis, pulmonary and extra-pulmonary TB and chronic diarrhea. In line with studies by Damtie, it showed that respondents with CD4 lymphocyte counts <200 showed that the most common opportunistic infections were TB (29.5%), oral candidiasis (22.53%) and chronic diarrhea (5.63%) (Damtie , 2013). In line with the Study by Jamil, in RSUD dr. Zainoel Abidin Banda Aceh, got the three most opportunistic infections with CD4 lymphocyte count <200 were pulmonary TB (32.97%), chronic diarrhea (26.37%) and oral candidiasis (23.08%) (Jamil, 2014). These results are also in line with studies in Gondar by Mala and Oberoi, finding that the three most opportunistic infections were oral candidiasis (40.8%), Criptosporidiasis (23.68%) and TB (5.92%) (Mala, 2015).

Studies that analyzed the incidence of pulmonary TB and extrapulmonary TB by Sutariya SB, et al in HIV-infected respondents also showed that respondents with CD4 lymphocyte counts <200 received the highest percentage of pulmonary TB coinfection (72.2%) and extrapulmonary TB (76 , 1%) (Sutariya, 2015). Another study by Depari A and Kembaren T, which analyzed opportunistic infections in respondents with an average CD4 lymphocyte count <200 in people with HIV / AIDS with diarrhea caused by intestinal opportunistic protozoa of 28.2% (Siregar, 2018).

Based on multiple logistic regression analysis, the most dominant risk factor affecting the mortality of patients in this study was co-infection with encephalopathy (cerebral toxoplasmosis) [OR: 3.25; 95%: CI (0.945 - 11.190)]. In line with the findings at Dr. Hospital M. Djamil Padang received in 2012 opportunistic infections that cause most mortality was cerebral toxoplasmosis (Putri, 2015).

Cerebral toxoplasmosis coinfection is still the most important cause of morbidity and mortality in HIV-infected patients with advanced immunosuppression characterized by low CD4 cell counts (CD4 <200 cells / mm3), with the percentage of patients with death outcomes (98.0%) and discharged (88.0) %) in line with Martin's study (2017) getting a cerebral toxoplasmosis mortality ratio in one year (0.02, 95% CI: 0.01-0.05)..

In line with various theories that the microorganism that causes TE is T. Gondii, where immunocompromised hosts have a low number of immune factors that are needed to control the spread of disease. Inflammatory processes that are accompanied by low CD4 levels cause rapid and persistent replication of tachizites, resulting in progressive breakdowns that cause organ failure (Necrotizing Encephalitis, pneumonia and myocarditis) to cause death (Chioccola, 2009; Pohan, 2015).

The weakness of this study is to use a retrospective design, a small sample and only evaluate three predictors of mortality.

Conclusion

Based on the results of data analysis in this study, it was concluded that the dominant risk factor for mortality was Toxoplasmosis Encephalopathy (TE) where HIV infected patients with TE coinfection had a 3.25 times risk of patient mortality [p: 0.061 OR: 3.25; 95% IK (0.945 - 11,190)].

Suggestion

Based on the results of this study it is recommended to conduct further research with a prospective design, using a larger sample and adding other predictor factors such as the status of antiretroviral therapy, adherence to antiretroviral therapy, nutritional status, psychological status of the patient to obtain better results.

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