Mortality among Hospitalized HIV-Infected Patients with Tuberculosis in Cipto Mangunkusumo Hospital, Jakarta, Indonesia: A Retrospective Cohort Study

Agus J Sunggoro[1], Zulkifli Amin[2], Cleopas M Rumende[2]

[1]Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

[2]Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

Background: *Indonesia is the world's fourth highest tuberculosis (TB) burden in the world. TB is the second leading cause of death for all age in the country. Mortality rate remains high among hospitalized TB patients compared to the non-TB patients. The risk of death is significantly higher in HIV-infected patients with tuberculosis (TB). TB is the leading killer of HIV-infected individuals worldwide.*

Objective: *To describe the characteristics and to determine mortality rate among hospitalized HIV-infected patients with TB in Cipto Mangunkusumo Hospital (CMH), Jakarta, Indonesia.*

Methods: *A retrospective cohort study was performed among hospitalized TB/HIV patients in CMH between January 2008 and September 2013. Data were collected at initiation of inpatients period and the main outcome was all-cause mortality during hospitalization. Analyzed factors included age, sex, history of previous anti-TB treatment, sputum smear positivity, hypoalbuminemia, BMI, pulmonary radiographic lesion and comorbidity (CCI score). Data were analyzed using Chi-square test or Fischer test.*

Results: *A total of 191 TB/HIV patients were evaluated in this study. There were 157 (82.6%) male and 34 (17.4%) female patients. Median age was 31 (range 20 to 71) years old and median length of stay was 11 (range 1 to 57) days. In-hospital mortality rate was 29,8%. One hundred and thirty patients had CD4 count data, and 128 (98,5%) of them had CD4<200 cell/uL. Factorsassociated with in-hospital mortality were history of previous TB treatment, (p=0,001), hypoalbuminemia (p<0,001) and cavitary lesion in chest radiographic (p<0,001).*

Conclusion: *In-hospital mortality rate was 29,8%. The majority of TB/HIV patients had low CD4 count (<200cell/uL). Factors associated with in hospital mortality were history of previous TB treatment, hypoalbuminemia and cavitary lesion in chest radiographic.*

Key words: *Tuberculosis, HIV positive, in-hospital mortality*

ABSTRAK

Latar belakang: Indonesia merupakan negara peringkat keempat penyumbang kasus tuberkulosis (TB) terbanyak di dunia. TB adalah penyebab kematian kedua terbanyak di Indonesia. HIV dan TB merupakan kombinasi mematikan karena HIV melemahkan sistem imun. TB merupakan penyebab kematian utama pada penderita HIV.

Tujuan: Mengetahui karakteristik dan angka mortalitas pasien TB/HIV saat rawat inap.

Metode: Penelitian ini merupakan studi kohort retrospektif pada pasien rawat inap di Rumah Sakit Cipto Mangunkusumo (RSCM) dalam kurun Januari 2008 sampai dengan 31 September 2013. Data klinis dan laboratorium beserta status luaran (hidup atau meninggal) selama perawatan diperoleh dari rekam medis. Faktor yang berhubungan dengan kematian dianalisis pada variabel kelompok usia, jenis kelamin, riwayat pengobatan TB sebelumnya, status BTA, hipoalbuminemia, IMT, gambaran radiologis toraks lesi kavitas, serta komorbiditas *(skor Charlson Comorbidity Index)*. Variabel dianalisis menggunakan uji Chi-Square. Jika tidak memenuhi syarat, digunakan uji Fischer.

Hasil: Sebanyak 191 pasien TB/HIV diikutsertakan pada penelitian ini. Jenis kelamin laki-laki sebanyak 157 (82,6%) pasien sedangkan jenis kelamin perempuan sebanyak 34 (17,4%) pasien. Median usia subjek adalah 31

Korespondensi
dr. Agus Jati Sunggoro
Email:
agusjati@gmail.com

Indonesian Journal of
CHEST
Critical and Emergency Medicine
Vol. 1, No. 3
July - September 2014

dengan rentang usia 20-71 tahun. Didapatkan angka mortalitas selama perawatan sebesar 29,8%. Penyebab kematian paling banyak adalah syok sepsis sebanyak 27 (48,2%) pasien, diikuti gagal napas sebanyak 24 (42,9%) pasien. Kadar CD4 didapatkan pada 130 pasien; 98,5% pasien mempunyai kadar CD4 <200 sel/uL. Ditemukan faktor yang berhubungan dengan kematian, yaitu riwayat pengobatan TB sebelumnya (p=0,001), hipoalbuminemia (p<0,001), dan lesi kavitas (p<0,001).

Kesimpulan: Angka mortalitas pasien TB/HIV saat rawat inap sebesar 29,8%. Sebagian besar pasien memiliki kadar CD4 <200 sel/uL. Faktor yang berhubungan dengan kematian saat rawat inap meliputi riwayat pengobatan TB sebelumnya, hipoalbuminemia, dan gambaran radiologis toraks lesi kavitas.

Kata kunci: Tuberkulosis, HIV positif, kematian saat rawat inap

INTRODUCTION

Tuberculosis (TB) remains a major global health problem. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320 000 deaths among HIV-positive people). An estimated 1.1 million (13%) of the 8.6 million people who developed TB in 2012 were HIV-positive.[1]

Prevalence of TB in Indonesia is around 730 000. It is estimated that the prevalence of HIV among the adult population is 0.2% nationally and there are about 190 000 people living with HIV in Indonesia. The estimated number of people coinfected with TB/HIV is 12 000 (ranging between 7200 and 19 000) in Indonesia. Mortality of TB/HIV patients in Indonesia accounts up to 21 00 (ranging 18 00 and 3 000).[1,2]

Worldwide, as many as 4 million people affected with HIV also have TB, making TB the major killer in HIV-infected patients.[3] The risk of death from TB is significantly higher in the HIV-infected population, even if the organism responds well to anti-TB medications.[4] Each of TB and HIV adversely affects the clinical course of the other, including increased mortality.[5]

Alvarez et al reported, the prevalence of HIV in hospitalized TB patients were 41%. Compared with those with TB alone, patients with dual HIV/TB infection had a significantly higher probability of dying in hospital rather than being discharged alive.[6] This retrospective cohort study aims to describe the characteristics and to determine mortality rate among hospitalized HIV-infected patients with TB in Cipto Mangunkusumo Hospital (CMH), Jakarta, Indonesia.

METHODS

Study Area and Subject

Retroscpective cohort study was performed on TB/HIV patients admitted in the medical wards of CMH between January 2008 and September 2013. CMH is a tertiary referral hospital with a bed capacity of 1000 patients. Patients were eligible to be included in the study if they: 1) were admitted to medical wards during 1 January 2008-30 September 2013, 2) were at least 18 years of age, and 3) had a diagnosis of active TB at discharge and also HIV positive.

A total of 191 patients files were retrieved from medical record unit and reviewed. For each patient, data on demographic and clinical were recorded.

Diagnosis of TB

The clinical definition of pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) as recommended by Indonesian TB guideline and WHO guideline were used to define the cases included in this study. PTB was defined if one of two initial sputum smears had proved positive for acid fast bacilli (AFB, smear-positive cases). Cases with sputum smears negative for AFB but positive culture or two sputum smears negative for AFB but compatible clinical and radiologic features with active TB were considered to be smear-negative cases.[7,8]

EPTB included TB of organs other than lungs, such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones and meninges. Diagnosis of EPTB was based on minimal one specimen examination positive for *M. tuberculosis* or histopatological examination consistent with TB infection or strong clinical evidence consistent with active EPTB.[7,8]

Outcome Measure

The primary outcome measure of the study was in-hospital mortality (all cause mortality). Secondary outcomes were the demographic and clinical profiles. We assessed comorbidity in this sample using the Charlson comorbidity index (CCI). A CCI score was derived by converting secondary diagnosis into the 19 clinical conditions identified in the Charlson comorbidity index.

Ethical Consideration

Ethical clearance was obtained from the Ethic Research Committee, Faculty of Medicine, University of Indonesia, CMH. Permission to conduct the study and to access the data was obtained from the CMH authorities.

Data Analysis

Data were analyzed using the Statistical Package for Sosial Science (SPSS) programme version 20.0. Association between categorical variable and mortality
were analyzed using Chi-square test or Fischer test. All
reported *p* values are two-sided. A *p* value of less than 0.05 was considered statistically significant.

RESULT

A total of 191 TB/HIV patients were included in the study. The overall median age of the patients was 31 years (rage 20 to 71 years). One hundred and fifty seven (82,2%) were male and 34 (17,8%) were female. Demographic and clinical characteristics of the study population are given in Table 1.

One hundred and thirty six (75,4%) subjects had PTB, and 47 (24,6%) had both PTB and EPTB. Common sites of EPTB (n=47) were miliary TB 25 (53,2%), meninges 17 (36,2%), lymph node 4 (8,5%) and abdomen-periotenal 1 (2,1%).

Table 1. Demographic and Clinical Characteristcs (n=191)

Characteristcs	
Sex, n (%)	
Male	157(82.2)
Female	34 (17.8)
Age (years), median (min-max)	31 (20-71)
Age category, n (%)	
<60 years old	189 (99)
≥60 years old	2 (1)
TB clinical presentaton, n (%)	
Isolated pulmonary TB (PTB)	136 (75.4)
Both PTB and ETB	47(24.6)
Extra-pulmonary TB locaton, n (%)	
Miliary TB	25 (53.2)
Meningeal TB	17 (36.2)
Lymph node TB	4 (8.5)
Peritoneal TB	1 (2.1)
History of previous TB treatment, n (%)	
No	121 (63.4)
Yes	70 (36.6)
Sputum smears AFB, n (%)	
Smear-positve	27 (14.1)
Smear-negatve	147 (76.9)

Continuation of Table 1.

Characteristcs	
Missing data	17 (9)
Body mass index (BMI) , n (%)	
<18,5 kg/m^2	134 (70.1)
≥18,5 kg/m^2	55(28.8)
Missing data	2(1)
Albumin serum, n (%)	
Albumin serum <3 g/dl	125 (65.5)
Albumin serum ≥3 g/dl	60 (31.4)
Missing data	6 (3.1)
Chest radiographic, n (%)	
Cavitary lesion	29 (15.2)
No cavitary lesion	162 (84.8)
CD4 counts, n (%)	
<200cells/ul	128 (67)
≥200 cells/ul	2 (1)
Missing data	61 (32)
Comorbidity, n (%)	
Chronic liver disease	88(46.1)
Chronic kidney disease	7 (3.7)
Chronic heart failure	1 (0.5)
Malignancy	1 (0.5)
Laboratory result in hospital admission	
Hemoglobin, mean (SD)	10.1 (2.52)
Leucocyte, median (min-max)	5 955 (707-23800)
Creatnin serum, median (min-max)	0,7 (0.3-4.2)
Albumin serum, median (min-max)	2.7 (1.20-4.40)
Blood glucose, median (min-max)	104 (59-447)
Length of stay (days), median (min - max)	11 (1-57)
Outcome, n (%)	
Discharge	134 (70.2)
Death	57 (29.8)
Cause of death, n (%)	
Septc shock	27 (42.9)
Respiratory failure	24 (48.2)
Pulmonary emboli	3 (5.4)
Increased intracranial pressure (meningits tuberculosa)	2 (3.6)

The majority of patients (63,4%) had no history of previous TB treatment. Twenty seven (14,1%) patients had positive sputum smears for AFB and 147 (76,9%) patients had negative sputum smears. There were 17 (9%) patients who had no data of sputum smear. One hundred and thirty four (70,1%) patients were malnourished on admission (body mass index[BMI] <18,5 kg/m^2).

One hundred and thirty (68,1%) patients had CD4 count data; 128 (98,5%) of them had CD4<200 cell/uL. Sixty one (32%) patients had no CD4 count data. One hundred and sixty two (84,8%) patients had no cavitary lesion in chest radiographic at admission.

The most common comorbidity was chronic liver disease 88 (46,1%). The median length of stay was 11 (range 1 to 57) days.

Among all patients, 57 (29,8%) patients died in hospital. Septic shock (42.9%) and respiratory failure (48.2%) were the most common cause of death in this study.

Association between clinical characteristics and in-hospital mortality were analyzed using Chi-square test or Fischer test. Table 2 shows clinical characteristics that had significant association with death in univariate analysis. Death during hospitalization is significantly associated with history of previous TB treatment (p=0,001), hypoalbuminemia (albumin serum <3g/dL; p<0.001) and cavitary lesion in chest radiographic at admission (p<0.001).

Table 2. Univariate analysis risk factors and their effects on mortality in TB/HIV co-infected patents

Variable	Frequency		p value
	Death n (%)	Discharge n (%)	
Sex (n=191)			
Male	44 (28)	113 (72)	0.24
Female	13 (38.2)	21(61.8)	
Age category (n=191)			
≥60 years old	2 (100)	0 (0)	0.88
<60 years old	55 (29.1)	134(70.9)	
History of previous TB treatment (n=191)			
Yes	31 (44.3)	39 (55.7)	0.001
No	26 (21.5)	95 (78.5)	
Sputum smears AFB, (n=174)*			
Smear-positve	4 (14.8)	23 (85.2)	0.93
Smear-negatve	45 (30.6)	102 (69.4)	
BMI (n=189)*			
BMI <18,5 kg/m^2	43 (32.1)	91 (67.9)	0.248
BMI ≥18,5 kg/m^2	13 (23.6)	42 (76.4)	
Albumin serum, (n=185)*			
<3 mg/dl	49 (39.2)	76 (60.8)	<0.001
≥3 mg/dl	5 (8.3)	55 (91.7)	
Chest radiographic, (n=191)			
Cavitary lession	20 (69)	9 (31)	<0.001
No cavitary lession	37(22.8)	125 (77.2)	
Charlson Comorbidity Index (CCI) , (n=191)			
CCI score >5	56(29.6)	133 (70.4)	0.509
CCI score ≤5	1 (50)	1 (50)	

**There were missing data in sputum smears (17 patents), BMI (2 patents), albumin serum (6 patents)*

DISCUSSION

Our findings reveal that TB/HIV patients at CMH were mostly young adult, with median age 31 years (range 20 to 71 years) old. These findings are similar with a study done by Singal and Jaiswa in India which reported that the incidence of TB/HIV coinfection was highest in productive age group of 16-45 years old (75%).[9] A study from Malaysia reported similar result with mean age of 34 years (standard deviation 7.8, range 18 to 76 years) old.[10]

The majority of study population were male (82,2%). These findings are similar with study done by Mohammad and Naing in Malysia. They reported that male patients presented the majority of the cases of TB/HIV coinfection (94.6%).[10]

PTB was the most common clinical form of TB in CMH. These findings are similar to studiesby Inge et al and Wiwatworapan et al.[11,12] Study from Malaysia reported similar result that PTB accounted for most clinical form of TB in patients with TB/HIV coinfection (78.5%).[10]

In this study, 130 (68,1%) patients had CD4 count data and 128 (98,5%) of them had CD4<200 cells/uL. These findings are similar to a study conducted by Belay et al, which found that 79.5% of tuberculosis infection occurred in low CD4 level (<200 cells/μL).[13] In another study done by Debriew, about two-third (67.2%) of the TB/HIV patients had CD4 count of less than 200/μL.[14]

In this study, 61 (32%) patients did not have documented CD4 counts (missing data). We did not analyze the relationship between the CD4 count and in-hospital mortality because of limited data on the CD4+ count results. Further analysis could warrant bias.

One hundred and forty seven (76,9%) patients had negative sputum smears and almost all of that number had low CD4. These results may come from the fact that smear-negative is associated with paucibacillary disease, which is a feature of advancing immunosuppression compared with the more robust immunological profile in patients presenting with smear-positive.[15]

The majority (84,8%) of patients had no cavitary lesion in chest radiographic at admission. These findings are similar with many studies in African countries in the early HIV epidemic showing that in patients seemingly producing no sputum or having negative sputum smears, chest X-rays showed little change or diffuse pulmonary infiltrates without cavitation.[16]

TB and HIV contribute to each other's progression. Patients co-infected with TB and HIV have higher mortality rates in comparison with those with

one of the two.[17] In this study, in-hospital mortality rate was 29,8%. Regarding mortality in HIV-infected TB patients, Perriens et al stated that although they respond as well to anti-tuberculosis chemotherapy as HIV-negative TB patients, they may have a higher short-term mortality.[4]

Although high, the 29.8% mortality in this current study was still a conservative estimate, because deaths among patients defined as all-cause mortality and the follow up was short-termed (in hospitalization period). In TB/HIV study by Perriens et al with involved long-termed follow up, mortality showed a similiar high rate, while a retrospective cohort in Thailand showed mortality rate 12% among those who received 6 months of therapy.[4,18]

Three clinical variables (history of previous TB treatment, hypoalbuminemia, cavitary lesion in chest radiographic at admission) were significantly associated with death during hospitalization. In another study, history of previous TB treatment found as an independent risk factor for multi drug-resistant TB (MDR-TB) with Odds ratio 5.1.[19] In studies where drug susceptibility testing were performed, infection with a multi drug-resistant strain of TB was universally associated with increased risk of death.[15]

In this study, hypoalbuminemia (albumin serum < 3 g/dL) was significantly associated with in-hospital mortality. Similarly, Matos and Lemos reported a strong positive association between serum albumin at admission and in-hospital death due to TB and a greater risk of death in patients with serum albumin levels <2.7 g/dl at the time of admission. That study emphasises the importance of measuring the serum albumin levels of all TB patients at admission.[20]

Cavitary lesion on chest radiographic at admission was associated with in-hospital mortality. Another study in Rusia found that cavitary lesion on chest X-ray was an independent predictor of mortality in TB patients (OR 2.45).

Some limitations are noted in this study. This is a retrospective analysis of TB/HIV patients and the findings might not be generalized. There were many missing data such as lack of CD4+ count information. Whether the description of chest x-ray findings is accurate might come into question, thus, an evaluation by a blinded observer radiologist is needed in future studies. Furthermore, a prospective cohort study or survival analysis may be appropriate to see the associations and estimate the risk in future studies.

ACKNOWLEDGEMENTS

The authors wish to thank the members of the staff at Cipto Mangunkusumo Hospital, especially the Division of Respirology and Critical Care, Department of Internal Medicine and the Medical Records Department for their cooperation and help in data access and retrieval.

REFERENCES

1. WHO. Global Tuberculosis Control 2013. Geneva: World Health Organization; 2013.
2. WHO Regional Office for South-east Asia. Tuberculosis control in the South-East Asia Region 2012. New Delhi: World Health Organization; 2012.
3. World Health Organization. Fight AIDS, Fight TB, Fight Now: TB/HIV Information Pack. Geneva:WHO; 2004.
4. Perriens JH, Colebunders RL, Karahunga C, et al. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with 'standard' chemotherapy in Kinshasa, Zaire. Am Rev Respir Dis 1991; 144:750-5.
5. Whalen C, Horsburgh C R, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. Am J Respir Crit Care Med 1995; 151:129-135.
6. Alvarez G.G, Thembela B.L, Muller F.J, Clinch J, Singhal N, Cameron D.W. Tuberculosis at Endale hospital in Pietermaritzburg, Kwazulu Natal, South Africa. Int J Tuberc Lung Dis 2004; 8(12):1472-8.
7. World Health Organization. Treatment of tuberculosis guidelines, fourth edition. Geneva: WHO; 2010.
8. The Indonesian Respirology Society. Tuberkulosis: pedoman diagnosis dan penatalaksanaan di Indonesia. Jakarta: PDPI; 2011.
9. Singhal S, Jaiswa P. Presentation of tuberculosis in TB-HIV co-infection patients and the treatment outcome with directly observed short course therapy. Asian Pacific Journal of Tropical Biomedicine 2011; S266-7.
10. Mohammad Z, Naing NN. Characteristics of HIV-infected tuberculosis patients in Kota Bharu Hospital, Kelantan from 1998 to 2001. Southeast Asian J Trop Med Public Health 2004; 35(1):140-3.
11. Ige OM, Sogaolu OM, Ogunlade OA. Pattern of presentation of tuberculosis and the hospital prevalence of tuberculosis and HIV co-infection in University College Hospital, Ibadan: a review of five years (1998-2002). African Journal of Medicine and Medical Sciences 2005; 34:329-33.
12. Wiwatworapan T, Anantasetagoon T. Extra-pulmonary tuberculosis at a regional hospital in Thailand. Southeast Asian Journal of Tropical Medicine and Public Health 2008; 39:521-5.
13. Belay A, Alamrew Z, Berie Y, Tegegne B, Tiruneh G, Feleke A. Magnitude and correlates of tuberculosis among HIV patients at Felege Hiwot Referral Hospital, Bahir Dar City, Northwest Ethiopia. Clinical Medicine Research 2013; 2(4):77-83.
14. Deribew A, HaileMichael Y, Tesfaye M, Desalegn D, Wogi A, Daba S. The synergy between TB and HIV co-infection on perceived stigma in Ethiopia. BMC Research Notes 2010 Oct; 3:249.
15. Waitt CJ, Squire SB. A systematic review of risk factor of death in adult during and after tuberculosis treatment. Int J Tuberc Lung Dis 2011; 15(7):871-85
16. Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries. Lancet 1990; 335:387-90.
17. Tabarsi P, Chitsaz E, Moradi A, Baghaei P, Farnia P, Marjani M, et al. Treatment outcome, mortality and their predictors among

HIV-associated tuberculosis patients. Int J STD AIDS 2012; 23(9):e1-e4.

18. Poprawski D, Pitisuttitum P, Tansuphasawadikul S. Clinical presentations and outcomes of TB among HIV-positive patients. Southeast Asian J Trop Med Public Health 2000; 31:140-2.
19. Vashakidze L, Salakaia A, Shubladze N, Cyanamon M, Barbakadze K, Kikvidze M, et al. Prevalence and risk factor for drug resistance among hospitalized tuberculosis patients in Georgia. Int J Tuberc Lung Dis 2009; 13:1148-53.
20. Matos ED, Moreira-Lemos AC. Association between serum albumin levels and in-hospital deaths due to tuberculosis. Int J Tuberc Lung Dis 2006; 10:1360-6.
21. Kourbatova EV, Borodulin BE, Borodulina EA, Rio C, Blumberg HM, Leonard MK. Risk factor for mortality among adult patient with newly diagnosed tuberculosis in Samara, Rusia. Int J Tuberc Lung Dis 2006; 10(11):1224-30.