MORTALITY AMONG HIV/AIDS PATIENTS WITH AND WITHOUT CRYPTOCOCCOSIS IN SOUTHERN THAILAND

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Abstract: Cryptococcosis can be a health problem among AIDS patients. The aim of this study was to compare mortality among HIV/AIDS patients with and without cryptococcosis to determine if it increases mortality significantly or not. We conducted a retrospective case cohort study among HIV/AIDS patients from southern Thailand registered with the local Center for Diseases Control and Prevention in Thailand. The data were accessed for January 1993 - April 2010. Data from a total of 52,459 HIV/AIDS patients were accessed from southern Thailand covering 14 provinces. Of these, 2,117 HIV/AIDS patients were reported to have cryptococcosis during the study period. A total of 2,117 HIV/AIDS patients without cryptococcosis were randomly selected by computer from the HIV/AIDS database for comparison. The Cox's proportional hazard model was used to assess associations between cryptococcosis and mortality. We found a significant association between cryptococcosis and mortality among study subjects. Study subjects with cryptococcosis were 1.35 times more likely to die than those without cryptococcosis (hazard ratio: 1.35; 95% confidence interval: 1.18 - 1.54) after adjusting for confounding factors. In summary, cryptococcosis was associated with greater mortality among HIV/AIDS patients in southern Thailand.

Keywords: HIV/AIDS, cryptococcosis, mortality, southern Thailand

INTRODUCTION

Infection with the Human Immunodeficiency Virus (HIV) is a major public health problem and may result in acquired immunodeficiency syndrome (AIDS) if untreated. A major cause of mortality among AIDS patients is opportunistic infections (OIs), which are the most common complication of advanced immunodeficiency (Ramesh *et al*, 2015). Cryptococcosis is an important opportunistic fungal infection among HIV/AIDS patients, particularly in Africa and Southeast Asia. It is estimated that more than 600,000 individuals-infected with

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AIDS die from cryptococcosis each year worldwide (Srichatrapimuk and Sungkanuparph, 2016). Rajasingham *et al*, (2017) reported the average prevalence of cryptococcal antigenemia worldwide was 6.0% [95% confidence interval (CI): 5.8-6.2]. It is estimated the number of deaths caused by cryptococcal meningitis each year worldwide is 181,100 cases (95%CI: 119,400-234,300) (Rajasingham *et al*, 2017; Arsenijević and Denning, 2018). The highest incidence of cryptococcal cases and mortality occurs in Sub-Saharan Africa (Park *et al*, 2009). Cryptococcal meningitis is responsible for 15% of AIDS-related mortality (Rajasingham *et al*, 2017).

Cryptococcus is the causative agent of cryptococcosis. The most common species of *Cryptococcus* that cause infections in humans are *Cryptococcus neoformans* and *Cryptococcus gattii* (Recio and Perez-Ayala, 2018). *Cryptococcus neoformans* can cause meningitis, especially among AIDS patients (Nascimento *et al*, 2017). *Cryptococcus gattii* usually occurs in immunocompetent individuals (Villanueva-Lozano *et al*, 2018). The most common clinical presentation of cryptococcosis is cryptococcal meningitis (Srichatrapimuk and Sungkanuparph, 2016). Cryptococcal meningitis has a high mortality rate among HIV/AIDS patients (Chu *et al*, 2017). The most common clinical signs and symptoms of cryptococcal meningitis are headaches, fever, cranial neuropathy, unconsciousness, lethargy, memory loss and meningeal irritation (Srichatrapimuk and Sungkanuparph, 2016; Naik *et al*, 2017; Touma *et al*, 2017).

Cryptococcosis can cause disease in HIV-seronegative individuals (Pasquier *et al*, 2018). A systematic review of studies of cryptococcal meningitis cases (Pasquier *et al*, 2018) revealed a one-year mortality rate ranged from 13% to 78% among HIV-infected individuals with cryptococcosis. The one-year mortality rate of cryptococcal meningitis cases among those with advanced AIDS-defining illnesses in one study was found to be 69% (Naik *et al*, 2017). There are few studies of the mortality associated with cryptococcosis among HIV/AIDS patients in southern Thailand. The aim of this study was to determine the association between cryptococcosis and mortality among patients infected with HIV/AIDS in southern Thailand.

MATERIALS AND METHODS

We conducted this retrospective case cohort study of HIV/AIDS patients registered with the 11th and 12th Regional Offices of the Center for Diseases Control and Prevention, Nakhon Si Thammarat and Songkhla Provinces, Thailand. The data were obtained from those Centers for Diseases Control and Prevention for the period January 1993-April 2010. The HIV/AIDS patients included in this study were treated at secondary and tertiary care hospitals in the 14 provinces of southern Thailand.

We reviewed the data and identified 2,117 patients who had been diagnosed with having cryptococcosis. We also randomly computer selected 2,117 HIV/AIDS patients without a diagnosis of cryptococcosis for comparison. We recorded the following demographic data for all study subjects: age, sex, marital status, race, occupation, and area of residence. The first variable determined was the time from HIV/AIDS diagnosis to death. This was presented as a continuous outcome. The second variable was the cause of death among subjects who died, including cryptococcosis. This was presented as a categorical outcome. Those variables had

been recorded by physicians at the study hospitals. The primary outcomes among cryptococcosis patients were recorded by health professionals working for the Centers for Diseases Control and Prevention.

Descriptive statistics were used to analyze studied variables. The Kaplan-Meier method was used to estimate the probability of survival among study subjects with cryptococcosis. The Cox's proportional hazard model was used to quantify the association between cryptococcosis and mortality among study subjects.

We used three methods to identify factors associated with mortality: bivariate analysis, initial multivariate analysis and final multivariate analysis. On bivariate analysis, we entered all possible factors into the model. Variables associated with mortality due to cryptococcosis with a p-value ≤ 0.25 on bivariate analysis were included in the initial multivariate analysis. On initial multivariate analysis with backward elimination, factors with a p-value>0.05 were eliminated and the remaining factors were entered into the final model for multivariate analysis. The hazard ratio (HR) was then calculated and variable with a HR>1 with 95% confidence interval (95%CI) were presented to be a significantly associated with death among subjects with cryptococcosis.

This study was approved by the Ethics Committee on Human Rights Related to Human Experimentation, Thaksin University, Thailand.

RESULTS

A summary of the demographics of the study subjects is shown in Table 1. The average [±standard deviation (SD)] age of study subjects was 31.7 (±7.6) years, 73.3% were male, 57.0% were married and 98.1% were Thai. Sixty point one percent of cryptococcosis subjects were employees, 18.7% worked in agriculture and 58.7% lived in rural area; 70.2% identified themselves as heterosexual and in 80.5% the risk factor for acquiring HIV infection was sexual intercourse. Eighty-five point nine percent were inpatients and in 70.4% it was not recorded if they were receiving treatment for HIV infection or not.

The following are data for the non-cryptococcosis cases. The average (±SD) age was 32.8 (±10.5) years, 69.9% were male, 53.4% were married and 95.8% were Thai. Fifty-seven point eight percent of non-cryptococcosis subjects were employees, 18.5% worked in agriculture and 52.1% lived rural areas. Fifty-seven point one percent identified themselves as heterosexual and in 61.9% the risk factor listed for acquiring HIV infection was sexual intercourse. Sixty-three point five percent were inpatients and in 72.5% it was not recorded if they were receiving treatment for HIV infection or not.

The factors associated with mortality among cryptococcosis patients are shown in Table 2. The results from using the Cox's model show subjects who were employees were 1.22 times more likely to die from cryptococcosis (HR=1.22; 95% CI: 1.04-1.44) than those who worked in agriculture. Subjects who resided in urban areas were 1.54 times more likely to die from cryptococcosis (HR=1.54; 95%CI: 1.22-1.95) and those who resided in rural areas were 1.44 times more likely to die from cryptococcosis (HR=1.44; 95%CI: 1.15-1.80) than those who resided in unidentified areas. Heterosexual subjects were 1.31 times more likely to die from cryptococcosis (HR=1.31; 95%CI: 1.15-1.50) than those who were non-heterosexual. Subjects admitted to the hospital were more than twice as likely to die from cryptococcosis (HR=2.27; 95%CI:

Table 1
Selected demographics of study subjects with and without cryptococcosis.

Demographic factor	Study subjects, *n* (%)	
	With cryptococcosis (*n* = 2,117)	Without cryptococcosis (*n* = 2,117)
Age		
Mean ± SD (Min, Max)	31.72 ± 7.58 (1, 76)	32.76 ± 10.47 (1, 74)
Sex		
Male	1,551 (73.3)	1,479 (69.9)
Female	556 (26.7)	638 (30.1)
Marital status		
Single	734 (34.7)	706 (33.3)
Married	1,206 (57.0)	1,130 (53.4)
Divorced/separated/others	177 (8.3)	281 (13.3)
Race		
Thai	2,076 (98.1)	2,029 (95.8)
Others	41 (1.9)	88 (4.2)
Occupation		
Agriculture	396 (18.7)	391 (18.5)
Official/office staff	106 (5.0)	97 (4.6)
Employee	1,272 (60.1)	1,224 (57.8)
Others	343 (16.2)	405 (19.1)
Area of residence		
Urban	617 (29.2)	657 (31.0)
Rural	1,243 (58.7)	1,104 (52.1)
Unknown	257 (12.1)	356 (16.8)
Sexual identification		
Homo/bisexual	15 (0.7)	34 (1.6)
Heterosexual	1,485 (70.2)	1,208 (57.1)
Unknown	617 (29.1)	875 (41.3)
Probable mode for contracting HIV infection		
Intravenous drug use	147 (7.0)	221 (10.4)
Sexual intercourse	1,705 (80.5)	1,310 (61.9)
Others	13 (0.6)	72 (3.4)
Unknown	252 (11.9)	514 (24.3)
Type of patients		
Outpatient	298 (14.1)	643 (36.5)
Inpatient	1,818 (85.9)	1,117 (63.5)
Combined treatment		
No	282 (13.3)	356 (16.8)
Yes	344 (16.3)	227 (10.7)
Unknown	1491 (70.4)	1,534 (72.5)

SD, standard deviation; HIV, human immunodeficiency virus.

Table 2
Evaluation of potential factors associated with mortality among study subjects.

Factor	Crude HR	95%CI	*p*-value
Age			0.876
Age	1.00	(0.99 - 1.01)	
Sex			0.922
Male	Reference		
Female	0.99	(0.87 - 1.14)	
Marital status			0.688
Single	Reference		
Married	0.97	(0.85 - 1.11)	
Divorced/separated/others	1.06	(0.86 - 1.30)	
Race			0.152
Thai	Reference		
Others	1.28	(0.92 - 1.77)	
Occupation			0.039
Agriculture	Reference		
Official/office staff	0.93	(0.66 - 1.30)	
Employee	1.22	(1.04 - 1.44)	
Others	1.19	(0.97 - 1.46)	
Area of residence			<0.000
Unknown	Reference		
Urban	1.54	(1.22 - 1.95)	
Rural	1.44	(1.15 - 1.80)	
Sexual identification			<0.001
Unknown/homo/bisexual	Reference		
Heterosexual	1.31	(1.15 - 1.50)	
Probable mode for contracting HIV infection			0.497
Intravenous drug use	Reference		
Sexual intercourse	1.02	(0.83 - 1.26)	
Others		(0.47 - 1.32)	
Unknown	1.12	(0.86 - 1.47)	
Type of patients			<0.001
Outpatient	Reference		
Inpatient	2.27	(1.90 - 2.71)	
Combined treatment			0.002
No	Reference		
Yes	0.76	(0.65 - 0.89)	
Unknown	0.86	(0.70 - 1.06)	
Cryptococcosis			<0.001
No	Reference		
Yes	1.42	(1.26 - 1.61)	

HR, hazard ratios; CI, confidence interval; HIV, human immunodeficiency virus.

Table 3
Multivariate analysis of factors associated with mortality among study subjects with cryptococcosis.

Present of cryptococcosis	Crude HR (95%CI)	Adjusted HR (95%CI)[a]
	<0.001	<0.001
No	Reference	Reference
Yes	1.42 (1.26 - 1.61)	1.35 (1.18 - 1.54)

[a]Adjusted for 10 potential confounders: age, sex, marital status, race, occupation, area of residence, sexual identification, probable mode for contracting HIV infection, type of patients and combined treatment.

1.90-2.71) than those who were not hospitalized. Subjects with cryptococcosis were 1.42 times more likely to die (HR=1.42; 95%CI: 1.26-1.61) than those without cryptococcosis. Subjects who had combined treatment were 24% more likely to live longer (HR=0.76, 95%CI: 0.65-0.89) than those who had no combined treatment.

An adjusted Cox's proportional hazard model with backward elimination showed subjects with cryptococcosis were 1.35 times more likely to die (HR=1.35; 95%CI: 1.18-1.54) than those without cryptococcosis after adjusting for confounding factors (Table 3). The Kaplan-Meier method was used to calculate the probability of survival among HIV/AIDS patients with and without cryptococcosis (Fig 1).

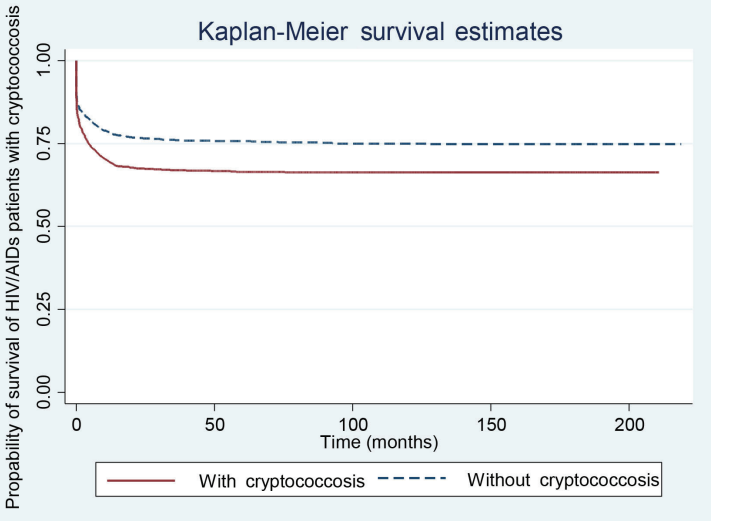

Fig 1 - Kaplan-Meier survival time estimate for HIV/AIDS patients with and without cryptococcosis.

DISCUSSION

This case cohort study determined the association between mortality and cryptococcosis among HIV/AIDS patients. We found a significantly positive association between mortality and cryptococcosis among study subjects. This association may have nothing to do with the cryptococcosis, since 85.9% of cryptococcosis cases were hospitalized versus 63.5% of non-cryptococcosis cases, suggesting the cryptococcosis cases were sicker and may have had lower immunity and/or other opportunistic infections. In our study, hospitalized patients were 2 times more likely to die than non-hospitalized patients (HR=2.11, 95%CI: 1.76-2.53). However, there was lower risk for dying

when the patients received highly active antiretroviral therapy (HAART) at first diagnosis. This may minimize the risk for mortality in the present study.

A hospital-based retrospective study from India (Naik *et al*, 2017) reported the mortality rate of cryptococcal meningitis among HIV patients to be 30%. Approximately 5-10% of patients with AIDS developed cryptococcal meningitis prior to the introduction of the HAART (Naik *et al*, 2017). A retrospective, observational study of secondary laboratory data, conducted in Gauteng Province, South Africa (Britz *et al*, 2016) reported the incidence of cryptococcal meningitis to be 62.3% over a four-year period. The overall incidence of cryptococcal meningitis in South Africa declined from 24.4 in 2009 to 18.7 in 2012 and from 178.2 to 144.7 among HIV-infected persons (cases per 100,000 persons).

A multicenter cohort study conducted in the Caribbean and Central and South America (Crabtree Ramírez *et al*, 2017) reported HIV patients diagnosed with cryptococcal meningitis after beginning HAART had a significantly greater risk of mortality. The probability of survival in this study was not significantly different between patients who started HAART within 2 weeks of developing cryptococcal meningitis and those who started HAART 2-8 weeks before developing cryptococcal meningitis. A study from Denmark (Touma *et al*, 2017) found the overall mortality rate following cryptococcal meningitis was high and the mortality rate during the first 4 months after beginning HAART had not changed substantially over time. A retrospective analysis of three sequential prospective cohorts of HIV-infected adults in Uganda (Flynn *et al*, 2017) reported *Cryptococcus* was the most common pathogen in 63% of patients with AIDS.

A study from the United States using the national inpatient database for 2000 - 2007 (Shaheen *et al*, 2018) found 64% of cryptococcal cases occurred among patients with AIDS. A cross-sectional study from Tunisia (Chelli *et al*, 2016) found 70.4% of HIV cases died and the leading causes of death were: *Pneumocystis jiroveci* pneumonia and cryptococcal meningitis. A study from South Africa (Adeyemi and Ross, 2014) found patients with severe cryptococcal meningitis on admission were three times more likely to die within 14 days (OR=3.2; 95%CI: 0.9-10.7).

A strength of this study was the results are representative of the HIV/AIDS population in southern Thailand. Our study had some limitations. There were a large number of cryptococcosis cases in our study, but many had missing or incomplete data: 8.5% had missing data with multiple logistic regression analysis and 14.9% had missing data with the Cox's proportional hazard model.

In conclusion, in our study, subjects with cryptococcosis were more likely to die than those without it.

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