UNIVERSITI TEKNOLOGI MARA

CONFERENCE PROCEEDING

ICITSBE 2012

1ST INTERNATIONAL CONFERENCE ON INNOVATION AND TECHNOLOGY FOR SUSTAINABLE BUILT ENVIRONMENT

16 -17 April 2012

Organized by:
Office of Research and Industrial
Community And Alumni Networking
Universiti Teknologi MARA (Perak) Malaysia
www.perak.uitm.edu.my

PAPER CODE: GT 43

SURVIVAL AND PROGNOSTIC FACTORS OF ADULT HUMAN IMMUNODEFICIENCY VIRUS (HIV) PATIENTS IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) FROM 2002 TO 2006

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Abstract
The estimated number of persons living with HIV around the world in 2007 was 33.2 million. It was estimated that 80, 938 people have been infected with HIV in Malaysia and 10, 334 died from AIDS from 1986 till December 2007. Drug abuse through injection was the dominant mode of HIV transmission in Malaysia.The objectives of this study were to identify the prognostic factors of HIV patients in HUSM. The design for this study was a retrospective record review. All the patients diagnosed as HIV positive in HUSM during the study period of 1st January 2002 until 31st December 2006 (5 years) will be recruited as respondents in this study. Additional follow up for this study was about 12 months, from 1st January 2007 till 31st December 2007. All HIV cases who fulfill the selection criteria in this study were 107 patients. Data of HIV patients were collected from medical record unit using data collection sheet. The patient's survival status was obtained from medical record or contact by phone call. The process of data entry for this study was done using SPSS version 12.0.1. Data was transferred into STATA version 9.0 program using STAT Transfer software version 6.0. The statistical analysis were used in this study was Cox Proportional Hazard Regression analysis. Prognostic factors that were found to be significant during simple cox regression analysis were co-infections, opportunistic infections, clinical stage and clinic visit frequency. During multiple cox regression analysis, prognostic factors such as clinical stage and clinic visit frequency were significant in this study. Final model in this study only had clinical stage as prognostic factor (Adjusted HR=2.40; 95%CI: 1.42, 4.01, p=0.001). Overall median survival time in this study and survivorship among HIV/AIDS patients in HUSM was low. The five years survival in this study was affected by late diagnosis as HIV positive and the unavailability of HAART in HUSM. The prognostic factor that influenced the risk of death among HIV patients was clinical stage. Prognostic factors such as CD4 count, viral load and HAART will be included in this final model in future in order to increase the strength of the model to predict survival of HIV patients in HUSM.

Keywords: Survival, Proportional Hazard Regression, HIV.

1. Introduction

HIV stands for Human Immunodeficiency Virus while AIDS stands for Acquired Immunodeficiency Syndrome. HIV that causes AIDS can be defined as a retrovirus that infects cells and destroys human immune system. HIV infection is a communicable disease that lead to a continuum of progressive damage to the immune system from the time of infection to the manifestation of severe immunologic damage by neoplasm, opportunistic infection (OI), wasting or low CD4 lymphocyte count that define AIDS (Osmond, 1998). AIDS can be defined as a severe disease syndrome that represents the late clinical stage of infection with HIV (WHO, 2001). AIDS was first recognized in 1981 but it was probably existed at a low endemic level in Central Africa before epidemic HIV spread began to occur in several areas of the world during the 1970s (WHO, 2003). Patients in clinical stage 4 based on World Health Organization (WHO) classification of HIV/AIDS were AIDS patients.

The estimated number of person living with HIV around the world in 2007 was 33.2 million. It was estimated that 2.5 million people around the world became newly infected with HIV while 2.1 million deaths were caused by AIDS in year 2007. New HIV infection and AIDS death in year 2007 were among adult and children under 15 years. Sub-Saharan Africa was the most affected region with AIDS remaining leading cause of death. The estimated number of person living with HIV in Sub-Saharan in 2007 was 22.5 million people. It was estimated that 1.7 million people in Sub-Saharan Africa became newly infected with HIV in 2007. The majority of people living with HIV in Sub-Saharan Africa were women (UNAIDS & WHO, 2007). The first AIDS case in Malaysia was reported in December 1986. HIV screening activities in Malaysia were started in 1986 among IDU, blood donors, sex workers arrested by police, prisoners, STI patients, delinquent girls in the rehabilitation center and those suspected to be exposed to HIV (WHO, 2003). The incidence rate and mortality rate of HIV infection (all forms) per 100, 000 populations in Malaysia were 21.88 and 1.43 in 2006. The incidence rate and mortality rate of AIDS per 100, 000 populations in Malaysia were 6.91 and 3.66 in 2006 (MOH, 2006).
The study on HIV/AIDS patients in Malaysia often produced descriptive statistics such as percentage of patients infected through risk category and that having opportunistic infections such as pulmonary tuberculosis (PTB) and many more on. Different survival probabilities of HIV positive patients may be due to the demographic profiles, healthcare utilizations and clinical characteristics. The purpose of this study is to identify prognostic factors of HIV patients.

2. Literature Review

2.1 Natural History of HIV

The natural history of HIV is different between geographic regions and person to person. Some of the HIV patient's progress to AIDS within 2-3 years infection and the other HIV patients remain free from AIDS more than 12-13 years. All viral, societal, geographic, host factors (age, gender, exposure category, immunologic/genetic) may influence the natural history of HIV both at an individual and population level (Wei *et al.,* 2008). Knowledge of the natural history and survival after HIV-1 infection among various populations was important in order to estimate the extent of the epidemic, the number of individuals that need intervention and to evaluate interventions (Rangsin *et al.,* 2007). HIV infections caused a spectrum of clinical problems beginning at the time of seroconversion and terminated with AIDS and death (Mindel & Tenant, 2001).

2.2 Mode of Transmission and Prevention of HIV

HIV infection can be transmitted through heterosexual, homosexual, bisexual, sharing needle among IDU, sex with sex worker and blood transfusion. IDU that infected with HIV can spread the HIV virus by sharing needles with the other IDU which is not infected with HIV anymore. Vertical transmission which is transmission of HIV infection from mother to child is also a mode of HIV infection. HIV can also spread through contaminated blood, either through sharing of needles and syringes used for illicit intravenous drugs, transfusion of blood and blood products, or contaminated needles and equipment in medical care settings (Abdool Karim *et al.,* 2007). HIV infection from mother to child can happen during pregnancy/process of childbirth and breast feeding. A study by Kaagayi *et al.* (2008) in Uganda among infants born to HIV positive mothers found that the cumulative 12 month probability of infant mortality was 18% among the infants that used formula feeding compared to 3% among the infants with breast feeding [Crude HR= 6.1; 95% CI: 1.7 , 21.4; $p< 0.01$].

2.3 Prognostic Factors

Prognostic factor such as race, age at diagnosis, gender, stage of disease, risk category, clinic visit frequency, number of admission in hospital, OI, co-morbidity and co-infection are potential factors to be studied in order to know their effect on survival rate of HIV patients.

2.3.1 Age

A study by Greenbaum *et al.* (2008) found that older HIV patients had fewer OI but their survival was shorter. A study by Zingmond *et al.* (2000) in United States of America found that older non-whites (age≥50) had fewer symptoms and were less likely to have AIDS but at follow-up they had a trend toward lower survival.

2.3.2 Co-Infections

Sexual transmitted infections (e.g. syphilis) increase susceptibility to HIV and increase the risk of transmitting HIV (WHO, 2007). A study by Kumarasamy *et al.* (2003) in India found that HIV patients that infected with

hepatitis C virus more likely to die compared with HIV patients without hepatitis C virus (Crude HR=7.84; 95% CI: 1.61, 38.22; p value=0.01). The small sample size affected the 95% CI of HR. The 95% CI for HR was wide because of small sample size.

2.3.3 Clinical Stage

A study by Losina *et al.* (2008) in Jamaica found that patients that diagnosed earlier in HIV stage (asymptomatic HIV and symptomatic HIV) had a lower hazard of dying (Adjusted HR=0.32; 95 % CI: 0.29, 0.35 and Adjusted HR=0.49; 95% CI: 0.44, 0.55) compared with HIV patients first identified with AIDS. The p value of variable initial stage HIV infection was not reported. The 95% CI of adjusted HR of variable initial stage did not include value of one. Therefore, initial stage was significant prognostic factor of survival.

2.3.4 Opportunistic Infections

A study by Losina *et al.* (2008) in Jamaica found a greater number of OI was strongly associated with mortality caused by HIV. HIV patient that did not have OI were less likely to die compared with HIV patients that having two number of OI (Adjusted HR= 0.36; 95%CI: 0.32, 0.4). HIV patient that had only one OI were less likely to die compared with HIV patients that having two number of OI (Adjusted HR= 0.55; 95%CI: 0.48, 0.62). The 95% CI of adjusted HR of variable OI did not include value of one and the interval estimation was not wide. Therefore, opportunistic infections was significant prognostic factor and the estimation 95% CI adjusted HR of OI was precise. However, the p value was not reported.

2.3.5 Co-Morbidity

A study by Whalen *et al.* (1997) in United States of America found that the site of culture-proven TB at presentation and the history of previous OI were important predictors of survival in HIV-infected patients with TB. HIV patients that having both PTB and extra PTB were 4.0 times more likely to die compared with HIV patient with only PTB (Adjusted HR= 4.0; 95% CI: 1.93, 8.22). HIV patients having extra PTB were 2.2 times more likely to die compared with HIV patient with PTB (Adjusted HR= 2.2; 95% CI: 0.92, 5.42). Only variable both PTB and extra PTB was significant because 95% CI of adjusted HR did not include value of one.

3. Methodology

The design for this study was a retrospective record review. Records of patients from Medical Record Unit will be retrospectively reviewed to obtain information of HIV patient in Hospital Universiti Sains Malaysia (HUSM). All patients diagnosed as HIV positive in HUSM from 1st January 2002 till 31st December 2006 recruited in the study. Inclusions criteria for HIV patient to be included in this study were diagnosed as HIV by ELISA and/ or Western Blot result, referred from other hospital as documented HIV positive, diagnosed as AIDS and age must be greater than or equal 18 years old. The exclusion criteria were HIV patients with incomplete medical information data for study variables such as race, age, co-infections, clinical stage, OI, gender, risk category, clinic visit frequency, number of admission in hospital and co-morbidity higher than 30% will be excluded from this study.

Sample size was calculated using Power and Sample Size Calculation (PS) software (Dupont& Plummer, 1997). The value of significance level (α) was 0.05 and the power of study (1- β) was 0.8. The ratio of control to experimental patients (m) and median survival time on control (m1) was obtained from literature review. Total sample size ware 107 patients.

Survival analysis was used in this study which concerns time to event data. It can be accessed relationship between covariates and survival time. The process of data entry for this study was done using Statistical Package for Social Science (SPSS) version 12.0.1 (SPSS Inc, 2003). Data entry from Statistical Package for Social Science (SPSS) version 12.0.1 (SPSS Inc, 2003) program were transferred into STATA version 9.0 (Stata Corp, 2003) program using STAT Transfer software version 6.0 (STAT/TRANS, 2001). STATA version 9.0 (Stata Corp, 2003) program used to analyze data.

4. Result and Analysis

All the possible factors were analyzed one by one using simple cox regression were age at diagnosis, gender, race, heterosexual, IDU, clinical stage, OI, co-morbidity, co-infections, clinic visit frequency and number of admission in hospital. Only variables namely OI, co-infections, clinical stage and clinic visit frequency were significant. Then Variables that contributed significantly in the Simple Cox Regression analysis (p-value< 0.25) and clinically or biologically important were analyzed in the Multiple Cox regression analysis. Only variables

namely clinical stage and clinic visit frequency were significant in the Multiple Cox Regression (table 1). Furthermore, we did check for interaction term and found that no interaction exists. The multicollinearity was checked between clinical stage (VIF=1.0) and clinic visit frequency (VIF=1.0). Both variables had variance inflation factor (VIF) less than 10.

Moreover, assumptions for proportional hazard were checked using Log minus log plot, and hazard function plot. Both showed that the assumption of hazard was proportionate over time met. Overall, we can conclude that those HIV positive patients with clinical stage 4 had 2.4 times hazard of dying compared with HIV patient in combination clinical stage 1, 2 and 3.

Table 1: Prognostic factors of HIV positive patients in HUSM using Multiple Cox Regression (n = 107)

Variables	Adjusted HR[a] (95%CI[b])	Wald[c] statistic	P value[d]
Clinical stage			
1/2/3	1.00[f]	4.46	<0.001
4	3.46 (2.01, 5.98)		
Clinic visit frequency*	0.82 (0.75, 0.90)	-4.05	<0.001

[a]Adjusted Hazard Ratio for others variable [b] Confidence Interval [c] Likelihood Ratio statistic [d] p value for LR statistic [f] reference * continuous data
LR statistic=34.32 p value for LR statistic <0.001

The final model for this study had only clinical stage as prognostic factor. A study by Losina *et al.* (2008) also showed that clinical stage as one of their significant prognostic factors. Those without HAART were at higher risk of death. Variables such as co-infections, OI, clinical stage and clinic visit frequency were significant during univariable analysis. Variables clinic visit frequency was significant during multivariate analysis. After treated TVC and done the LR test, it was found to be not significant. Thus, the variable was not one of the prognostics factors for this study. The deaths among patients in clinical stage 4 were highest among the other clinical stage because the highest HIV infections in this study were among patients in clinical stage four. It means that the progression to death was higher among patients in clinical stage 4 compared with combination clinical stage 1, 2 and 3. Therefore, the clinical stage was the prognostic factor for the final model.

5. Conclusion

The prognostic factor that influenced the risk of death among HIV patients in HUSM was clinical stage. Progression from HIV infection to death caused by HIV related causes based on clinical stage. Diagnosis at late stage of HIV positive during course of HIV infection may influence the risk of death. The higher the stage of HIV infection caused the higher the risk of death. This study also showed that some other prognostic factors were found to be not significant probably due to small sample size. The results of this study show that early detection of HIV was crucial in order to manage the patient and provide intervention early as clinical stage is a significant prognostic factors. Voluntary, counseling and test activities should be implemented to all high risk groups so that early intervention will improve their survival.

Acknowledgement

We would like to express highest gratitude to all who were directly or indirectly involve in this study.

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