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Determinant factors of survival time in a cohort study on HIV patient using by time-varying cox model: Fars province, south of Iran

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ABSTRACT

Background and aims: The pandemic of AIDS is a global emergency and one of the biggest challenges in social and individual life. This study aimed to evaluate the survival time of HIV patients and its effective factors.

Methods: This historical cohort study was conducted on the individuals infected with HIV in Fars province, south of Iran, during 2006 to 2013. The study data were obtained from information documented in the patients' records. For statistical analysis, at first, Kaplan-Meier survival analysis was used as univariate method and then, time varying Cox regression model was applied as multiple analyses.

Results: The findings of the present study implied that some variables could play the role of risk factors in HIV patients, and shorten the patients' life span e.g. older age, female gender, unemployment, delay in HIV diagnosis, drug injection, and higher Hemoglobin (HGB) levels.

Conclusion: Many factors affect HIV patients' survival time. Some of these factors, such as gender and genetic factors, are irreversible. However, some others, including drug injection, are preventable. This implies that in order to slow down the speed of HIV conversion to AIDS and delay the occurrence of death, special attention must be paid to these factors and changing the patients' conditions accordingly.

Original article

Keywords: Survival analysis, Cox regression, HIV, AIDS, Iran.

INTRODUCTION

Although the life expectancy of patients with Human Immunodeficiency Virus (HIV) has largely improved with introduction of Antiviral Therapy (ART) and Highly Active Antiviral Therapy (HAART), HIV and Acquired Immunodeficiency Disease (AIDS) continue to be a major health problem threatening people around the world.[1-3] Current statistics indicates that until 2013, there were 35 million HIV-positive individuals around the world among whom, 31.8 million were adults and 3.2 million

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were children below 5 years of age. In addition, global statistics showed that 2.1 million people were newly infected with HIV in 2013.[4] Based on Iran's statistics in 2013, the prevalence of HIV was 0.2% in the patients between 15 and 49 years old. It was also estimated that there were 86,000 HIV-positive patients in the country.[5] The importance of this issue is manifested more by considering the fact that up to now, no definitive treatment has been found for AIDS and these patients died by various factors, such as Tuberculosis (TB), hepatitis B and C, liver diseases, non-AIDS-related malignancies, and problems related to HAART such as heart diseases.[2,6,7] In 2013, one and half million people worldwide and 4300 ones in Iran died due to AIDS.[4,5]

Roshanayee and colleagues conducted a study entitled "survival rates of human immunodeficiency virus and tuberculosis co-infected patients" in Iran, examining 807 patients who were only infected with TB and 21 patients who were simultaneously diagnosed with TB and HIV. In that study, Kaplan-Meier method and Log Rank test were used for data analysis. Their study results showed that co-infection of TB and HIV significantly increased death rate. Accordingly, the rate of death was 20.7 folds (Hazard Ratio (HR)= 8.1 to 53) higher in the patients infected with both HIV and TB compared to those who were only infected with TB. Moreover, marital status was introduced as a risk factor for survival of HIV patients and the death HR was 2.1 folds higher in married individuals compared to single ones.[8] In another study conducted by Mirzaee and colleagues on 585 HIV-positive patients in Hamadan, Iran, the information registered in the patients' health records was used. In that study, Cox proportional hazard model was used for survival analysis. The results indicated that using HAART could act as a protective factor, because death HR was 4.1 folds higher in the patients who did not receive HAART compared to those who used this treatment. On the other hand, TB and HIV co-infection was one of the most important risk factors for the patients' survival.[9] Antiretroviral Therapy Cohort Collaboration (ATCC) also carried out a research on 39272 HIV-positive patients who had participated in 13 retrospective cohort studies. The results showed that more than 85% (1597) of the HIV patients' deaths could be attributed to the specific factors. So as to 49.5%, 11.8%, 8.2%, 7.7%, 7%, and 6.5% of deaths were related to AIDS, malignancies uncorrelated to AIDS, infections uncorrelated to AIDS, violence or drug abuse, liver diseases, and heart diseases, respectively.[6]

Overall, the pandemic of AIDS is a global emergency and one of the biggest challenges in social and individual life.[10-12] Furthermore, it forms and undermines social and economic growth around the world. Although, global statistics of the disease have decreased especially in developed countries, unfortunately, this trend is increasing in Iran.[13,14] Therefore, the present study aims to evaluate HIV patients' survival time and its effective factors. In this way, application of appropriate educational and interventional proceedings could prolong HIV patients' lifetime.

METHODS

This historical cohort study was conducted on individuals infected with HIV in Fars province, south of Iran, during 2006-2013. The study data were collected using the information documented in the patients' records. These records have been archived by Behavioral Disease Consulting Center of Shiraz University of Medical Sciences, Shiraz, Iran.

The information in the patients' records consisted of three types of variables: 1. The

dependent variable; i.e., survival time; 2. Repeatedly measured independent variables, such as White Blood Cells (WBC) count, Total Leukocyte Count (TLC), Platelet (PLT) count, Hematocrit (HCT) levels, Hemoglobin (HGB) level, and Erythrocyte Sedimentation Rate (ESR); 3. Other variables that were covariates, including gender, education level, marital status, occupation, addiction status, HIV transmission way, joint injection, Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), prophylaxis for TB, HAART, HIV level at diagnosis, CD4 cell count and age. Method of stratification of the categorical variables has been presented in Table 1 in the "Results" section.

In this study, the samples were selected through census method. In doing so, all the HIV-infected individuals identified during the aforementioned years who had three measurements of CBC (n=1052) were recruited into the study. HIV infection was confirmed by two ELISA positive test results and a Western blot test result. These tests were performed for the patients voluntarily or, in some cases, because of requirements, such as marriage or employment. After confirmation of HIV infection through these tests, the patients were introduced from the laboratory to the health center located at their place of residence, so that Behavioral Disease Consulting Center could cover the patients and perform the necessary periodical testing and follow-up. In this study, 1052 out of the 1565 HIV-positive patients with three CD4 measurements in their records were selected for statistical analysis.

In this study, the desired outcome was the HIV patients' survival time from diagnosis to death. Repeatedly measured independent variables were measured at baseline and six months and one year later. Although the missing values of this study were low (less than 5%), multiple imputation method (regression) with 5 times integration was employed for estimation of missing values. At first, the relationship between the above-mentioned factors and survival time was evaluated by Kaplan-Meier survival analysis as the univariate method. It should be mentioned that Log Rang test was utilized for determining the significance level of Kaplan-Meier results. In univariate analysis, the factors with $P<0.2$ were considered to be significant and were entered into multiple analysis. For multiple modeling, time-varying Cox regression model was used. In multiple modeling, the factors with $P<0.05$ were considered to be significant. All these analyses were performed using the SPSS statistical software, version 21 and Stata software, version 11.

RESULTS

This study was conducted on 1052 HIV positive persons that 286 of them died and their median survival time was equaled to 5 years. Also, whose descriptive statistics according to the categorical variables have been presented as number (n) and percentage (%) in the upper part of Table 1. The method of stratification of the categorical variables has also been shown in Table 1. Besides, number (n) and mean of the patients in terms of continuous variables have been displayed in the lower part of Table 1.

Table 1: Characteristic of the patients based on categorical and continuous variables

Categorical Variables		**n**	**%**
Gender	Male	822	78.1
	Female	230	21.9
Education level	Illiterate	81	7.7
	Elementary school	329	31.3
	Middle school	396	37.6
	High school	208	19.8
	Academic education	38	3.6
Marital status	Divorced	152	14.4
	Married	502	47.7
	Single	382	36.3
	Temporary marriage	16	1.5
Occupation	Unemployed	462	43.9
	Employed	590	56.1
TB prophylaxis	No	284	27.0
	Yes	768	73.0
HAART	No	441	41.9
	Yes	611	58.1
HCV result	Positive	749	71.2
	Negative	303	28.8
HBS result	Positive	830	78.9
	Negative	222	21.1
HIV level	Asymptomatic	776	73.8
	Advanced clinical stage	276	26.2
Addiction status	None	231	22.0
	Quitted	198	18.8
	Using	623	59.2
Transmission way	Drug injection	701	66.6
	Sex	320	30.4
	Transfusion	31	2.9
Joint injection	Yes	749	71.2
	No	303	28.8
Continues variables		**n**	**Mean(SD)**
HIV duration		1052	5.54(1.88)
Age		1052	35.28(42.90)
Baseline CD4 count		1052	342.13(192.98)
WBC		1052	4875.46(1601)
TLC		1052	1684.51(629)
PLT		1052	200.81(64)
HCT		1052	36.80(6.37)
HGB		1052	12.46(1.8)
ESR		1052	43.16(20)

The univariate analysis findings of Kaplan-Meier survival analysis showed that age, gender, marital status, occupation, TB prophylaxis, HAART, HCV, HIV level, addiction status, drug injection, total CD4 count, WBC count, TLC, PLT count, HCT level, HGB level, and ESR were significantly (their Log Rank test $P<0.2$) associated with the patients'survival time (Table 2). It should be mentioned that this table only shows the variables that were related to survival time, but does not display the direction and magnitude of the associations.

Table 2: Univarite survival analysis results using Kaplan-Meier and Log Rank methods

Variables		Mean of survival time (year)			Log Rank (Mantel-Cox)		
		Estimate	95% confidence interval		Chi-square	df	Sig
			Lower	Upper			
Age	Year	5.58	5.44	5.72	3.24		0.07
Gender	Male	5.61	5.44	5.78	3.80	1	0.05
	Female	5.47	5.20	5.74			
Education level	Illiterate	5.42	4.92	5.91	1.12	4	0.28
	Elementary school	5.81	5.54	6.07			
	Middle school	5.47	5.25	5.70			
	High school	5.66	5.34	5.99			
	Academic	5.08	4.41	5.75			
Marital status	Divorced	5.48	5.11	5.85	2.93	3	0.08
	Married	5.50	5.29	5.70			
	Single	5.68	5.45	5.91			
	Temporarily married	5.75	5.40	8.09			
Occupation	Unemployed	5.72	5.50	5.94	10.12	1	0.00
	Employed	5.45	5.26	5.63			
TB prophylaxis	No	5.69	5.41	5.97	1.67	1	0.19
	Yes	5.54	5.37	5.70			
HAART	No	5.45	5.27	5.64	2.43	1	0.12
	Yes	5.78	5.56	6.00			
HCV	Positive	5.70	5.53	5.87	3.60	1	0.05
	Negative	5.31	5.05	5.58			
HBV	Positive	5.50	5.18	5.81	0.14	1	0.7
	Negative	5.60	5.44	5.76			
HIV level	Advanced	5.48	5.31	5.64	2.27	1	0.13
	Asymptomatic	5.89	5.62	6.16			
Addiction status	None	5.52	5.24	5.81	1.66	1	0.19
	Quitted	5.46	5.13	5.80			
	Using	5.64	5.45	5.83			
Transmission way	Drug injection	5.61	5.43	5.79	0.61	1	0.43
	Sex	5.47	5.23	5.72			
	Transfusion	6.16	5.23	7.09			
Joint injection	No	5.66	5.48	5.83	7.47	1	0.00
	Yes	5.39	5.14	5.63			
Baseline CD4	≤ 100	5.47	4.86	6.07	0.14	1	0.70
	> 100	5.59	5.44	5.74			
Total CD4	≤ 100	5.51	5.36	5.66	3.84	1	0.05
	> 100	6.05	5.69	6.42			
WBC	mg/dL	5.58	5.44	5.72	549.491	238	0.00
TLC	mg/dL	5.58	5.44	5.72	445.94	206	0.00
PLT	mg/dL	5.58	5.44	5.72	816.23	382	0.00
HCT	mg/dL	5.58	5.44	5.72	429.13	192	0.00
HGB	mg/dL	5.58	5.44	5.72	412.01	173	0.00
ESR	mg/dL	5.58	5.44	5.72	1572.47	627	0.00

Time varying Cox regression analysis outputs as multiple analysis indicated that age, occupation and HIV level at diagnosis significantly affected the patients' mean survival time (P≤0.05). Among these variables, age was negatively associated with the HIV patients' survival time, because it's HR was more than one. Accordingly, increase in the patients' age resulted in a decrease in their survival time. The results of time varying Cox regression also showed that jobless patients and those with advanced stage of HIV at diagnosis had lower survival time compared to the patients who did not have these characteristics. Among the variables that were measured repeatedly, only HGB level had a significant negative effect on the patients' survival (Table 3).

Table 3: The results of multivariate survival analysis using time varying Cox (TVC) regression

Variables		Hazard ratio	SE	Z	P>|Z|	95% Conf. interval
Age		0.44	0.16	-2.17	0.03	0.21-0.92
Gender		0.83	0.19	-0.97	0.33	0.47-1.20
Education level	Illiterate	1				0.96-1.02
	Elementary	0.99	0.03	1.68	0.65	1.00-1.05
	Middle	1.03	0.04	1.15	0.17	0.98-1.03
	High	1.01	0.02	1.36	0.27	0.96-1.14
	Academic	1.05	0.04	1.22	0.22	
Marital status	Divorced	1				
	Married	0.98	0.05	-1.07	0.23	0.95-1.07
	Single	0.96	0.03	-1.05	0.19	0.94-1.04
	Temporarily	0.94	0.04	-1.04	0.29	0.91-1.01
	Occupation	1.25	0.10	2.65	<0.001	0.85-1.04
	TB prophylaxis	1.16	0.11	1.65	0.09	1.06-1.49
	HAART	1.09	0.10	0.93	0.35	0.97-1.20
	HCV	1.16	0.13	1.31	0.19	0.90-1.31
	HBS	1.09	0.10	0.93	0.35	0.92-1.45
	HIV level	0.78	0.08	-2.11	0.03	0.90-1.33
	Addiction status	0.91	0.07	-1.19	0.23	0.63-0.98
	Transmission way	0.84	0.11	-1.29	0.19	0.77-1.06
	Joint injection	1.23	0.17	1.50	0.13	0.64-1.09
TVC*	CD4	1.01	0.02	0.89	0.37	0.93-1.62
	WBC	0.99	4.04	-0.98	0.32	0.97-1.06
	PLT	1.00	0.00	0.11	0.90	0.99-1.00
	HCT	0.99	0.00	-0.36	0.72	0.99-1.00
	HGB	1.20	0.01	3.55	0.04	0.99-1.00
	ESR	1.00	0.00	1.12	0.26	1.19-1.20

**: TVC= Time Varying Cox.*

DISCUSSION

This study aimed to determine the effective factors in HIV patients' survival time. The study findings implied that some variables were risk factors in HIV patients, accelerated disease progression, and shortened the patients' life span. These variables included older age, female gender, unemployment, delay in HIV diagnosis,

drug injection, and higher HGB levels. In contrast, some factors, including middle age (20-40 years), receiving HAART, and higher values of some CBC factors such as TLC and HCT,could slow down HIV progression and prolong the patients' lifetime.

The findings of the present study displayed that older ages affected development of AIDS symptoms and occurrence of early death. Several studies have also shown that the higher the HIV patients' age, the more quickly their infection will be converted to AIDS.[15-17] In one study, for example, the median time from serocon version to AIDS without therapy was 15 years for 16-24-year-old patients, but 6 years for those who were 35 years old or above.[18] Similarly, another study indicated that in the absence of HAART, faster overall progression to AIDS occurred with increasing age, especially after the age of 40 years. Also, the speed of disease progression was higher among younger children, especially newborn HIV-positive patients. On the other hand, the slowest rate of progression was seen in teenager patients. This might be justified by the fact that with increasing age, CD4 cell replacement power is decreased because fewer and naïve CD4 cells are generated by the thymus gland. An alternative explanation is that with increasing age, there are lower levels of chemokines to intervene with HIV's ability to infect CD4 T-cells.[15,19]

According to the findings of our study, female gender was a risk factor for HIV patients' survival time. Similarly, Hongbo Jiang et al. conducted a cohort study in China and showed that a larger number of women compared to men entered AIDS after 1 year (23% vs. 17%) and 3 years (45% vs. 35%).[20] Moreover, other studies showed that the mean of HIV-RNA varied between men and women for given CD4 count strata and was higher in women compared to men. Moreover, the mean of survival time was less in women compared to men.[21,22] The dominant idea is that gender itself does not affect HIV progression, morbidity, or mortality, but some differences can be attributed to the effect of confounders, such as poverty and poor access to medical care. Furthermore, gender via other factors, such as genetic, hormonal, and psychological variables, makes differences between men and women. Such studies indicated that host genetic factors, e.g. chemokine receptors CXCR4 and CCR5 and their natural ligands, and immune response play important roles in progression of HIV to AIDS or death.[23,24] Many studies have also identified a role for HLA genotype for HIV outcomes.[25] Rapid progression to AIDS has been associated with HLA alleles A24, B35, B37, B56, B58S, and A1-B8-DR3.[26] In contrast, alleles B57, B27, B14, and C8 have been associated with long-term non-progression.[27]

The results of the present study indicated a negative association between HGB level and HIV patients' survival time. Slama and colleagues conducted a study on 1500 HIV-uninfected and 1357 HIV-infected men with a median of 11 visits for each participant for over 13 years. At Fasting Blood Sugar (FBS) level of 125 mg/dL, the median HGBA1c among the HIV-infected men was 0.21% lower than that among the HIV-uninfected ones.[28] In another study accomplished by Alavi et al. in Iran, a strong correlation was observed between CD4 count and TLC (r=0.645, P=0.001), but no correlation was seen between CD4 count, and HGB and HCT levels (r=0.451, P=0.056 and r=0.375, P=0.816, respectively). That study showed that TLC was a suitable surrogate marker for CD4 count. However, HGB and HCT levels were of limited value in predicting CD4 count and should not be substituted for CD4counts.[29] These findings were not consistent with those obtained in Slama's study and the present one. This

difference might result from the small sample size of Alavi's study (n=100) and the fact that a few variables were entered into that study, which might have confounded the findings. In addition, they only used Pearson correlation coefficient method for data analysis and did not use multiple analysis for adjustment of confounders.

According to the findings of the current study, unemployment was a risk factor for progression of HIV to death. In general, patients who have a job have better nutrition compared to jobless ones. They also use health services more that can improve their health. Studies have demonstrated that micronutrient supplements might be benefit in some patients with HIV infection.[25-27] A randomized trial on 1078 pregnant women in Tanzania also showed that the women who received a multivitamin supplement (vitamins B, C, and E) had delayed progression of HIV compared to those receiving the placebo.[25]

The results of our study revealed that HIV infection through injection was a risk factor for accelerating the disease progression and shortening of survival time. Similarly, some studies have demonstrated that the patients who acquired their HIV infection through drug injection had higher death rates compared to those acquiring their infection via sex.[30,31] Moreover, the results of a study conducted on more than 22,000 patients from Europe and North America indicated that AIDS event rates decreased more rapidly in Men who have Sex with Men (MSM) in comparison to injection drug users.[31] Besides, the findings of a prospective, longitudinal study conducted on a cohort of 222 HIV-infected drug users in Camillus House, Miami showed that crack-cocaine users were 2.14 times [95% Confidence Interval (CI): 1.08 to 4.25, P=0.029] more likely to present a decline of CD4 to ≤ 200 cells/mL, independent of antiretroviral use.[32] Injection drug use could have an effect on HIV progression because drugs, such as opioids, may increase HIV replication in vitro.[33,34] Furthermore, drug use may negatively affect medication adherence and use of medical care.[35] Intoxicating effects of many drugs can change individuals' judgment and inhibition and cause them to take part in capricious and unsecure behaviors, which eventually worsen the patients' conditions.

The current study results indicated that receiving HAART and TB prophylaxis could slacken the speed of HIV conversion to AIDS and prolong patients' lifetime. In the same line, Pepe and his colleagues conducted a study on HIV patients and reported that the incidence of TB and HIV progress were lower in Isoniazid pill recipients than in the patients who received B6 vitamin alone (2.2 vs. 7.5 per 100 person-years).[36] In addition, in the study implemented by Peter et al. for determining the effect of different types of treatment on prevention of HIV, Kaplan-Meier estimates of progression rates to AIDS at 18 months were 13.6% (mono therapy), 4.7% (RTI combination therapy), and 3.9% (HAART).[37] Coinfection with other pathogens may influence the rate of HIV progression. For instance, coinfection with TB accelerates HIV-associated immunodeficiency and increases the levels of viremia. Therefore, it is evident that TB prophylaxis could delay HIV progression to death.[38]

Of course, there was some limitations in this research. Since many factors affect HIV progression and many of these factors have partial associations with each other (e.g. genetic factors have correlations with gender, sensitivity, and progression of HIV), not having any information about such variables (similar to this study) might induce confounding effects. As a result, cofounding could have aggravated, mitigated, or masked the observed correlations because its effect was not adjusted. Another limitation of the

current study was making use of recorded data. Since these data were collected for patients' follow-up and surveillance, they might not be of high quality. Finally, if the patients referred to the clinics in early stage of the disease, their morbidity was diagnosed in the first step. However, some patients might have referred to laboratory at advanced stages of the disease. If so, using HIV duration or baseline CD4 count might not give correct or appropriate results.

CONCLUSION

Many factors affect HIV patients' survival time. Some of these factors, such as gender and genetic factors, are irreversible. However, some others, including drug injection are preventable. This implies that in order to slow down the speed of HIV conversion to AIDS and delay the occurrence of death, special attention should be paid to these factors and changing the patients' conditions accordingly.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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