ORIGINAL PAPER

Identifying spatial pattern, risk factors, and effect of trajectory of CD4 count for mortality among HIV-infected patients

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Abstract

Introduction: Identifying areas that the burden of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) disease is concentrated could play an important role in public health. The purpose of the present study was to assess pattern of spatial inequalities in survival in Hamadan Province, and to examine the effect of prognostic factors and trajectory of CD4 on the risk of mortality among HIV-infected patients.

Material and methods: This registry-based cohort study was carried in Hamadan Province, Iran, from December 1997 to June 2020, and included 400 patients. Join modeling of longitudinal and spatially clustered survival data was used for analyzing data. Outcomes in longitudinal sub-model was the number of CD4 T-lymphocytes over time and time of HIV diagnosis, and outcomes in survival sub-model was time interval between HIV diagnosis and mortality.

Results: According to our results, among all the predictors, there was only a significant relationship between co-infection with tuberculosis and CD4 trajectory. The association for risk of mortality was significant for antiretroviral therapy (ART) and co-infection with tuberculosis. Also, the lower CD4 counts during follow-up were related to a higher risk of mortality. Regarding mapping of our results for risk of mortality, we identified three counties with slightly higher hazards and three counties with rather lower hazards in Hamadan Province.

Conclusions: The assessment of spatial pattern of HIV survival is helpful and appears to be dependent on socio-economic characteristics. Furthermore, our results suggest factors of access to ART and prevention of co-infection with tuberculosis, which may be useful to increase the length of patients' life.

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Key words: mortality, Bayesian inference, spatial random effect, HIV, AIDS.

Introduction

Globally, human immunodeficiency virus (HIV) infection has been a major problem, irrespective of great efforts to fight the disease. The World Health Organization (WHO) reported that nearly 75 million people have been infected with HIV, out of which about 35 million have died because of acquired immunodeficiency syndrome (AIDS)-associated conditions [1]. Currently, there is no effective cure for HIV-infected patients, but antiretroviral treatment (ART) could reduce mortality rate, sup-

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press HIV viral replication, and slow down AIDS progression process [2]. Fortunately, with the beginning of ART, the trend of annual number of mortality has reduced in the world [3, 4]. On the other hand, late testing and diagnosis delay the initial treatment of ART and therefore, these patients have significantly shorter survival because the disease already progressed considerably by the time of diagnosis [5]. In addition, these patients present poorer health conditions and miss the opportunities to avoid the spread of the disease to others, for example, by reducing high-risk behaviors [6, 7]. Therefore, early diagnosis and appropriate treatment are crucial because survival disparities between those with access to ART and those without access to ART are well-proven.

In contrast, a large number of studies have shown that health outcomes depend on socio-economic conditions and geographic regions [8, 9]. Communities with low socio-economic levels tend to experience a high mortality rate and poorer public health. In other words, undeveloped areas of a city with poor housing are more likely to be vulnerable to diseases [10]. Patients suffering from HIV/AIDS have a weak immune system, so they are very susceptible to opportunistic diseases, including tuberculosis, meningitis, bacterial pneumonia, encephalitis, and specific cancers [11]. Prior studies have calculated HIV/AIDS survival with a hazard model, showing that it depends on socio-economic status and residency [12]. Also, poor socio-economic status leads to inadequate medical care, which is significant for HIV patients [13]. A large number of studies have shown an important role of health insurance (which is linked to socio-economic grade) in mortality of HIV patients [14-16]. Identifying areas and populations that the burden of HIV/AIDS disease is concentrated, could play an important role in successful surveillance programs and help to prevent new HIV infections. Geographical analysis and mapping of the results could provide some information that would be helpful for healthcare organizations. Since the understanding of geographical inequalities in the area of HIV/AIDS disease can be crucial in successful surveillance programs and help to prevent new HIV infections.

CD4 cell count of a healthy individual must be at least 500 cells/mm3, and a result below this level is an indication of unhealthy condition. CD4 cell count is affected by HIV infection [17], and such that, CD4 cell count has been reported to be low among individuals presenting for care in many areas [18]. Also, patients with low CD4 cell count are at higher risk of mortality during the initial year after starting ART [19].

However, to the best of our knowledge, there is no research on geographic variations that explain spatial inequality among sub-populations in Iran as well as evaluations of CD4 trajectory and other prognostic factors on the survival of HIV patients. Due to lack of knowledge in this area, the purpose of the present study was to assess patterns of spatial inequalities in survival in Hamadan Province, Iran, and to examine the effect of prognostic factors and trajectory of CD4 on the risk of mortality, while considering spatial clustering among counties.

Material and methods

This registry-based cohort study was carried in Hamadan Province, Iran, from December 1997 to June 2020, and included 400 HIV-positive patients. The ethics committee of the Hamadan University of Medical Sciences approved the protocol of the study (IR.UMSHA.REC.1399.247). The following independent variables were available in health records: gender, marital status, age, educational level, mode of HIV transmission, presence in prison, drug abuse, ART, and co-infection with tuberculosis (TB). Moreover, patients' health records were employed to collect data, including date of HIV diagnosis, date of mortality, and patient's county of residence. Time interval between HIV diagnosis and mortality was considered as an event time response variable. Patients who were lost to follow-up or did not experience mortality until June 30, 2020, were considered as censored.

CD4 T-lymphocytes were also measured over time from the time of HIV diagnosis. Moreover, patients who their CD4 count was measured at least two times were included in this study. The median of CD4 counts was 383 cells/mm3. The CD4 counts distribution by explanatory variables indicated right skewness, so the square root transformation of CD4 cell counts was used. Longitudinal trajectories of $\sqrt{\text{CD4}}$ measurements for all individuals and overall mean trajectory are shown in Figure 1.

Statistical analysis

In this study, join modeling of longitudinal and spatially clustered survival data was used for analysis. Our joint model consisted of two separate models for each component, including linear mixed-effects model and spatial survival model. In HIV data, $\sqrt{\text{CD4}}$ measurements were considered as time-varying covariate, with an error of measurement. Hence, linear-mixed model with random intercepts and random slopes was considered for $\sqrt{\text{CD4}}$ measurement of i^{th} individual living in k^{th} county as:

$$\sqrt{\text{CD4}}_{ik} = \mathbf{X}\tilde{\boldsymbol{\beta}}_{1k} + b_{1ik} + b_{2ik}t_{ik} + \varepsilon_{ik}.$$

Regarding spatial survival sub-model for the risk of mortality, the proportional hazard model, with exponential function for baseline hazard was specified as:

$$h_{ik}(t \mid \mathbf{x}_{ik}, b_{ik}) = \exp(\mathbf{X}\tilde{\boldsymbol{\beta}}_{2k} + \gamma_1 b_{1ik} + \gamma_2 b_{2ik} + W_k),$$

where g quantifies the strength of association between CD4 measurements with the risk of mortality. Also, the patients included in this study were from different counties, and because of that, spatial random effects Wk were considered in survival model. Intrinsic conditional auto-regressive (ICAR) distribution for spatial random effects was used. Bayesian estimation procedure and R software were employed in this study.

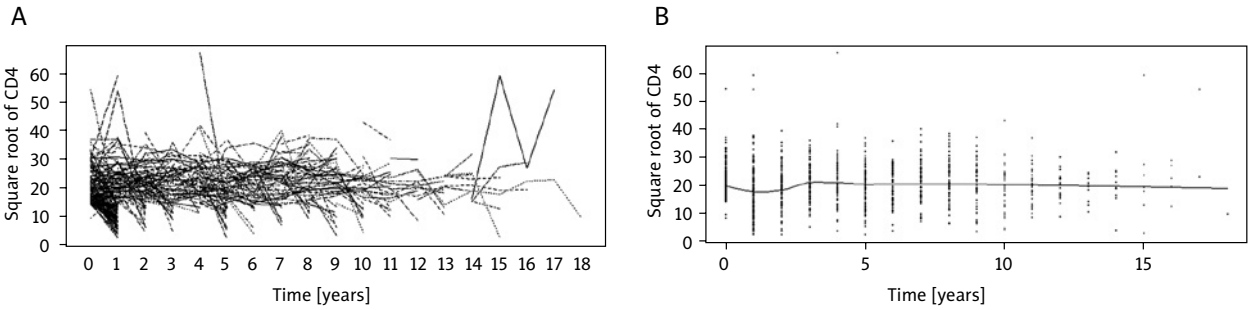

Figure 1. Longitudinal trajectories of CD4 measurements (left) and the overall mean trajectory of CD4 (right).

Table 1. Demographic characteristics of the study patients by their final outcome

Variable	Censored		Mortality		Total		*p*-value
	n (324)	% (81)	*n* (76)	%(19)	*n* (400)	% (100)	
Gender							
Male	229	76.8	69	23.2	298	74.5	< 0.001
Female	95	93.1	7	6.9	102	25.5	
Marital status							
Single	105	71.9	41	28.1	146	36.5	0.005
Married	141	87.6	20	12.4	161	40.3	
Divorce	54	83.1	11	16.9	65	16.3	
Widow	24	85.7	4	14.3	28	7.0	
Age							
1-24	39	76.5	12	23.5	51	12.8	0.573
25-44	246	81.2	57	18.8	303	75.8	
45-74	39	84.8	7	15.2	46	11.5	
Educational level							
High (≥ school)	63	91.3	6	8.7	69	17.3	0.016
Low (< school)	261	78.9	70	21.1	331	82.8	
Mode of HIV transmission							
Injection drug users	209	75.5	68	24.5	277	69.3	< 0.001
Sexual	101	93.5	7	6.5	108	27.0	
Mother to child	14	93.3	1	6.7	15	3.8	
Presence in prison							
No	139	90.8	14	9.2	153	38.3	< 0.001
Yes	185	74.9	62	25.1	247	61.8	
Drug abuse							
No	115	94.3	7	5.7	122	30.5	< 0.001
Yes	209	75.2	69	24.8	278	69.5	
Antiretroviral therapy							
No	13	46.4	15	53.6	28	7.0	< 0.001
Yes	311	83.6	61	16.4	372	93.0	
Tuberculosis infection							
No	308	82.4	66	17.6	374	93.5	0.009
Yes	16	61.5	10	38.5	26	6.5	

Results

In total, 400 HIV-infected patients were eligible for analysis. The mean time of follow-up was 7.96 (range, 0-22) years. The mean age of patients was 33.35 (range, 0-74) years. Of the 400 HIV-positive patients, 298 (74.5%) were men, 102 (25.5%) were women, and most of the patients were infected through injections (Table 1). The patients were divided into two categories based on final outcome: those who died (19%) and those who were censored (81%).

From the results of chi-square test, there was a significant difference between distribution of final outcome across all characteristics of the patients, except age (Table 1). For

Table 2. Posterior estimation results of spatial joint for HIV/AIDS data

Variable	$\sqrt{CD4}$ trajectory		Mortality	
	Mean (SD)	(95% credible interval)	Mean (SD)	Hazard ratio (95% credible interval)
Intercept	19.78 (1.64)	(16.49, 22.86)	–4.71 (0.82)	0.01 (0.001, 0.04)
Gender				
Male	Reference			
Female	–0.87 (1.26)	(–3.34, 1.57)	–0.07 (0.75)	1.22 (0.20, 3.84)
Marital status				
Single	Reference			
Married	0.31 (0.87)	(–1.42, 2.02)	–0.32 (0.30)	0.75 (0.39, 1.31)
Divorce	0.40 (1.01)	(–1.57, 2.39)	–0.34 (0.35)	0.75 (0.34, 1.38)
Widow	0.66 (1.46)	(–2.17, 3.57)	0.20 (0.64)	1.48 (0.31, 3.94)
Age				
1-24	Reference			
25-44	1.28 (1.15)	(–0.99, 3.55)	–0.25 (0.35)	0.82 (0.40, 1.60)
45-74	1.79 (1.44)	(–1.04, 4.60)	–0.03 (0.52)	1.11 (0.33, 2.63)
Educational level				
High (≥ school)	Reference			
Low (< school)	–0.17 (0.84)	(–1.86, 1.45)	0.58 (0.43)	1.97 (0.80, 4.40)
Mode of HIV transmission				
Injection drug users	Reference			
Sexual	–0.96 (1.32)	(–3.54, 1.65)	–0.55 (0.81)	0.78 (0.10, 2.56)
Mother to child	–1.21 (2.25)	(–5.64, 3.21)	–1.25 (1.58)	0.75 (0.008, 4.04)
Presence in prison				
No	Reference			
Yes	–1.13 (1.09)	(–3.29, 0.99)	–0.10 (0.39)	0.96 (0.42, 1.99)
Drug abuse				
No	Reference			
Yes	–1.96 (1.30)	(–4.52, 0.61)	0.78 (0.68)	2.77 (0.58, 8.56)
Antiretroviral therapy				
Yes	Reference			
No	–0.25 (1.22)	(–2.66, 2.14)	0.71 (0.35)	**2.16** (1.07, 3.94)
Tuberculosis infection				
No	Reference			
Yes	–2.77 (1.33)	**(–0.15, –5.40)**	1.05 (0.30)	**2.96** (1.52, 5.07)
Time	0.20 (0.11)	(–0.01, 0.43)	–	–
γ_1	–	–	0.002 (0.04)	–
γ_2	–	–	–0.05 (0.14)	–

example, the probability of mortality was higher among men and those who were in prison and did not receive ART.

The effects of demographics and prognostic factors on the trajectory of CD4 are demonstrated in Table 2. Among all the predictors, there was only a significant relationship between TB co-infection and CD4 count, which meant that patients who were co-infected with TB had a lower mean of CD4 count as compared to other patients. The effects of prognostic factors on hazard ratio of mortality, while considering the spatial clustering among counties, are displayed in Table 2. From the estimates of HR, there was a significant relationship between predictors of ART and TB co-infection with mortality. In other words, the risk of mortality in patients who did not receive ART and were co-infected with TB was higher, such that the adjusted hazard ratio was 2.16 and 2.96, respectively. Finally, based on estimates of g, the lower CD4 counts during follow-up were related to a higher risk of mortality, although this relationship was not significant.

We now continue to map the results. Figure 2 displays the map that the spatial risk of mortality was represented in counties of Hamadan Province based on a joint model that considered the covariates effects as well as the unobserved spatial variation. As shown in Figure 2, for risk of mortality, we identified three counties with fairly higher hazard and three counties with relatively lower hazard in Hamadan Province.

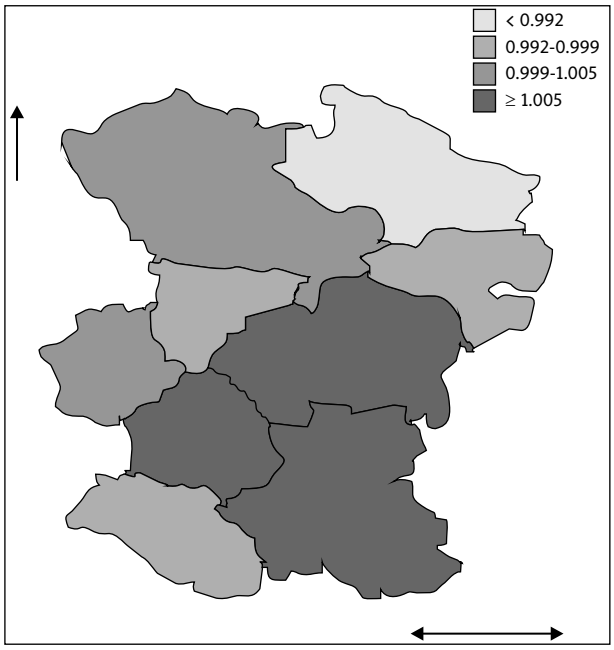

Figure 2. Map of spatial relative risk for mortality based on spatial joint model

Discussion

According to our results, the injection was the most popular mode of transmission among HIV-infected patients (69.3%). Consequently, a screening program in this group could be conducted regularly to reduce the risk of HIV transmission and also the time between initiation of HIV infection and diagnosis.

The association for trajectory of CD4 count was significant for TB co-infection. Also, the effect of predictors was assessed on the time of HIV diagnosis to mortality, while considering the spatial clustering among counties. According to hazard ratio estimates, there was a significant association between ART and TB co-infection and the risk of mortality. In other words, patients who did not receive ART presented about two times higher risk of mortality as compared to other patients, and also, patients who were co-infected with TB had about three times higher risk of mortality, as compared to patients infected with HIV only. These findings were in agreement with a meta-analysis study that reported 2 and 6 years survival rates of mortality in patients receiving ART as 87% and 78%, respectively, while in patients not receiving ART, 48% and 18%, respectively [4]. Poorolajal et al. showed a relationship between ART and co-infection with TB and mortality [2].

Regarding vulnerability of place, some studies showed that poor urban regions were more vulnerable to diseases [10]. With respect to HIV, an understanding of geographic inequalities of mortality could play a significant role to identify populations that need intervention programs. Therefore, contrary to a homogeneous distribution of resources within a country, optimizing resource allocation could be applied. The current study investigated the spatial inequalities in HIV/AIDS survival in Hamadan Province. From its' results, for the risk of mortality, one high-risk cluster with three counties was identified. Moreover, three counties were recognized as the low-risk cluster. The low-risk cluster in mortality had counties with a low-rate population density, as compared to other counties. Also, these counties were in remote areas and with a distance to most populous counties. However, the high-risk cluster in mortality consisted of some counties with the highest rate of population density. Also, Hamadan County (capital of the Province of Hamadan) was in a high-risk cluster, even though people living in this county were more likely to receive medical treatment and other essentials for living with HIV. This is contrary to previous researcher, who suggested that there was a poor survival in remote areas and better survival in urban areas [20].

In this regard, previous studies have assessed spatial inequalities in HIV/AIDS data in different countries worldwide. Oppong et al. evaluated HIV cases between 1999 and 2008 years in Dallas County, Texas. They reported differences in survival in socio-economic status, so regions with high socio-economic grade had significantly lower HIV mortality, as compared to individuals with low socio-economic grade. They explained this finding, as individuals with high socio-economic status were more likely to be able to afford treatment options either through personal finance or personal health insurance. Also, individuals with high socio-economic status had a low percentage of late tester, while individuals with low socio-economic status would have likely lost critical time

of initial diagnosis and treatment [10]. Jongstepongpanth and Bagchi-sen have shown a significant geographical variation in HIV/AIDS mortality rates (2000-2004) at a sub-district level in Thailand [21]. In the United States (1996), in Northeast part of the country and in large metropolitan areas, the prevalence of AIDS was higher [22, 23]. Studies performed in Brazil have shown that the process of diffusion of AIDS started in large metropolises and cities, while smaller cities showed lower level of epidemic [24, 25]. A study evaluated the epidemic of AIDS in the city of Rio de Janeiro (1988-1996), and showed high rates in the center of the city and in coastal areas, such that the epidemic expanded from the coast to interior part over time [26]. Based on the results of a study that was conducted in Brazil, areas more distant from the most populous states were with a higher risk of mortality [20].

The assessment of spatial pattern of HIV survival was helpful and appeared to depend on the socio-economic status. The results of the present study suggest that attention needs to be paid to at-risk groups in urban regions by offering free government programs. In addition, factors, such as access to ART and prevention of co-infection with tuberculosis may be useful for targeted interventions to increase the length of life of HIV/AIDS patients.

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Conflict of interest

The authors declare no conflicts of interest.

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