Identifying risk factors for progression to AIDS and mortality post-HIV infection using illness-death multistate model

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Abstract

Background: There has remained a need to better understanding of prognostic factors that affect the survival or risk in patients with human immunodeficiency virus (HIV) acquired immunodeficiency syndrome (AIDS), particularly in developing countries. The aim of the present study aimed to identify the prognostic factors influencing AIDS progression in HIV positive patients in Hamadan province of Iran, using random survival forest in the presence of competing risks (death from causes not related to AIDS). This method considers all interactions between variables and their nonlinear effects.

Methods: A data set of 585 HIV-infected patients extracted from 1997 to 2011 was utilized. The effect of several prognostic factors on cumulative incidence function (probability) of AIDS progression and death were investigated.

Results: The used model indicated that using antiretroviral therapy tuberculosis co-infection are two top most important variables in predicting cumulative incidence function for AIDS progression in the presence of competing risks, respectively. The patients with tuberculosis had much higher predicted cumulative incidence probability. Predicted cumulative incidence probability of AIDS progression was also higher for mother to child mode of HIV transmission. Moreover, transmission type and gender were two top most important variables for the competing event. Men and those patients with IDUS transmission mode had higher predicted risk compared to others.

Conclusions: Considering nonlinear effects and interaction between variables, confection with tuberculosis was the most important variable in prediction of cumulative incidence probability of AIDS progression.

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1. Introduction

The human immunodeficiency virus (HIV) is the first leading cause of death from infectious disease worldwide and it has remained as a major public health issue (1). Acquired immunodeficiency syndrome (AIDS), that is the final and most serious stage of HIV infection, leads to severe damages to the body immune system.1,2 About 78 million people have been infected with the HIV virus and about 35 million people have died of AIDS-related diseases since the beginning of the epidemic.3 The prevalence of HIV/AIDS in the overall population of Iran is less than 1% which is surpassed about 5% in high risk groups like injecting drug users (IDUs).4 In Iran until August 2016, a total of 30,727 people with HIV/AIDS has been identified which 6016 patients have died.5,6 Although, no functional cure is available for HIV infection at present, the advent of antiretroviral treatment (ART) has led to a decline in the HIV-related mortality which in turn has helped patients to return to a relatively healthy and productive lives.1,2,7 Art also slows down AIDS progression process in an HIV-infected person and prolongs the survival of the patients.8 On the other hand, treatment of the HIV/AIDS can be complicated through several prognostic factors like chronic pathologies associated with immunodeficiency, chronic viral and bacterial infections.1,2 There are good evidences that show life span can be prolonged and the quality of life can be improved significantly if the levels of HIV...
remain suppressed and the CD4 count remains high (above 200).2 On the contrary, co-infection of HIV with other opportunistic infections especially tuberculosis (TB) may result in an increase in the risk of mortality.1,2,9

In spite of a decline in the HIV-related mortality, better understanding of the prognostic factors affecting the survival of the HIV-positive patients is of great importance to improve their life expectancy, especially in developing countries.1 However, limited studies have been conducted regarding survival of HIV-infected patients in these countries, especially those in the Eastern Mediterranean Region.1,2,10

There can be found several clinical and epidemiological follow-up studies that survival of the patients is the eventual outcome of interest, whereas during the study period individuals may experience some intermediate events.11 To model the passage of subjects through states the usual approach is utilizing separate analyses for every single endpoint.11 Nevertheless, an important drawback and shortcoming of this approach is that it does not account for the relationships between different endpoints.12 To overcome this issue, multistate models can be utilized for this type of data.13 Constructing multistate models provide a relevant modeling framework as well as a comprehensive view of a disease process. Moreover, by using multistate models proportions of individuals who are in the various states at some specific time in the future can be estimated and more efficient use of incomplete information can be made when only fairly short portions of individual’s disease histories are available.14

In HIV/AIDS disease, the data related to the survival of the patients has a structure that appropriately fits into multistate models because there is an intermediate event (AIDS) for the patients and some of the patients die without getting AIDS suggesting that the time from HIV to death process should be modeled by an illness-death multi-state model (Fig. 1). This is an important point that has not been considered in most HIV/AIDS studies.1,2 However, as mentioned the results (the coefficients of the covariates and their standard errors so their related Pvalues) can be affected dramatically which is because of the fact that they may fail to show the relations between different types of events.15

Designing the effective intervention strategies aimed to increase the life expectancy of HIV-infected patients is feasible through collecting reliable information about their survival times and the potential risk factors.1,2,9 On the other hand, appropriate statistical models can be utilized to reliable identification of important prognostic factors which helps to improve prediction accuracy of patients’ survival. Therefore, the present study aimed to estimate the effect of potential risk factors on survival of HIV/AIDS patients based on an illness-death multi-state model.

![Illness-death Model for HIV data.](image)

2. Materials and methods

2.1. Data description

This retrospective cohort study was conducted in Hamadan, Iran, from 1997 to 2011 approved by the local Human Subject Review Board of Hamadan University of Medical Sciences. The number of 585 patients with HIV/AIDS was enrolled. The data was extracted from patients’ medical records available at the triangular clinics (The triangular clinic is a kind of clinic established by the Iranian Ministry of Health and Medical Education and works for education, counseling, medical prevention and treatment in the three areas of consultation and treatment of addiction, consultation and treatment of AIDS and consultation and treatment of sexually transmitted diseases (other than AIDS). The services of these clinics are free of charge and they are performed anonymously. Therefore, patients need not introduce themselves or disclose their name and identity to use counseling).

The data collection was done using a predetermined checklist including following variables: age, gender, mode of HIV transmission (injection drug users [IDUs], sexual, mother to child, IDUs/sexual, unknown), co-infection with TB, stage of HIV infection at diagnosis (asymptomatic/symptomatic/unclear), date of HIV diagnosis, date of progression to AIDS, date of death (if any), cause of death (if known) and receiving combination antiretroviral therapy (cART). All registered patients with a determined HIV infection were included in this study irrespective the age, gender, stage of the disease and date of diagnosis.

An HIV-infected case is defined as an individual with HIV infection regardless of clinical stage confirmed by laboratory criteria according to country definitions and requirements.2 In the Islamic Republic of Iran, the definitions of an HIV case and AIDS case are as follows respectively16,17: 1) an individual whose two sequential enzyme-linked immunosorbent assay tests were positive for HIV antibody followed and confirmed by a Western blot test; 2) an individual with a presumptive or definitive diagnosis of stage 3 or stage 4 condition and/or CD4 count <350 per mm 3 of blood in an HIV-infected subject.

There were three different outcomes of interest for investigation in this study: 1) the duration of time between diagnosis of HIV infection and progress to AIDS, 2) the duration of time between diagnosis of AIDS and occurrence of death from AIDS-related causes, and 3) the duration of time between diagnosis of HIV and occurrence of death from causes other than AIDS. Other patients who were lost to follow-up were considered as censored. The effect of several prognostic factors on the survival time to AIDS was investigated including gender, age, marital status, mode of HIV transmission, co-infection with TB and ART which is typically the name given to aggressive antiretroviral drugs used to suppress HIV viral replication and the progression of HIV to AIDS. Usually, it includes several drugs (typically three or four), taken in combination, such as two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or other such combinations.2

2.2. Data pre-processing and dealing with missing values

Pre-processing of the data set was done in two stages: 1) fields with spelling errors, additional tokens, other irregularities and irrelevancies like outliers were corrected or removed; 2) Little MCAR test18 was performed to assess the missing completely at random (MCAR) mechanism for missingness (p = 0.953). So, the MCAR assumption did not reject and persons with at least one missing variable were removed from analysis.
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