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Hierarchy of Determinants Underlying Death among HIV-Infected Patients in French Guiana

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Abstract

Objective: In order to determine how risk factors of death among HIV-infected patients in French Guiana interact with one another and to define high risk population segments, an alternative statistical method to Cox proportional hazards models was used.

Patients and methods: Data from HIV+ patients followed in the three main hospitals of French Guiana were used. Data were extracted from the prospective French Hospital Database for HIV (FHDH). To examine the nature of the relationships between time of death since the first consultation and a set of predictor variables (age at enrolment, gender, nationality, CD4 count at enrolment, presence or absence of HAART at enrolment, a declared addiction, and mode of acquisition of the virus) a survival tree analysis was used. Survival rates at 5 years and 10 years and their 95% confidence interval were also calculated.

Results: This analysis permitted to reveal a new specific subgroup of HIV+ patients particularly at risk in French Guiana not already mentioned in the literature: the HIV+ female patients with a declared addiction.

Conclusions: Prevention and care in this vulnerable segment of the HIV+ population identified by this methodology should be reinforced.

Keywords: HIV/AIDS; Mortality; Female; Addiction; Epidemiology; Risk factor; French Guiana; Tree based method

Introduction

French Guiana is the French overseas territory where the HIV epidemic is most prevalent. HIV prevalence among pregnant women is 1.5%. AIDS incidence is 10 times greater than in metropolitan France [1]. Transmission occurs through heterosexual sex in over 90% of cases. The standards of healthcare are close to those of mainland France. Approximately three-quarters of HIV-infected patients are foreign citizens [1].

In French Guiana, a previous study using a single failure Cox proportional hazards model had identified the main risk factors for death among a cohort of HIV+ patients since the introduction of HAART (Highly Active Antiretroviral Therapy) [2]. In this study, having declared an addiction, age >60, male gender and CD4 count < 50 cells/µL were independently associated with death. However, it is still difficult to disentangle how these risk factors interact with one another and to define high risk HIV+ population segments which could be specifically targeted by public health interventions.

Tree-structured models for survival data is a nonparametric methodology that has the ability to efficiently segment populations into meaningful subgroups and thus could be a useful tool for this task. In this perspective, this study, by using tree-structured models for survival data, aimed to find which factors, and which combinations of factors, could be particularly predictive of death in view to determine specific HIV+ patient sub-groups the most at risk of early death in French Guiana.

Patients and Methods

HIV+ patients followed at the Cayenne, Saint Laurent du Maroni and Kourou General Hospitals between 1 January 1996 and 31 December 2007 were obtained from the French Hospital Database for HIV (FHDH). The FHDH is an ongoing prospective observational nationwide, hospital based cohort to which patients have been continuously recruited in 62 hospitals since 1992. The only FHDH inclusion criteria are HIV type 1 or 2 infection and written informed consent. Data are collected prospectively by trained research assistants using standardized forms. Demographic data are recorded at inclusion. A follow-up form is completed at least every 6 months or at each visit or hospital admission during which a new illness is diagnosed, a new treatment is prescribed, or a noteworthy change in biological markers is noted. Patient identity is encrypted before the data are sent to the Ministry of Health and the Institute National de la Recherche Médicale, which centralizes data from COREVIHs (Regional Coordination of the fight against HIV) throughout France. This data collection is approved by the Commission Nationale Informatique et Libertés.

The outcome of interest was time elapsed between the first consultation and death. The same explanatory variables as previous study were used. These were age at enrolment, gender, nationality (French citizens or non-French citizens), CD4 count at enrolment, presence or absence of HAART at enrolment, a declared addiction and mode of acquisition of the virus. The studied failure event was death. Right censoring occurred at the last visit.

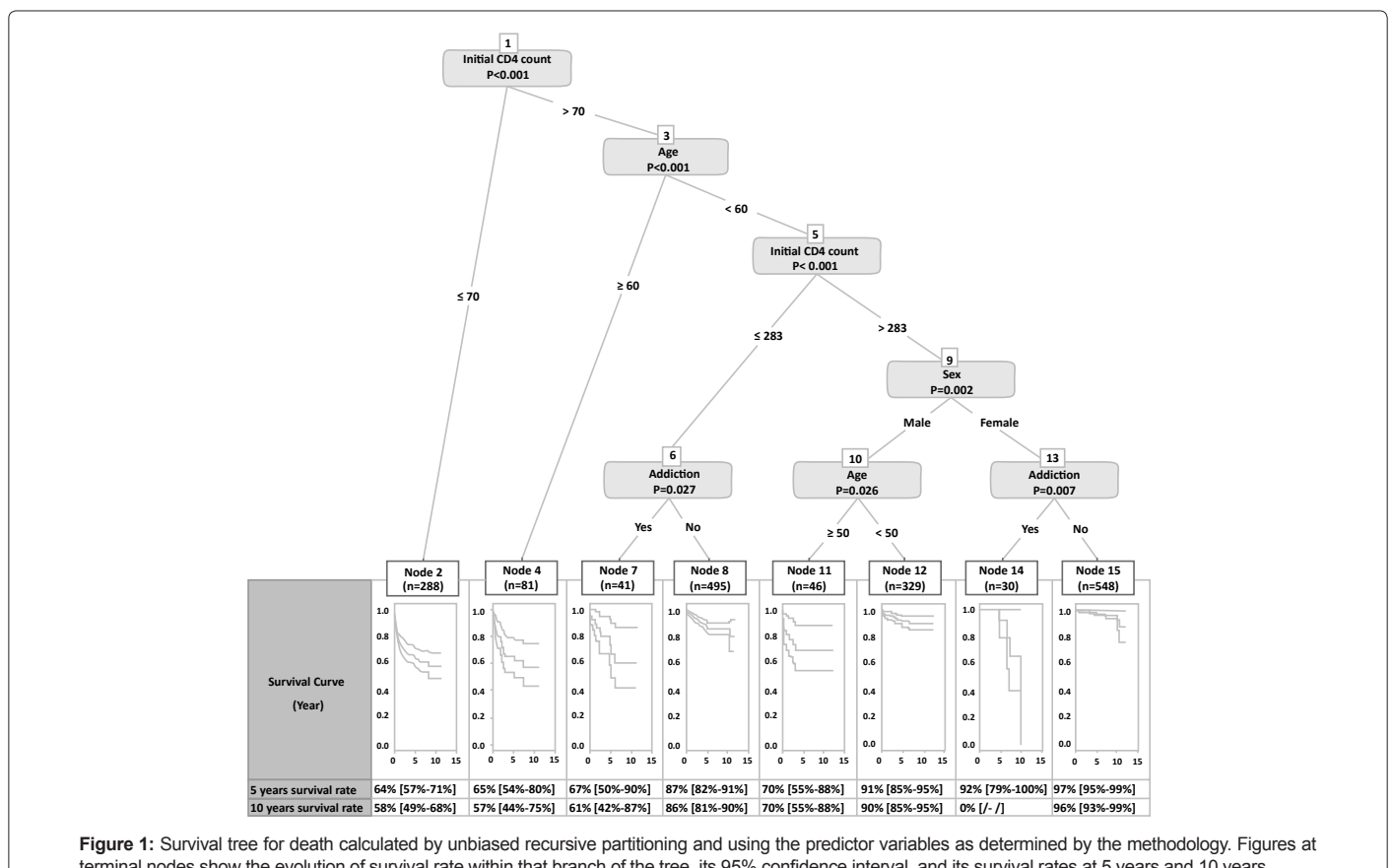| Variable	N	%
Gender		
Female	967	52
Male	891	48
Mode of acquisition of the virus		
Heterosexual relation	1557	84
Homosexual/bisexual relation	47	3
Others/unknown	254	14
Nationality		
French citizens	313	17
Non-French citizens	1110	60
Unknown	435	23
having a declared addiction		
No	1723	93
Yes	135	7
With at least alcohol	75	56
With at least marijuana	17	13
With at least crack cocaine	67	50
Having a HAART at enrolment		
No	1538	83
Yes	320	17
Death recorded in the database		
No	1662	89
Yes	196	11
Variables	**Mean (min - max)**	**Standard dev.**
Age at enrolment	42 (0 - 88)	12,5
CD4 count at enrolment	343 (1 - 1655)	271

Table 1: Main characteristics of the study sample.

To examine the nature of the relationships between time elapsed between the first consultation and death and its predictor variables, a survival tree analysis (STA) called unbiased recursive partitioning was used [3]. STA are ideally suited for the analysis of epidemiological data with hierarchical and complex relationships among the predictor variables [3]. It requires a statistically significant difference ($p < 0.05$), adjusted with Bonferroni correction, and a node size superior to 200 in order to partition the data, which minimizes bias and prevents over-fitting and the need for pruning. The party package within the R statistical language was used to implement STA [4]. A survival tree was plotted and the survival rates at 5 and 10 years for each terminal node and their 95% confidence interval were also calculated.

Results

A total of 1858 subjects were included in the analysis of whom 196 had a death date recorded in the database. The mean age of patients was 42 years (S.D=12.5 years). Forty eight percents were male. A high proportion had contracted HIV through a heterosexual relation (84%) and was non-French citizens (60%). Seven percents of patients have a declared addiction (of whom 50% with at least crack cocaine and 55% with at least alcohol) and 17 % had an HAART at enrolment. The mean CD4 count at enrolment was 343 (S.D=271) (Table 1).

After STA calculation, the regression tree in figure 1 was obtained. A combination of 4 predictors over the 7 initial variables was used by the final tree produced by the STA: initial CD4 count, patient age, sex, and declared addictions. While overall HIV+ survival rate was 85% [CI: 83% - 87%] at 5 years and 81% [CI: 78% - 85%] at 10 years, this rate in

Figure 1: Survival tree for death calculated by unbiased recursive partitioning and using the predictor variables as determined by the methodology. Figures at terminal nodes show the evolution of survival rate within that branch of the tree, its 95% confidence interval, and its survival rates at 5 years and 10 years.

HIV+ patients was divided into 8 groups according to the STA, varying from 64% to 97% at 5 years and from 0% to 96% at 10 years.

Five groups particularly at risk were identified: HIV+ patients with initial CD4 count less than 70 cells/μL (5 years survival rate: 64%, 10 years survival rate: 58%), patient ≥ 60 years with initial CD4 count ≥ 70 (5 years survival rate: 65%, 10 years survival rate: 57%), patients < 60 years with initial CD4 count ≥ 70 and <263 with a declared addiction (5 years survival rate: 67%, 10 years survival rate: 61%), male patients aged between 50 and 60 years with an initial CD4 count ≥ 263 (5 years survival rate: 70%, 10 years survival rate: 70%), female patients aged <60 years with an initial CD4 count ≥ 263 and a declared addiction (5 years survival rate: 92%, 10 years survival rate: 0%).

Discussion

In survival analysis, risk stratification schemes for mortality of HIV positive patients are typically based on multivariate single failure Cox proportional hazards analysis. STA has the advantage to consider predictors in combination rather than in isolation. In this study, the clinical decision tree produced by the STA provides a simple and reliable model of the risk stratification for mortality of HIV+ patients and permits to reemphasize and identify subgroups of patients particularly at risk of an early death in French Guiana.

It is now well established that an early diagnosis of HIV infection is important to reduce the risk of HIV transmission to other partners and to reduce morbidity and mortality rates [5]. In French Guiana, it was estimated that around 40% of patients diagnosed with AIDS ignored their HIV status at the time of diagnosis [1]. Not surprisingly, a preponderant role of CD4 count at enrolment in the tree construction was retrieved and confirms that getting persons to do the HIV test and avoid late diagnosis still remains a challenge in French Guiana [1]. Further studies have thus to be conducted to better identify barriers to testing and collect evidence to improve testing in French Guiana [6].

A second important point reemphasised in this analysis is that additional efforts to reduce the high mortality of addicted patients are required in French Guiana. A large part of addictive HIV+ patients were alcohol dependent (55%) or crack users (50%). In French Guiana, crack cocaine and alcohol consumption are both increasing problems with serious social and health consequences [7]. Recent studies have strengthened the argument for an association between cocaine and alcohol use and acceleration of HIV disease [7-9]. The present study clearly shows the magnitude of the consequences of crack cocaine and alcohol on death of HIV+ patients in French Guiana.

In addition, the use of STA analysis revealed a new specific subgroup particularly at risk of death in French Guiana never mentioned in the literature: HIV+ female patients with a declared addiction. They represented the subgroup with the most compromised survival at 10 years (0%). Some potential processes that could account for this gender specificity could be greater sexual risk taking and insecurity, poorer diet and nutrition, substandard living conditions, a lower use of the medical care system, and other social mechanisms [8]. Furthermore, due to the fact that most female addictions described in French Guiana concerned crack or alcohol consumption, another alternative hypothesis could be that the adverse effects of cocaine or alcohol on the immune system may vary by gender [10]. Further studies should elucidate the potential pathways of this gender specificity in French Guiana.

Our results have several limitations. First, a bias consecutive to a possible under reporting of HIV-related deaths occurring outside of hospital could not be excluded in this analysis. Furthermore, this analysis cannot control for the multiple potential confounders related to predictors (especially for addiction). Self reporting of addictions also underestimates the true prevalence of addictions. However, the present study, by using an alternative statistical method to analyze survival data, has the merit to reemphasize the magnitude of the consequences of addiction on survival of HIV+ patient, a public health problem which is at present met with scarce resources in French Guiana (few existing resources mostly located in cities, no real political involvement,...). It points that HIV+ females with a declared addiction are particularly at risk of death in French Guiana. This knowledge should lead to strengthening prevention and care in this particularly vulnerable segment of the HIV positive population.

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