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Spatial risk of death in patients with AIDS in Campinas, São Paulo, Brazil

Risco espacial de óbito de pacientes com aids em Campinas, São Paulo, Brasil

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ABSTRACT: *Objective:* To analyze the spatial risk of AIDS mortality in census tracts in a large Brazilian city. *Method:* We studied three retrospective cohorts of individuals with AIDS, who were residents in the city of Campinas, in the State of São Paulo, Brazil. The occurrence of death was analyzed from 1980 to 1990 (cohort 1), 1996 to 2000 (cohort 2), and from 2001 to 2005 (cohort 3). We adjusted a Bayesian semi-parametric model, using the Integrated Nested Laplace Approximation (INLA) method, which allowed for the mapping of mortality risk for the three cohorts. *Results:* The incidence of death in cohorts 1, 2 and 3 were, respectively, 72.73, 32.21 and 13.11%. The death risk maps showed a tendency of mortality decrease, and presented the sectors with the highest and lowest risk for each period. The model showed that, in the three cohorts, factors associated with the highest risk of death were: being male, and having an age at diagnosis greater than 49 years old. The homosexual/bisexual orientation was associated with lower risk of dying. *Conclusions:* Even considering the reduction in the risk of death from AIDS in recent years, after access to highly active antiretroviral therapy, the highest incidence was found among the poorest individuals in the three studied cohorts. The maps and risk factors obtained suggest possible actions for monitoring the disease in the city.

Keywords: AIDS. Mortality. Antiretroviral therapy, highly active. Survival analysis.

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RESUMO: *Objetivo:* O estudo teve como objetivo analisar o risco espacial de mortalidade por aids em setores censitários de município brasileiro de grande porte. *Método:* Foram estudadas três coortes retrospectivas de indivíduos notificados por aids e residentes no município de Campinas, São Paulo, nos períodos de 1980 a 1990 (coorte 1), 1996 a 2000 (coorte 2) e 2001 a 2005 (coorte 3), a fim de identificar a ocorrência do óbito. Foi ajustado um modelo semiparamétrico Bayesiano, empregando o método de Aproximação de Laplace Aninhada e Integrada (INLA), que permitiu obter mapas de risco de óbito nas três coortes estudadas. *Resultados:* A incidência de óbito nas coortes 1, 2 e 3 foram, respectivamente, 72,73; 32,21 e 13,11%. Os mapas de risco de óbito apontaram tendência de queda da mortalidade e evidenciaram os setores que apresentaram maior e menor risco em cada período. O modelo mostrou que, nas três coortes, os fatores associados ao maior risco de óbito foram: ser do sexo masculino e possuir idade de diagnóstico superior a 49 anos. A orientação homossexual/bissexual foi associada ao menor risco de morrer. *Conclusões:* Mesmo diante da diminuição do risco de morte por aids nos últimos anos, após o acesso à terapia antirretroviral altamente ativa, a maior incidência se concentra entre os mais pobres nas três coortes estudadas. Os mapas e o fatores de risco obtidos orientam possíveis ações e monitoramento da doença no município.

Palavras-chave: Aids. Mortalidade. Terapia antirretroviral. Análise de sobrevida.

INTRODUCTION

Over the past three decades, the AIDS epidemic has been affecting several segments of the population, particularly young adults. The epidemic has a major impact on the finances and the quality of life of individuals[1].

Several studies point to a drastic reduction in AIDS mortality in several parts of the world due to the use of antiretroviral therapy (TARV)[1-4]. In Brazil, the Ministry of Health has guaranteed access to combined antiretroviral medication since 1996. Its impact on increasing patient survival, reducing hospitalizations and opportunistic infections, and on the increase of chronic diseases has been recorded in several studies in the country[3,5-7].

Geospatial approaches have been used to study AIDS epidemic trends in Brazil, and they point to regional disparities with regard to the risks of becoming ill and dying[8,9].

In the State of São Paulo, in the 1980s, the disease affected mainly homosexual people, individuals using injectable drugs, and patients undergoing transfusions. In the following decades the epidemic reach several other groups in society, and underwent a process where heterosexual people, women, and impoverished people also became affected. Currently, the disease has expanded in young adults with a low socioeconomic status[10,11].

Considering this perspective, and in order to understand the dynamics of the AIDS epidemic in the city of Campinas, São Paulo, Brazil, the cases reported by the Information System for Notifiable Diseases (*Sistema de Informação de Agravos de Notificação* – SINAN) and the death of city dwellers reported in the Mortality Information System (*Sistema de Informação sobre Mortalidade* - SIM) database. The objective was to analyze the spatial risk of death among patients reported to have AIDS in the census tracts of this city, over time.

METHODS

The study involved three retrospective cohorts of patients who were over 13 years of age, reported to have AIDS according to SINAN, and who were residents of the city of Campinas, located in the northeast region of the State of São Paulo (approximately 1 million inhabitants). We excluded 1,091 (26.13%) patients whose report coincided with the date of death, in order to reduce the impact of the survival time of these patients, focusing instead on the results of the survival time of patients with access to follow-up and treatment.[6] One cohort was composed of individuals who reported having AIDS in the early years of the epidemic. This was done in order to identify occurrence of death from 1980 to 1990 (cohort 1 – follow-up of 10 years, with an average survival time of 5.7 years, and with a standard deviation of 6.5 years). Another cohort reported from 1996 to 2000 (cohort 2 – follow-up of 10 years, with an average survival time of 9.2 years, and with a standard deviation of 5.6 years). And a third was from 2001 to 2005 (cohort 3 – follow-up of 7 to 9 years, with an average survival time of 8.9 years, and with a standard deviation of 3 years). In addition to SINAN, information was obtained in the SIM regarding the deaths of the reported patients. Patients who were not on the SINAN notification list were not included. After checking for duplication and inconsistency in the database, the final variables used in the study were: gender, age at diagnosis, schooling, transmission category (sexual: homosexual / bisexual or heterosexual, use of injectable drugs), and CD4 T lymphocyte cell count categorized into counts less than or equal to 350 cells per mm^3 of blood as a criterion for AIDS. They were all analyzed in the model as a continuous variable. In addition, the location of the geo-referenced residences in the census tracts was also obtained. In cohort 1, there were a total of 286 individuals, 245 (85.66%) men and 41 (14.34%) women. In cohort 2, the data showed 1,456 individuals, consisting of 1,006 (69.09%) men and 450 (30.91%) women. In cohort 3, there were 1,342 individuals, 831 (61.92%) men and 511 (38.08%) women.

To model the death risk, an approach was necessary that would take into account the variables of interest and the spatial information of the cases. We used a semi-parametric regression model in a Bayesian scenario, which allowed us to model the risk of death in relation to the census tracts.

The semi-parametric Bayesian model used was implemented in program R, of the INLA package[12,13].

The assumption was that the times until death are partitioned into a finite interval, $0 = S_0 < S_1 < \cdots < S_X$, $t_i < S_Z$, for $\forall t_i$ with i = 1 $\cdots$, n, and that baseline risk is constant over time $]S_{k-1}$, $S_k]$, with $k = 1 \cdots$, K, so, $h_0(t) = h_k$, for each $t \in]S_{k-1}, S_k]$. The model for the i-th individual in the k-th time interval belonging to the j-th census sector is given by (Equation 1):

$$h_{ikj}(t) = h_0(t) \exp\{X'_i\,\beta + f(z_j)\} = \exp\{X'_i\,\beta + f(z_j) + b_k\} = \exp\{\eta_{ikj}\}, \tag{1}$$

So that:
h_{ikj}: risk rate function;
$b_k = log[h_0(t)]$;
$\beta = (\beta_1, \ldots, \beta_p)'$: dimension vector 1×p of parameters associated to covariates;

x_i: dimension vector $p{\times}1$ of covariates observed for the i-th individual; and
$f(z_j)$: spatial effect in the j-th census sector of the city of Campinas, São Paulo.

For the $f(z_j)$, component, the ICAR model was adopted[14], which can be expressed by (Equation 1):

$$f(z_j)\,|\,f(z_w) \sim N\left(\frac{1}{l_j}\sum_{j\sim w}f(Z_w),\frac{1}{l_j\tau_z}\right)$$

(2)

So that:
l_j: the number of sectors that share the same border with the j; and
$j\sim w$: two census tracts j e w are neighbors;

For the parameter vector, Gaussian prioris are,$\beta\sim N(0\;;10^4I)$ for the vector $b=(b_1,\cdots,b_k)$, Gaussian prioris, $b_{k+1}\text{-}b_k\sim N(0,\tau_b^{-1})$, of a first order random walk (RW1) and for the hyperparameters, τ_b e τ_z, independent prioris with gamma distribution, $\Gamma(1;0,0001)$.

Considering the Bayesian scenario, in order to make inferences from this model, the Bayesian Integrated Nested Laplace Approximation (INLA) approach is an alternative to the Markov Chain Monte Carlo (MCMC)[15].

Basically, the INLA methodology was created for a class of structured additive regression models.

The central idea of the INLA methodology is to make numerical integrations in a Bayesian context, in which only deterministic approximations are used to obtain the posterior distributions, thus obtaining an expressive computational gain[15].

In order to aggregate the residential locations of the individuals belonging to the same census sector, we used the QGIS 2.8.2 software and a map of the city of Campinas, São Paulo, which was obtained from the website of the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE) of the Urban Census Bureau from the year 2000. All of the statistical analyzes were carried out using the R program[13].

In order to identify the regions of the city with the greatest social and environmental disadvantages, a spatial distribution map from the Socio-environmental Disadvantage Index (*Índice de Carência Socioambiental* – ICSA) was used, according to socioeconomic and environmental classes according to coverage area of the Health Centers in Campinas, which was developed by Costa et al.[16]. This map makes it possible to extract three low, moderate and high socioenvironmental disadvantages from a statistical analysis of the main components of demographic and socioenvironmental variables, based on the Foundation of the Brazilian Institute of Geography and Statistics (*Fundação Instituto Brasileiro de Geografia e Estatística* – FIBGE) Census in 2000.

RESULTS

Initially, a description of the variables in the three cohorts studied was presented in Table 1. Comparing cohort 1 with cohorts 2 and 3, there was an increase in the percentages of AIDS

diagnoses: in women, heterosexual individuals, and in the age groups older than 30 years old. In relation to schooling, the majority of the diagnoses occurred in individuals with less than 8 years of schooling. There was a reduction in the category of transmission for use of injectable drugs among the reported patients, which can be seen in cohorts 2 and 3. When the

Table 1. Number and proportions of individuals diagnosed with AIDS according to the variables in the three cohorts studied, Campinas, São Paulo.

Variable	Cohort 1		Cohort 2		Cohort 3	
	n (%)	P-value	n (%)	P-value	n (%)	P-value
Sex						
Male	245 (85.7)	< 0.01*	1006 (69.1)	< 0.01*	831 (61.9)	< 0.01*
Female	41 (14.3)		450 (30.9)		511 (38.1)	
Schooling (years)						
< 8	81 (50.6)	0.87	564 (66.2)	< 0.01*	484 (54.3)	0.01*
≥ 8	79 (49.4)		288 (33.8)		407 (45.7)	
Age (years old)						
< 30	142 (49.6)	< 0.01*	466 (32.0)	< 0.01*	363 (27.0)	< 0.01*
30 to 49	133 (46.5)		897 (61.6)		850 (63.3)	
≥ 50	11 (3.8)		93 (6.4)		129 (9.6)	
Injectable drugs						
Yes	100 (45.7)	0.20	391 (32.7)	< 0.01*	242 (20.5)	< 0.01*
No	119 (54.3)		806 (67.3)		940 (79.5)	
Homosexual/bisexual						
Yes	128 (55.9)	0.07	279 (23.1)	< 0.01*	317 (25.5)	< 0.01*
No	101 (44.1)		930 (76.9)		924 (74.5)	
Death						
Yes	208 (72.7)	< 0.01*	469 (32.2)	< 0.01*	176 (13.1)	< 0.01*
No	78 (27.3)		987 (67.8)		1116 (86.9)	
CD4 (cells/mm^3)						
≤ 350	8 (72.7)	0.13	720 (93.6)	< 0.01*	898 (82.4)	< 0.01*
> 350	3 (27.3)		49 (6.4)		192 (17.6)	

*Statistically significant for p < 0.05; **the schooling, injectable drug, homosexual/bisexual and CD4 variables presented, respectively, the following numbers and percentages of lack of information: cohort 1: 126 (44%), 67 (23%), 57 (20%) and 275 (96%); cohort 2: 604 (41%), 259 (18%), 247 (17%) and 687 (47%); cohort 3: 451 (34%), 160 (12%), 101 (7%) and 252 (19%).

death variable is evaluated, a drastic drop in the number of deaths in cohort 3 was observed, when compared to the other two cohorts. In all three cohorts, most of the reported individuals had a CD4 cell count lower than 350 cells per mm³ at the time of diagnosis.

A large percentage of information loss was observed in the three study periods, as shown in Table 1. Because cohort 1 presented 96% lack of information on the CD4 variable, which is understandable considering the reality of services available in the first decade of the epidemic, it was not included in the model fit of cohort 1. Also, it was considered a continuous variable in the model adjustments in order to maximize the information.

Table 2 presents the results of the adjustment of the semi-parametric model (Equations 1 e 2) with the subsequent estimates (mean and standard deviation). Table 3 shows the risk

Table 2. Subsequent estimates (mean, standard deviation and 95% credible interval) of the parameters of the semi-parametric model for the variables in cohorts 1, 2 and 3.

Variable Category	Cohort 1		Cohort 2		Cohort 3	
	Mean (SD)	95%CI	Mean (SD)	95%CI	Mean (SD)	95%CI
Intercept						
-	-8.78 (0.44)	- 9.71 – -7.99	-10.90 (0.26)	-11.46 – -10.43	-12.01 (0.32)	-12.68 – -11.99
Sex						
Male	0.23 (0.21)	-0.18 – 0.66	0.444 (0.12)	0.22 – 0.67	0.65 (0.18)	0.30 – 1.02
Female	–	–	–	–	–	–
Schooling (years)						
< 8	0.01 (0.16)	-0.31 – 0.32	-0.34 (0.10)	-0.53 – -0.14	0.18 (0.15)	-0.12 – 0.49
≥ 8	–	–	–	–	–	–
Age (years old)						
≤ 30	–	–	–	–	–	–
30 – 49	0.78 (0.15)	0.49 – 1.08	0.25 (0.11)	0.04 – 0.46	0.34 (0.20)	-0.04 – 0.74
≥ 50	0.84 (0.35)	0.12 – 1.48	0.92 (0.18)	0.56 – 1.25	0.95 (0.25)	0.46 – 1.44
Injectable drugs						
Yes	-0.31 (0.16)	-0.63 – 0.00	0.09 (0.11)	-0.11 – 0.30	0.01 (0.19)	-0.38 – 0.38
No	–	–	–	–	–	–
Homosexual/ bisexual						
Yes	-0.72 (0.17)	-1.05 – -0.38	-0.57 (0.13)	-0.84 – -0.32	-0.72 (0.22)	-1.16 – -0.30
No	–	–	–	–	–	–
CD4*	–	–	-0.006 (0.001)	-0.007 – -0.005	-0.001 (0.003)	-0.004 – 0.004

*CD4 cell count in cells by mm³, continuous variable; 95%CI: credible interval of 95%.

ratios associated with the study variables and their respective 95% credible intervals (95%CI). In cohort 1, the effects of gender, schooling and category of transmission due to use of injectable drugs were not significant, since the posteriori average equal to zero was found in the 95%CI. In cohorts 2 and 3, the category of transmission due to use of injectable drugs was not significantly associated with the risk of dying. In cohort 3, it was also observed that the effects of the variables of age, in the range of 30 to 49 years old, schooling and CD4 count were not significant.

The risk of death in cohort 3 for men was 1.91 times higher (95%CI 1.36 – 2.73) than for women. For those older than 49 years old, the risk of death was 2.59 (95%CI 1.58 – 4.24) times the risk in children under 30 years old. It was observed that in all cohorts, being older than 49 years old was a risk factor for death. For those with a homosexual / bisexual sexual orientation, the risk of death was 0.48 (95%CI 0.31 – 0.72) times (or 52% lower) than the risk among those in the heterosexual transmission category.

Table 3. Ratio of death risk and their respective 95% credible intervals obtained from the adjustment of the semi-parametric model, for individuals diagnosed with AIDS, in cohorts 1, 2 and 3, Campinas, SP.

Variable Category	Cohort 1		Cohort 2		Cohort 3	
	RR	95%CI	RR	95%CI	RR	95%CI
Sex						
Male	1.26	0.84 – 1.94	1.55	1.24 – 1.95	1.91	1.36 – 2.73
Female	–	–	–	–	–	–
Schooling (years)						
< 8	1.01	0.74 – 1.37	0.71	0.59 – 0.87	1.20	0.88 – 1.63
≥ 8	–	–	–	–	–	–
Age (years old)						
≤ 30	–	–	–	–	–	–
30 – 49	2.19	1.62 – 2.95	1.28	1.04 – 1.58	1.41	0.96 – 2.10
≥ 50	2.32	1.13 – 4.39	2.50	1.76 – 3.50	2.59	1.58 – 4.24
Injectable drugs						
Yes	0.73	0.53 – 1.00	1.10	0.89 – 1.35	1.01	0.68 – 1.46
No	–	–	–	–	–	–
Homosexual/Bisexual						
Yes	0.49	0.35 – 0.68	0.56	0.43 – 0.73	0.49	0.31 – 0.74
No	–	–	–	–	–	–
CD4 (cells/mm³)	–	–	0.994	0.992 – 0.995	1.00	0.99 – 1.01

RR: death risk ratio; 95%CI: credible interval of 95%.

The maps presented in Figure 1 (A, B and C) show the risk of death by census tract in the city of Campinas, indicating that the higher the value on the scale, the higher the risk of death of the individuals reported to have AIDS during the study period.

It can be observed in cohort 1 that the southwest, south and central regions of the city presented greater risks (Figure 1A). In cohort 2 (Figure 1B), the southwest, northwest, south, and central regions showed a greater risk of death. In cohort 3 (Figure 1C), the risk of death

A

Cohort 1: 1980–1990

Spatial risk of the area
(0.000126, 0.000263]
(−1,31e−05, 0.000126]
(−0.000111, −1.31e−05]
[−0.00036, −0.000111]

B

Cohort 2: 1996–2000

Spatial risk of the area
(0.000172, 0.000849]
(−4.13e−05, 0.000172]
(−0.000173, −4.13e−05]
[−0.000489, −0.000173]

C

Cohort 3: 2001–2005

Spatial risk of the area
(8.68e−05, 0.000577]
(1.27e−06, 8.68e−05]
(−0,000101, 1.27e−06]
[−0.00025, −0.000101]

D

ICSA
Classes of social-environmental disadvantages
small disadvantage
moderate
major disadvantage
0   10
km

N

BraZil
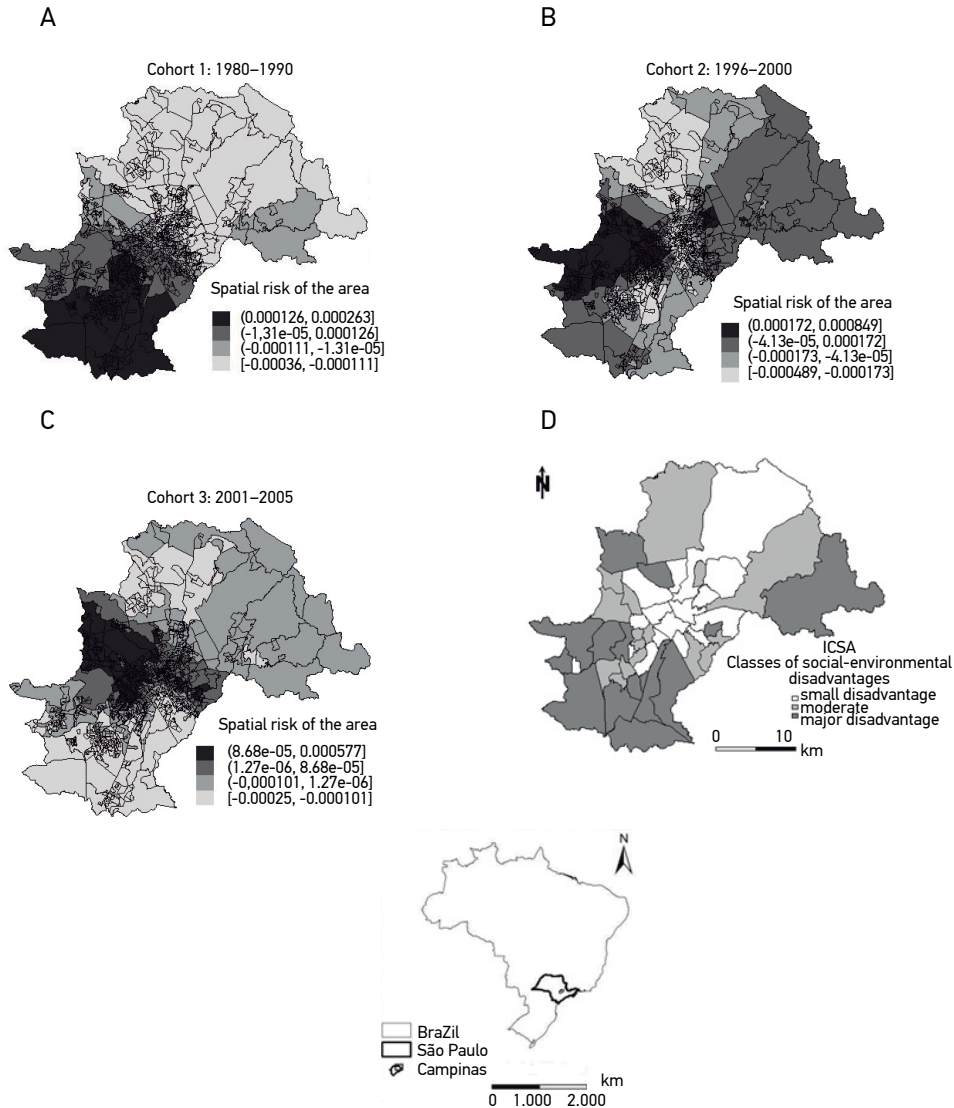São Paulo
Campinas
km
0 1.000 2.000

Figure 1. Maps of the spatial effects for the census tracts (posteriori means) for AIDS mortality in the cohorts studied (A, B, C) and a map of socio-environmental disadvantage classes (D, obtained from article Costa et al.[16]) of the city of Campinas, São Paulo.

was higher among the north, northwest, southwestern and central regions. The maps show differences in the spatial distribution with regard to the risk of dying, but the highest risk predominates in areas with precarious socio-environmental indicators, as shown in Figure 1D. Figure 2 shows the baseline risk graphs of the adjusted model in each of the cohorts. We emphasize that the risk of death decreases over time in cohorts 2 and 3, and becomes close to 0 after around 2,000 days of follow-up.

DISCUSSION

This study demonstrates the increasing decline in the risk of dying among residents reported to have AIDS in the city of Campinas in three periods. Mortality among patients has decreased over time, as has been pointed out in other studies in Brazil and in other parts of the world[3,4,6,17]. With access to highly active antiretroviral therapy (HAART) from 1996, (due to its availability from the Ministry of Health), patients obtained more effective control of viral proliferation, and immune system recovery.
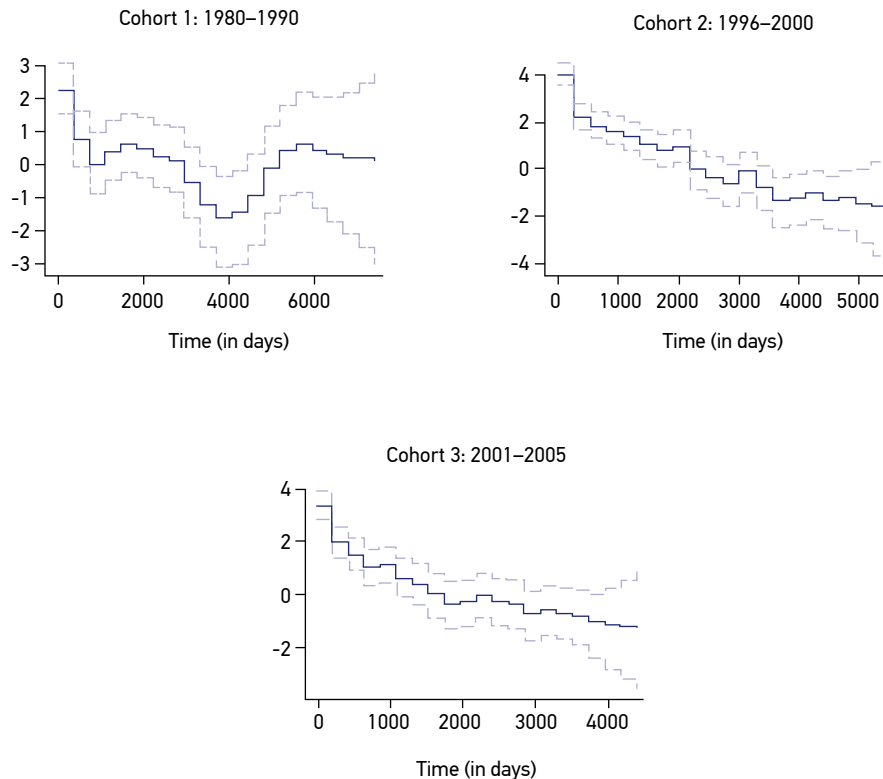

Figure 2. Posteriori mean (solid line) and credible interval of 95% (dashed line) to log the baseline risk of the adjusted model for mortality.

In addition to the impact on mortality, the morbidity of patients with an HIV infection has progressively decreased, increasing the survival and quality of life of infected patients. However, AIDS continues to be a disease that has a major impact on morbidity and mortality, and requires ongoing prevention and care.

Estimates of the analyzes in the cohorts studied identify men — older than 50 years old and in the sexual orientation heterosexual — as the ones with the highest risk of dying, according to the periods studied in Campinas.

Several authors have associated greater survival of patients with AIDS with the variables of age at diagnosis, sex, socioeconomic status and category of exposure, as observed in this study in Campinas[8,17-19]. The socioeconomic conditions of patients can influence the risk of dying due to differences in access to clinical follow-up, complication prevention, and adherence to antiretroviral, which are lower among poorer populations[4,11,17,18]. The maps presented show worse survival estimators in the south and southwestern regions of the city, especially in the first cohorts. The southwestern region is the most at risk in the 2001-2005 cohort in all of the maps. These regions coincide with areas of high socio-environmental disadvantages[16].

The spatial distribution of risk among the census tracts in Campinas shows differences among the cohorts. Although the risk scales are declining, the maps indicate that the poorest regions of the city (northwest, southwest) have always been those with the highest AIDS-related mortality. Possible explanations include precarious living conditions, lack of access to services, or the high percentage of drug use in the first decades of the epidemic.

The "aging" of the epidemic and a worse prognosis for patients over 50 years old have also been identified by other authors[20]. It is necessary to recognize this age group's vulnerability to infection, considering the lower perception of risk, less knowledge reduced access to prevention methods, in addition to late diagnosis in this age group[19].

Some clinical variables not addressed in this study have also been identified as survival predictors of patients with AIDS, such as opportunistic diseases, comorbidities, access to and adherence to therapeutic regimens, and specialized services[3,4,6,17]. Most individuals with a CD4 count ≤ 350 cells per mm^3 at the time of diagnosis suggest a late diagnosis of the disease. The negative association of a CD4 count at the first visit (continuous variable) with mortality in cohort 2 reinforces this laboratory parameter as a way to predict the worst clinical evolution. However, in cohort 3, other variables displaced CD4, including age and sex, which explained the death risk. Access to antiretroviral medication given at referral services in the city possibly decreased the influence of this laboratory indicator as a predictor of death. Campinas has two municipal reference centers for STIs / AIDS, a guidance center and a serological support center, as well as reference outpatient clinics at Hospital das Clínicas at the Universidade Estadual de Campinas (Unicamp) and at the Celso Pierro Hospital of the Pontifícia Universidade Católica (PUC) of Campinas, with a wide range of coverage of individuals with HIV / AIDS in the municipality and in the metropolitan region.

There are some limitations to this study, such as the use of secondary data for analysis. Case reporting does not always occur at the time of AIDS diagnosis. Many cases are detected

late, others are detected at the time of clinical intercurrence, or death. Excluding patients reported with AIDS at the time of death sought to reduce such distortions. The underreporting of AIDS cases and deaths may occur due to a lack of diagnosis or incomplete death certificates. In addition, the notification sheets are not always well filled out, thus providing inaccurate information. However, this study deals with a database that has valuable information on disease trends in Brazil and over time. On the other hand, the long follow-up period of the three cohorts implies that there will be a comparison between the cohorts in different risk contexts, with regard to therapeutic options and prevention, and in relation to impact on the prognosis of the patients. The study periods are certainly heterogeneous, as they result from different epidemiological conjunctures.

CONCLUSIONS

The study contributes to possible actions that monitor health services in the city of Campinas with regard to the groups and the regions of the city that are most at risk of dying, including the most disadvantaged areas, and the areas with the worst social and environmental conditions. Disease prevention and control measures, and particularly measures to increase patients' adherence to clinical follow-up and the correct use of available medication, can be better targeted. Even given the reduction in the risk of dying from AIDS in recent years, after access to antiretroviral therapy, the highest incidence of mortality from AIDS is concentrated among men, older people, heterosexual individuals, and among the poorest in the three cohorts studied. Both the maps and the risk factors found may guide possible actions to monitor the disease in the municipality.

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