Prevalence of clinical complications high risk associated with AIDS death

Prevalência do alto risco de complicações clínicas associadas ao óbito por Aids

Prevalencia del alto riesgo de complicaciones clínicas asociadas al óbito por SIDA

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Descritores
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Abstract
Objective: To investigate the high risk prevalence among deaths from the risk classification of clinical complications associated with AIDS and its relation with sociodemographic and therapeutic variables.
Methods: A retrospective epidemiological study involving 80 cases of death from AIDS between 2007 and 2015 in a Northeastern Brazilian state. Risk stratification considered follow-up indicators obtained in the infection diagnosis, assigning values of 1, 2 for viral load, and 1, 2 and 3 for CD4 + T lymphocytes indicators, number of opportunistic diseases, clinical manifestations and chronic diseases. ranging from 5 to 14. The higher this score, the greater the risk for clinical complications. Data were analyzed by estimating prevalence and prevalence ratio for high risk, followed by Weight of Evidence method and Somers' D statistic.
Results: Of the 80 cases studied, 51.2% were allocated to the high-risk stratum. The record of psychiatric history increased by 2 times the prevalence for high risk and age group was strongly related to this stratum. T-CD4 + lymphocyte count, opportunistic diseases and clinical manifestations were the indicators that showed the strongest association strength with risk stratification.
Conclusion: The study showed the prevalence of high risk for the development of clinical complications, greater associative strength in LT-CD4 + indicators, opportunistic diseases and clinical manifestations with proposed risk score. These results suggest the need for special attention from specialized care services to outpatients.

Resumo
Objetivo: Investigar a prevalência do alto risco entre casos de óbitos a partir da classificação de risco de complicações clínicas associadas a aids e sua relação com variáveis sociodemográficas e terapêuticas.
Métodos: Estudo epidemiológico, retrospectivo, envolvendo 80 casos de óbito por aids ocorridos entre 2007 e 2015 em um Estado do Nordeste brasileiro. A estratificação do risco considerou indicadores de acompanhamento obtidos no diagnóstico da infecção, atribuindo-se valores de 1, 2 para carga viral, e 1, 2 e 3 aos indicadores de linfócitos T CD4+, quantidade de doenças oportunistas, manifestações clínicas e doenças crônicas, com escore variando entre 5 e 14. Quanto maior esse escore, maior o risco para complicações clínicas. Os dados foram analisados estimando a prevalência e razão de prevalência para o alto risco, seguido do método de *Weight of Evidence* e estatística D de *Somers*.
Resultados: Dos 80 casos estudados, 51,2% foram alocados no estrato de alto risco. O registro de antecedentes psiquiátricos aumentou em 2 vezes a prevalência para o alto risco e a faixa etária apresentou forte relação com esse estrato. A contagem de linfócitos T-CD4+, doenças oportunistas e manifestações clínicas foram os indicadores que apresentaram maior força de associação com a estratificação de risco.
Conclusão: O estudo mostrou a prevalência do alto risco para o desenvolvimento de complicações clínicas, maior força associativa nos indicadores LT-CD4+, doenças oportunistas e manifestações clínicas com escore de risco proposto. Estes resultados sugerem a necessidade de atenção especial dos serviços de atenção especializada aos indivíduos acompanhados em nível ambulatorial.

Resumen
Objetivo: Investigar la prevalencia del alto riesgo de casos de óbitos a partir de la clasificación de riesgo de complicaciones clínicas asociadas al SIDA y su relación con variables sociodemográficas y terapéuticas.
Métodos: Estudio epidemiológico, retrospectivo, que incluyó 80 casos de óbito por SIDA ocurridos entre 2007 y 2015 en un estado del Nordeste brasileño. La estratificación del riesgo consideró indicadores de seguimiento obtenidos en el diagnóstico de la infección, con valores 1 y 2 para carga viral y 1, 2 y 3 para indicadores de linfocitos T CD4+, cantidad de enfermedades oportunistas, manifestaciones clínicas y enfermedades crónicas, con puntuación que varía de 5 a 14. Cuanto más alta la puntuación, mayor riesgo de complicaciones clínicas. Los datos fueron analizados estimando la prevalencia y razón de prevalencia del alto riesgo, seguido del método de *Weight of Evidence* y estadística D de *Somers*.
Resultados: De los 80 casos estudiados, el 51,2% fue ubicado en el estrato de alto riesgo. El registro de antecedentes psiquiátricos aumentó dos veces la prevalencia del alto riesgo y el grupo de edad presentó una fuerte relación con este estrato. El recuento de linfocitos T CD4+, enfermedades oportunistas y manifestaciones clínicas fueron los indicadores que presentaron mayor fuerza de asociación con la estratificación del riesgo.
Conclusión: El estudio demostró la prevalencia del alto riesgo de desarrollo de complicaciones clínicas, mayor fuerza asociativa en los indicadores LT CD4+, enfermedades oportunistas y manifestaciones clínicas con puntuación de riesgo propuesto. Estos resultados sugieren la necesidad de una atención especial a los servicios de atención especializada a los individuos acompañados de forma ambulatoria.

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Introduction

Acquired Immunodeficiency Syndrome (AIDS) has been considered a serious public health problem due to the dynamic epidemiological disease profile and alarming morbidity and mortality rates.[1] Increasing access to actions and services for the prevention, diagnosis and treatment of Human Immunodeficiency Virus (HIV) and AIDS were important coping strategies for the epidemic, whose consequences were the decline in new infections and disease-related morbidity and mortality.[2]

In 2017, about 36.7 million people were living with HIV worldwide, with two million new cases being reported due to the infection and one million deaths with AIDS as the underlying cause.[3] In Brazil, in 2017, 42,420 new cases of HIV and 37,791 cases of AIDS were diagnosed. Over a period of ten years, the rate of AIDS detection in the country fell by 9.4%, however, in the same period the Northeast region grew by 24.1%. In Paraíba State, in 2017 there was reporting of 533 cases and 139 deaths from AIDS as the underlying cause.[4]

With the introduction of antiretroviral therapy and preventive and prophylactic technologies, it is possible to observe a change in the disease course, which previously had a fast lethal outcome, turning into a disease classified as chronic. Life span of people with HIV has increased, equaling the life expectancy of a person without infection. However, this has led to a higher risk of developing comorbidities related to clinical complications and death.[5,6]

While recognizing the effectiveness of current therapeutic regimens in reducing mortality, AIDS has no cure and is recognized as the fifth leading cause of death among adults worldwide.[7]

Deaths are related to several factors, ranging from delayed diagnosis to late initiation of treatment. Also noteworthy is a change in the pattern of mortality, in which AIDS-related events such as opportunistic diseases, which were commonly the leading cause of death, are giving way to conditions considered non-AIDS as causes of death, including diseases. cardiovascular diseases, cancers, kidney disease, liver disease, osteopenia / osteoporosis, and neurocognitive diseases, as well as the side and toxic effects of antiretroviral drugs.[8,9]

This new configuration has been demanding care actions supported by the identification of people prone to negative outcomes. Little used nationally, clinical risk stratification has been constituted as a strategy to classify patients according to the risk of developing clinical complications.[10]

Stratification is a tool capable of identifying people and groups with similar health needs, its logic is based on differentiated management for those with similar risks.[11] Thus, risk-stratified care management provides planning of actions and resources, whether clinical, human or financial, according to the uniqueness of patients in a given region or locality.[6]

Therefore, the guiding questions of this study were: How to stratify clinical risk using indicators for monitoring the management of HIV infection in adults? What is the prevalence of high clinical risk in AIDS deaths? And what are the factors associated with high risk?

Given this context, the present study aimed to investigate the prevalence of high risk among deaths from the risk classification of clinical complications associated with AIDS and its relation with sociodemographic and therapeutic variables.

Methods

A retrospective epidemiological study from a secondary data source (medical records), conducted in two reference services for the treatment of infectious diseases in a Northeastern State of Brazil, which has actions and services to monitor HIV/AIDS infection.

The research sample was obtained from a research database entitled "*Análise de Óbitos de Pessoas com HIV Aids*", conducted from October 2015 to February 2016, for a population of 192 cases of death registered in the state between 2007 and 2015.

Inclusion criteria were cases with complete information on viral load (VL), CD4 + T-cell quantification (LT-CD4 +), clinical manifestations, chron-

ic diseases and opportunistic diseases, resulting in a final sample of 80 cases of deaths. The others were excluded because they did not contain complete information on the five indicators.

From the identification of cases, the following independent variables were added: age (<20 years; 20-39 years; 40 to 59 years; ≥60 years), gender (male; female), sexual orientation (heterosexual, homosexual, bisexual), color/race (brown; white; black/indigenous), marital status (single; married/stable union; separated/widowed), education (no schooling; <8 years of schooling; ≥ 8 years of schooling), alcohol use (yes/no), tobacco use (yes/no) , illegal drug use (yes/no) and psychiatric history (yes/no).

Clinical risk stratification, dependent variable, was constructed considering clinical monitoring indicators for the management of infection in adults obtained at the time of diagnosis, assigning values of 1, 2 for VL (Viral Load), and 1, 2 and 3. LT-CD4 + indicators, number of opportunistic diseases, number of chronic diseases and number of clinical manifestations of each participant.[12]

Indicators favorable to clinical management of infection (undetectable VL, LT-CD4 +> 500 cells/mm^3, no opportunistic disease, no chronic disease, and no signs and symptoms) were scored 1. Intermediate indicators (LT-CD4 + between 200 and 500 cells/mm^3, occurrence of an opportunistic disease, occurrence of a chronic disease and occurrence of a sign and symptom) and detectable VL were assigned score 2 and unfavorable indicators for clinical management of LT-CD4 + <200 cells/mm^3, two or more opportunistic diseases, two or more chronic diseases, and two or more signs and symptoms) score 3.

The sum of these indicators was determined quantitatively, ranging from 5 to 14. The higher this score, the higher the risk for clinical complications. These scores were categorized as follows:

- Low risk (score 5 to 9) = LT-CD4 +> 500 cells/mm^3 (=1) or LT-CD4+between 200 and 500 cells/mm^3 (=2) + undetectable VL (=1) + no opportunistic disease (=1) or occurrence of an opportunistic disease (=2) + no chronic disease (=1) or occurrence of a chronic disease (=2) + no signs and symptoms (=1) or occurrence of a sign and symptom (=2);
- High risk (score 10 to 14) = LT-CD4 + between 200 and 500 cells/mm^3 (=2) or LT-CD4 + <200 cells/mm3 (=3) + detectable VL (=2) + occurrence of opportunistic disease (=2) or two or more opportunistic diseases (=3) + occurrence of one chronic disease (=2) or two or more chronic diseases (=3) + occurrence of one sign and symptom (=2) or two or more signs and symptoms (=3).

Data were analyzed by estimating the prevalence and prevalence ratio for the high risk among the investigated variables considering a 95% confidence interval. Sequentially, the Weight of Evidence (WoE) method was used to verify relation strength among independent variables and the dependent variable (risk stratification), considering that <0.02 the predictor is not useful (very weak), from 0.02 to <0.1 the predictor has a weak relation, from 0.1 to 0.3 the predictor has a medium strength relation and> 0.3 the predictor has a strong relation to Odds Ratio.[13]

For the clinical follow-up indicators that integrated the risk score, the Somers' D statistic was performed to measure the strength and direction of this association on a scale of -1 to 1, considering that the closer to 1 is the stronger the value. association between indicator and risk score.

This study was approved by the Research Ethics Committee of Health Sciences Center of *Universidade Federal da Paraíba*, under Opinion 2,564,425.

Results

Of the total cases investigated (n=80), 41 (51.2%) individuals were included in the high risk category. There was a higher prevalence of high risk in the age group from 40 to 59 years old (63.3%), female (55.6%), bisexual (75.0%), self-declared black/indigenous (62.5%), single (55.8%), with less than 8 years of schooling (53.7%), who used alcohol (58.1%), non-smokers (51.1%), illicit drug users

(53.8%) and with a record of psychiatric history (80.0%) (Table 1).

Table 1. Prevalence and prevalence ratio for high risk of AIDS-related clinical complications from death according to sociodemographic variables

Variables		n(%)	PR (95%CI)
Age group (years)	<20	4(50.0)	1
	20-39	41(46.3)	0.93(033–2.61)
	40-59	30(63.3)	1.27(0.46–3.50)
	≥60	5(20.0)	0.40(0.05–2.98)
Gender	Male	53(49.1)	1
	Female	27(55.6)	1.13(0.73–1.75)
Sexual option*	Heterosexual	53(54.7)	1
	Homosexual	7(28.6)	0.52(0.16–1.73)
	Bisexual	4(75.0)	1.37(0.74–2.54)
Color/Race	Brown	49(46.9)	1
	White	15(53.3)	1.14(0.65–1.99)
	Black/Indigenous	16(62.5)	1.33(0.82–2.16)
Marital Status	Single	43(55.8)	1
	Married/Stable union	20(40.0)	0.72(0.39–1.30)
	Separated/Widow(er)	17(52.9)	0.95(0.56–1.60)
Schooling (study years)*	No schooling	14(50.0)	1
	<8	41(53.7)	1.07(0.59–1.95)
	≥8	15(53.3)	1.07(0.53–2.16)
Alcohol use*	Yes	43(58.1)	1.59(0.93–2.71)
	No	30(36.7)	1
Tobacco use*	Yes	26(46.2)	0.90(0.55–1.49)
	No	47(51.1)	1
Illegal drug use*	Yes	13(53.8)	1.08(0.61–1.89)
	No	60(50.0)	1
Psychiatric history*	Yes	10(80.0)	1.79(1.19–2.69)
	No	67(44.8)	1

P – prevalence; PR - prevalence ratio; 95% CI - 95% confidence interval. * The total number of these variables does not correspond to the 80 cases of deaths investigated, as some information was not available in the medical record.

When analyzing the association between the high risk of AIDS-related clinical complications and the effect of independent variables, it was observed that only cases with a history of psychiatric history were associated with this outcome (CI=1.19–2.69). These cases were approximately twice as prevalent for high risk compared to those without psychiatric history records (PR=1.9).

Considering relation strength among variables and the clinical risk stratification, using the WoE method, only age presented a strong relation (CVI = 0.98) with risk stratification (Figure 1).

Regarding the indicators used to construct the risk score, there was a higher prevalence among

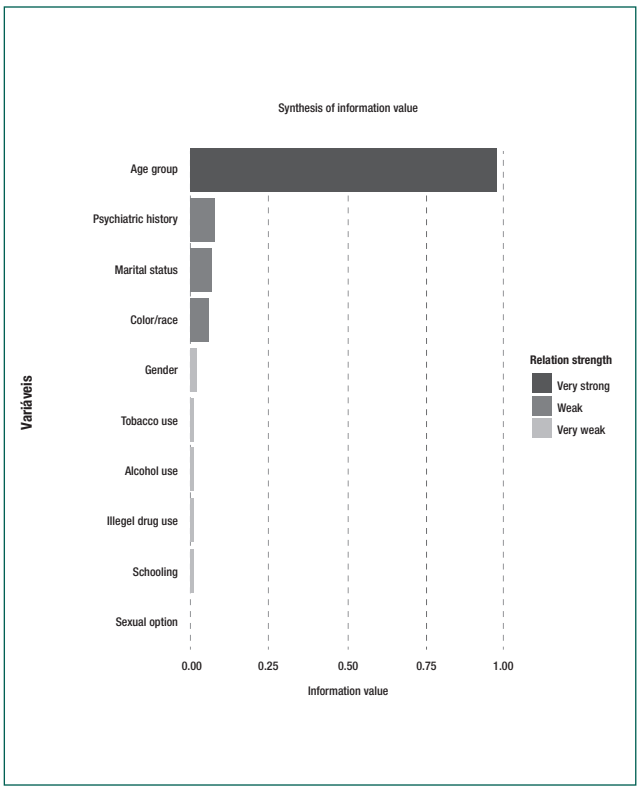

Figure 1. Relation of independent variables with risk stratification from Weight of Evidence (WoE)

cases with detectable VL (55.2%), LT-CD4 + between 200-500 cells/mm^3 (61.9%), two or more opportunistic diseases at diagnosis (91.7%), two or more clinical manifestations (65.0%) and one chronic disease (81.3%). Considering the prevalence ratio as a measure of association, it can be said that the high risk was approximately four and seven times more prevalent among cases that presented opportunistic diseases at the time of diagnosis, when compared to cases without any occurrence. Moreover, the presence of a chronic disease at the time of diagnosis increased the prevalence for high risk twice as compared to cases without any comorbidity (Table 2).

In the association analysis employed by the Somers D-statistic, it was shown that clinical follow-up indicators are good predictors for the risk classification of AIDS-associated clinical complications, with emphasis on opportunistic diseases (0.556), clinical manifestations (0.453). and LT-CD4 + (0.414) which presented higher values (Table 2).

Table 2. Prevalence and prevalence ratio for high risk of AIDS-related clinical complications from death according to clinical follow-up indicators

Variables		n(%)	PR (95%CI)	Somers' D
Viral load	Undetectable	13(30.8)	1	0.248
	Detectable	67(55.2)	1.79(0.77–4.17)	
LT-CD4+ (cells/mm^3)	<200	5(60.0)	1.30(0.60–2.80)	0.414
	200-500	21(61.9)	1.34(0.86–2.08)	
	>500	54(46.3)	1	
Opportunistic diseases	None	22(13.6)	1	0.556
	One	34(47.1)	3.45(1.14–10.48)	
	Two or more	24(91.7)	6.72(2.33–19.37)	
Clinical manifestations	None	7(14.3)	1	0.453
	One	13(7.7)	0.54(0.04–7.36)	
	Two or more	60(65.0)	4.55(0.73–28.2)	
Chronic diseases	None	56(41.1)	1	0.281
	One	16(81.3)	1.98(1.34–2.93)	
	Two or more	8(62.5)	1.52(0.82–2.83)	

P - prevalence; PR - prevalence ratio; 95% CI - 95% confidence interval; LT-CD4 + - CD4 + T lymphocytes

Discussion

Of the cases of deaths studied, more than 50% were allocated to the high-risk stratum, with higher prevalence among individuals with psychiatric history. The age group showed a strong relation with this stratum, and T-CD4 + lymphocyte count, opportunistic diseases and clinical manifestations were the indicators that showed the strongest association strength with risk stratification.

Studies show that HIV infection and psychiatric diagnoses are closely correlated. An estimated 50% of HIV-infected individuals are diagnosed with concomitant mental disorders.[14,15] Depression is the most common psychiatric disorder in this population, known for its association with poor adherence to treatment, negative impact on social relations, and faster progression to AIDS and death.[16,17] Thus, the presence of psychiatric history should be valued both at the time of HIV diagnosis and during clinical follow-up.

From the perspective of WoE, only the variable age group was strongly related to the high risk of clinical complications associated with AIDS. In the epidemiological conception, age is the most important determinant among the attributes related to people. In the study, the prevalence for high risk was higher in the age group 40 to 59 years. In Brazil, in 2017, there was a tendency to increase in AIDS mortality among women aged 15 to 19, men aged 20 to 24, and among individuals aged 60 and over.[4]

A study conducted in the capital of the Republic of Malawi, Africa showed that most adolescents and young women (aged 15-24) perceived little risk of HIV acquisition, even those at higher risk.[18] Low HIV testing, delayed testing, and consequent lack of awareness of positivity linked to low risk perception lead to delayed diagnosis and treatment.

Increased AIDS cases in Brazil among people aged 60 or older may be related to the invisibility of the elderly's sexuality by health professionals who do not assess the vulnerability of this population part to HIV and miss the opportunity to request serology, leading to a diagnosis. at a more advanced stage of the disease, interfering with its prognosis and progression of comorbidities.[19]

The study found a higher prevalence of high clinical risk among cases with detectable viral load, LT-CD4+ between 200-500 cells/mm^3, two or more opportunistic diseases at diagnosis, two or more clinical manifestations or a chronic disease.

Laboratory monitoring of VL values serves to evaluate the efficacy of ART and early detection of viral failure and treatment adherence problems.[20] Although there is no scientific evidence of correlation between VL and mortality, its occurrence is associated with negative prognosis.[6]

LT-CD4+ count is one of the most important biomarkers for assessing immune system impairment and immune response recovery with appropriate treatment.[21]

Opportunistic diseases/infections are considered major complications and leading cause of HIV-related hospitalization.[22] Such diseases have delicate management and high mortality.[23] In a study with patients on antiretroviral agents and one or more opportunistic diseases at the time of diagnosis, the risk of death was 5.33 times higher in individuals with more than one condition.[24] Prophylaxis of opportunistic diseases provides an important reduction in morbidity and mortality in individuals with immune dysfunction secondary to HIV infection, with LT-CD4 + count being the main parameter to guide the introduction and suspension of this prophylaxis.[21]

Result regarding opportunistic diseases also reveals us looking for a diagnosis based on the appearance of signs and symptoms, which reiterates the suggestion of late diagnosis.[25] Implementation of early diagnosis, proper management and correct coping are essential measures to reduce correlated lethality.[26]

Presence of two or more clinical manifestations characterizes the symptomatic phase of the infection, suggesting an advanced stage of the infection.[21] The significant association of this indicator with the risk classification is suggested based on its ability to cause damage to the specific treatment by influencing viral transmission, decreased sensitivity of the immune response to drugs, management and complex clinical coping, and high levels of early mortality.[27]

In the population studied, the presence of a chronic disease at the time of diagnosis increased the prevalence for high risk by twice. HIV-infected people are at increased risk for the development of cardiovascular disease due to the high prevalence of cardiovascular risk factors and ART-related metabolic changes, as well as systemic immune activation that promotes endothelial inflammation and atherosclerosis.[28]

Based on Somers' D statistic analysis, the high risk of AIDS-associated clinical complications was strongly associated with three follow-up variables: opportunistic diseases (0.556), clinical manifestations (0.453), and LT-CD4 + (0.414). Identification of acute risk from clinical risk stratification use enables the planning of strategies and implementation of interventions on the vulnerabilities of individuals, aiming at reducing clinical complications and mortality.

In Brazil, a satisfactory and lasting response to AIDS will only be possible when all dimensions of health care practices are embedded in an effective and well-structured public health system.[29]

Limitations of the study are in the retrospective nature of the data, quality of the information collected from a secondary source (medical records) and because it comes from a single Brazilian state restricting the generalization of results. The lack of information in medical records related to the indicators that made up the risk score also reflected in the sample number used, which may have influenced the absence of statistical significance between variables.

Conclusion

The study showed the prevalence of high risk for clinical complications development among cases of death, as well as the higher associative strength found in LT-CD4 + indicators, opportunistic diseases and clinical manifestations in the proposed risk score. These results suggest the need for special attention from specialized care services to outpatients, attesting to the need for health professionals to know about the real clinical and immunological status of users retained in continuous care. In addition to highlighting the importance of sociodemographic aspects and therapeutic characteristics in understanding the epidemic behavior, pointing out factors that need investigation and intervention in the care network for people living with the infection. Considering theme relevance, it is suggested that further studies be developed from the perspective of clinical risk stratification so that it becomes a standard practice in health services.

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Collaborations

Leadebal ODCP participated in conception and design, analysis and interpretation of data and preparation and approval of the final version of the manuscript; Pereira RR worked on the final writing and critical review for approval of the final ver-

sion to be published; Nobrega LMB and Oliveira JAM worked on conception, design and approval of the final version to be published; Chaves RB and Medeiros LB worked on methodology design, study design, data analysis and interpretation, and approval of final version to be published and Monroe AA and Nogueira JA worked on final writing and critical review for approval of final version to be published.

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