

## Epidemiological and clinical factors associated with lethality from Human Visceral Leishmaniasis in Northeastern Brazil, 2007 to 2018

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### ABSTRACT

Human Visceral Leishmaniasis (HVL) presents a subacute clinical evolution with systemic involvement, which can result in high case fatality, especially among untreated individuals or those with low socioeconomic status. This study aimed to identify epidemiological and clinical factors associated with HVL case fatality in the Ceara State, from 2007 to 2018. This is an analytical cross-sectional study. The bivariate analysis was performed by Stata 15.1 using Pearson's Chi-square or Fisher's exact test; and Poisson regression for age-controlled multivariate analysis. From 2007 to 2018, there were 4,863 new confirmed cases and 343 deaths from HVL (case fatality rate=7.05%). The risk factors associated with case fatalities were: age group (RR=8.69; 95%CI:3.56-21.20); black population (RR=2.21; 95%CI:1.45-3.35); jaundice symptoms (RR=1.72; 95%CI:1.38-2.14); edema (RR=2.62; 95%CI:2.10-3.26) and hemorrhagic phenomena (RR=1.63; 95%CI:1.26-2.10); and no prescription drug intake (RR=4.03; 95%CI:2.98-5.46). Treatment with pentavalent antimonial was a protective factor (RR=0.35; 95%CI:0.27-0.45). The number of deaths increased among the elderly, illiterate, urban residents, and black skin color individuals. The drugs pentavalent antimonial and amphotericin B showed an association with death, but were not considered causal factors. Treatment failure led to a high risk of death. In multivariate analysis, the risk factors for fatal cases were age group, black skin, symptoms of jaundice, edema and hemorrhagic phenomena; and failure to take the prescription drugs. Treatment with pentavalent antimonial was shown to be a protective factor. Knowing the factors associated with the fatality of VL-HIV cases may help to improve public policies, in order to refine the epidemiological surveillance program and, consequently, prevent deaths related to the disease in Ceara.

**KEYWORDS:** Visceral leishmaniasis. Lethality. Risk factors. Epidemiological surveillance.

### INTRODUCTION

Human Visceral Leishmaniasis (HVL) is a zoonotic disease caused by an intracellular protozoan, *Leishmania infantum*. In Brazil, the disease is transmitted by the vector *Lutzomyia longipalpis*<sup>1</sup>.

HVL is part of the group of neglected tropical diseases and its importance in public health is directly related to a further expansion of its area of influence. It evolves clinically with systemic involvement, which can result in high mortality, especially among untreated individuals or those with low socioeconomic status<sup>2</sup>.

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In Brazil, HVL is endemic and distributed in its five regions. The number of municipalities that have initiated the notification of cases has been increasing, with expansion to areas historically free of this disease, such as the municipalities in Southern Brazil<sup>3</sup>. From 2010 to 2018, Brazil registered 42,067 cases, which led to an average incidence of 1.92 cases per 100,000 inhabitants and 2,704 deaths<sup>4</sup>.

Northeastern Brazil stands out in the number of cases and deaths. Between 2008 and 2017, a total of 19,895 cases and 1,270 deaths were reported in this Brazilian region, with a case fatality rate of 6.4%. In this period, there was a gradual increase in the number of deaths from HVL, which increased from 517, in the period from 2008 to 2012, to 753 deaths from 2013 to 2017. From the total number of deaths in this period, 10.2% had been coinfecting with HVL and human immunodeficiency virus (VL-HIV), with a case fatality rate of 8.5% in this specific group<sup>5</sup>.

In the Ceara State, located in the north part of Northeastern Brazil, HVL has been detected since 1930, but only since 1986 has it been continuously reported by the Brazilian Ministry of Health (MH)<sup>6</sup>. This fact has led Ceara to be one of the Brazilian states with the highest number of cases. According to the risk stratification defined for HVL, the composite index for the triennium from 2016 to 2018 showed that Ceara had 20.3% (29/184) of its municipalities classified as priorities. The municipality of Fortaleza, the state's capital, was classified as having very intense transmission. Even though it is fully urbanized, this municipality is located in an area considered endemic and has high incidence coefficients<sup>7</sup>. Another four municipalities: Barbalha, Caucaia, Itapipoca and Juazeiro do Norte were classified with high transmission, and another 24 had medium transmission<sup>8</sup>.

The Brazilian Ministry of Health developed the Visceral Leishmaniasis Control Program (VLCP) to reduce the incidence, case fatality and degree of morbidity through early diagnosis and treatment as well as control of reservoirs and vectors. It is noteworthy that the early identification of patients is of fundamental importance to reduce case fatality through the implementation of timely prophylactic and therapeutic measures<sup>9</sup>.

However, despite the surveillance and control actions established by the MH, the case fatality of the disease has been attributed to factors such as late diagnosis, comorbidities and clinical complications<sup>10</sup>. The emergence of the disease in new geographical areas and the presence of hosts and intrinsic characteristics of the affected individual, – such as immunosuppression, malnutrition and coinfection with HIV, – are also factors associated with the case fatality due to HVL<sup>11</sup>.

The drugs used for the treatment of HVL are pentavalent antimonial and amphotericin B, considering that the choice

for each one depends on factors such as age, pregnancy and comorbidities<sup>1</sup>. It is recommended that patients over 50 years of age, kidney, heart and liver transplant recipients, and individuals coinfecting with HIV be treated with liposomal amphotericin B<sup>2</sup>. The patient can only be considered cured if he or she remains clinically stable after a follow-up six months later<sup>12</sup>.

One realizes that mortality data and related factors are quite scarce and generally represent only the deaths in healthcare facilities<sup>13,14</sup>. Due to the current context of HVL transmission in the Ceara State, and because it is a serious disease that can have high lethality, depending on the susceptible population<sup>14</sup>, there is a need to analyze its epidemiological aspects for effective planning of control strategies. Therefore, this study aimed to identify epidemiological and clinical factors associated with HVL case fatality in the Ceara State, from 2007 to 2018.

## MATERIALS AND METHODS

The study was conducted with data from the Ceara State, located in Northeastern Brazil. It has a population of almost nine million inhabitants in an area of approximately 149,000 km<sup>2</sup> divided into 184 municipalities. It has irregular rainfall distribution, average temperatures ranging from 29.4 °C (March) to 30.7 °C (November) and caatinga as the predominant biome<sup>15</sup>.

An analytical transversal study was conducted based on secondary data from new cases of HVL reported in the Information System for Notifiable Diseases (SINAN). We used all the new and confirmed resident and autochthonous cases with laboratory or clinical-epidemiological confirmation criteria and whose final classification was the evolution to cure or death from HVL.

In this study we defined as a case of HVL every person reported in SINAN whose diagnosis was made through rapid immunochromatographic tests and/or parasitological tests and/or immunological tests, like Indirect Immunofluorescence Reaction – IFTN; notifications in which “municipalities of residence” was outside the Ceara State and “diagnosis field” was inconsistent, that is, with errors or not filled in, were excluded.

The clinical evolution of the case to death by HVL or cure was considered as the dependent variable. The independent variables of this study included: sex, age group (distributed by 0 to 4, 5 to 9, 10 to 19, 20 to 39, 40 to 59, and 60 years or older); skin color (white, black, yellow, brown and indigenous); education (illiterate, elementary, high school, and higher education); municipality of residence; presence of VL-HIV coinfection; type of initial drug for treatment (pentavalent antimonial, amphotericin B, pentamidine,

liposomal amphotericin B, others, and not used); and presence of clinical manifestations (fever, weakness, weight loss, cough and/or diarrhea, splenomegaly, hepatomegaly, infectious condition, edema, jaundice, hemorrhagic phenomena, and pallor).

The database was processed and analyzed in Stata software (version 15.1, StataCorp, College Station, Texas, USA). For the bivariate analysis, Pearson's Chi-square test or Fisher's exact test with 95% significance was used, and the relative risks (RR) and their respective 95% confidence intervals (CI) were calculated.

Thereafter, the variables that presented statistical significance with  $p$ -value  $\leq 0.25$  were selected for the multivariate analysis. This analysis was performed by the generalized linear model (GLM) with logarithmic linkage and the Poisson distribution family to estimate the relative risks and confidence intervals, using robust error variances that evaluated the differences between categories

of explanatory variables for the outcome in the final model. Initially, the multivariate analysis was controlled by age group and those variables that remained significantly associated with the outcome ( $p < 0.05$ ) were taken into the final model.

The study was approved by the Research Ethics Committee of the Federal University of Ceara (CAAE N° 22785819.6.0000.5054).

## RESULTS

Between the years of 2007 and 2018, 6,066 confirmed cases of HVL were diagnosed in the Ceara State. Of these, 4,863 (80.17%) were classified as new cases and 343 evolved to death from HVL, with a case fatality of 7.05%. The male case fatality was 7.20%, 1.06 times higher than the female, but this difference was not statistically significant (95%CI:0.85 – 1.33;  $p = 0.572$ ) (Table 1).

**Table 1** - Sociodemographic characteristics of cases associated with deaths from Human Visceral Leishmaniasis in the Ceara State, 2007-2018.

Variables	Cases (n)	Deaths (n)	Case fatality (%)	Relative Risk (95%CI)	p-value
<b>Sex (n=4,863)</b>					
Female	1,477	107	6.76	1.0	
Male	3,043	236	7.20	1.06 (0.85 – 1.33)	0.572
<b>Age Group (4,853)</b>					
< 1-year-old	825	52	6.30	4.58 (2.51 – 8.35)	0.012
1 to 10 Years Old	945	13	1.38	1.0	
10 to 20 Years Old	522	14	2.68	1.95 (0.92 – 4.12)	0.395
20 to 50 Years Old	1,780	110	6.18	4.49 (2.54 – 7.94)	0.002
50 to 60 Years Old	387	54	13.95	10.14 (5.60 – 18.37)	<0.001
> 60 Years Old	394	100	25.38	18.45 (10.48 – 32.49)	<0.001
<b>Race (n=4,278)</b>					
White	346	26	6.99	1.0	
Black	87	14	13.86	1.98 (1.08 – 3.65)	0.027
Yellow	14	2	12.50	1.79 (0.46 – 6.89)	0.404*
Brown	3,808	269	6.60	0.94 (0.64 – 1.39)	0.772
Indigenous	23	1	4.17	0.60 (0.08 – 4.21)	0.595*
<b>Education (n=1,631)</b>					
Illiterate	81	27	25.00	12.00 (1.68 -85.77)	<0.001
Elementary School	1,022	81	7.34	3.52 (0.50 – 24.79)	0.165
High School	358	14	3.76	1.81 (0.24 – 13.43)	0.555
Higher Education	47	1	2.08	1.0	
<b>Residence Zone (n=4,387)</b>					
Urban	3,398	266	7.26	1.0	
Rural	946	65	6.43	0.88 (0.68 – 1.15)	0.362
Peri-urban	43	2	4.44	0.61 (0.16 – 2.38)	0.468*

\*Fisher's exact Chi-square test. The difference between the number of observations for the variables was due to the ignored and blank records excluded in all variables.

It is noteworthy that the age group over 60 years old has an 18.45 times higher risk of death (95%CI: 10.48 – 32.49) compared to the 1 to 10 years old age group; and the risk of death for those with black skin color was 1.98 times higher (95%CI: 1.08 – 3.65) than for those with white skin color (Table 1).

Among the illiterates, the case fatality rate was 12 times higher (95%CI: 1.68 – 85.77) when compared to cases with higher education; and 1.14 times higher (95%CI: 0.87 – 1.47) in urban compared to rural areas, but not statistically significant ( $p=0.617$ ) (Table 1).

A case fatality rate of 8.51% was identified in people coinfecting with HIV, but it was not statistically significant ( $p=0.162$ ). On the other hand, the groups of people treated with amphotericin B, liposomal amphotericin B, as well as those who did not take the drug, had an over four times higher

risk of dying compared to those treated with pentavalent antimonial ( $p<0.001$ ). Particularly noteworthy is the 16.36 times higher risk of death (95%CI: 11.62 – 23.03) in cases that were not treated with the specific drugs (Table 2).

The HVL case fatality rate in people who had no fever was 1.92 times higher ( $p<0.001$ ) than for those who had a fever. However, the cases that manifested weakness, infection, edema, jaundice, pallor or hemorrhagic phenomena had higher and statistically significant case fatality (Table 3).

In the multivariate analysis, the following variables remain associated with risk factors for LVH deaths: age groups: from 20 – 50 years old (RR=3.05 95%CI: 1.26 – 7.38;  $p=0.013$ ); from 50 – 60 years old (RR=5.54; 95%CI: 2.25 – 13.63;  $p<0.001$ ); 60 years old or more (RR=8.69; 95%CI: 3.56 – 21.20;  $p<0.001$ ); black-skinned

**Table 2** - Clinical and treatment characteristics associated with deaths from Human Visceral Leishmaniasis in the Ceara State, 2007-2018.

Variables	Case (n)	Death (n)	%	RR (95%CI)	p-value
HIV Coinfection (n=3,808)					
Yes	301	28	8.51	1.31 (0.89 – 1.91)	0.162*
No	3,253	226	6.50	1.0	
Starting Drug (n=4,685)					
Pentavalent Antimonial	2,949	8	2.77	1.0	
Amphotericin B	573	96	4.35	5.18 (3.91 – 6.86)	<0.001*
Pentamidine	13	1	7.14	2.58 (0.38 – 17.25)	0.321
Liposomal Amphotericin B	618	88	12.46	4.50 (3.38 – 5.99)	<0.001
Other	183	16	8.04	2.90 (1.73 – 4.86)	<0.001
Untreated	35	29	45.31	16.36 (11.62 – 23.03)	<0.001

\*Fisher's exact Chi-square test. The difference in number between the variables is due to the ignored and blank records excluded in all variables.

**Table 3** - Clinical manifestations associated with the occurrence of death from Human Visceral Leishmaniasis in the Ceara State, 2007-2018.

Clinical Manifestation	Cases (n)	Deaths (n)	%	RR (95%CI)	p-value
Fever (n=4,845)	4,280	306	6.67	0.48 (0.35 – 0.66)	<0.001
Weakness (n=4,796)	3,308	270	7.55	1.44 (1.10 – 1.87)	0.007
Weight Loss (n=4,780)	3,262	251	7.14	1.09 (0.86 – 1.39)	0.477
Cough and/or Diarrhea n= (4,734)	1,983	163	7.60	1.14 (0.93 – 1.40)	0.205
Splenomegaly (n=4,736)	3,347	244	6.79	0.90 (0.71 – 1.15)	0.407
Hepatomegaly (n=4,723)	2,908	225	7.18	1.08 (0.86 – 1.35)	0.512
Infectious Condition (n=4,585)	872	138	13.66	2.65 (2.15 – 3.27)	<0.001
Edema (n=4,666)	850	172	16.83	3.81 (3.11 – 4.67)	<0.001
Jaundice (n=4,653)	1,026	150	12.76	2.45 (1.99 – 3.01)	<0.001
Hemorrhagic Phenomena (n=4,615)	330	82	19.90	3.43 (2.73 – 4.31)	<0.001
Pallor (n=4,733)	2,845	241	7.81	1.34 (1.07 – 1.68)	0.012

The difference in number between the variables is due to the ignored and blank records excluded in all variables.

**Table 4** - Multivariate statistical analysis adjusted by age and final of variables associated with deaths from Human Visceral Leishmaniasis in the Ceara State, 2007 to 2018.

Variables (n=4674)	Age-Adjusted (95%CI)	Final (95%CI)
Age Group (n=4594)	-	
<=1-year-old		2.12 (0.86 – 5.25)
1 – 10		1
10 – 20		1.64 (0.59 – 4.52)
20 – 50		3.05 (1.26 – 7.38) *
50 – 60		5.54 (2.25 – 13.63) **
>60 Years Old		8.69 (3.56 – 21.20) **
Education (n=1631)	2.29 (1.59 – 3.28) **	-
Black Skin Color (n=4674)	1.77 (1.10 – 2.84)*	2.21 (1.45 – 3.35) **
Jaundice (n=4853)	2.42 (1.98 – 2.94) **	1.72 (1.38 – 2.14) *
Pallor (n=4853)	1.57 (1.26 – 1.95) *	-
Edema (n=4853)	3.33 (2.72 – 4.08) **	2.62 (2.10 – 3.26) **
Hemorrhagic Events (n=4853)	2.79 (2.20 – 3.53) **	1.63 (1.26 – 2.10) **
Pentavalent Antimonial (n=4674)	0.28 (0.21 – 0.36) **	0.35 (0.27 – 0.45) **
Amphotericin B (n=4674)	2.16 (1.72 – 2.71) **	-
Liposomal Amphotericin B (n=4674)	1.34 (1.03 – 1.73) *	-
No Drugs (n=4674)	5.24 (3.93 – 6.99) **	4.03 (2.98 – 5.46) **

\*0.01 < p < 0.05; \*\*p < 0.001.

people (RR=2.21; 95%CI: 1.45 – 3.35; p<0.001); jaundice symptoms (RR=1.72; 95%CI:1.38 – 2.14; p<0.001); edema (RR=2.62; 95%CI: 2.10 – 3.26; p<0.001); hemorrhagic events (RR=1.63; 95%CI:1.26 – 2.10; p<0.001); and no prescription drug intake (RR=4.03; 95%CI:2.98 – 5.46; p<0.001). On the other hand, the incidence of deaths was lower in the group that received initial treatment with the pentavalent antimonial drug (RR=0.35; 95%CI:0.27 – 0.45; p<0.001) (Table 4).

## DISCUSSION

This was the first study to assess the risk factors for HVL deaths in Ceara in the last 20 years. A case fatality rate of approximately 7% was observed and directly associated with socio-demographic and clinical factors, such as advanced age, individuals with black skin color, having co-infection with HIV and not using specific medication for treatment. The high case fatality of this disease, especially among untreated, older and HIV-infected individuals, makes HVL one of the six most important endemic diseases in the world<sup>16</sup>.

Although the Ceara State is considered endemic for HVL, its case fatality rate is close to the rates in Brazil (8.81%)<sup>15</sup> and the Americas (7.09%). However, to minimize it, the MH encouraged the states to implement surveillance and assistance actions for patients with HVL, following the

recommendation of the Pan American Health Organization (PAHO), which aims to reduce by 50% the case fatality rate of HVL in the Americas by the end of 2022<sup>5</sup>.

HVL is a disease with a cyclical and temporal trend and the increase in the number of cases is directly related to the infestation of new peripheral areas and to the difficulty in timely diagnosis of individuals, which leads to an increased lethality<sup>10</sup>. These same reasons were verified in a research carried out in Governador Valadares, Minas Gerais State, from 2008 to 2011, which identified a case fatality rate of 16.0%, higher than the national average of 6.7% in 2011<sup>16</sup>.

Other factors were also pointed out to justify the case fatality of the disease such as: toxicity of specific drugs, presence of comorbidities, low quality of healthcare as well as socioeconomic factors related to the individual and the environment<sup>11,17</sup>.

Being male was one of the epidemiological factors associated with death from HVL in Ceara. This corroborates some studies that point to a higher exposure of men to the vector because they are more often involved in household tasks or outdoor leisure activities, especially during the period of higher vector activity, in addition to the habit of not wearing a shirt due to high temperatures<sup>18</sup>. Along with these cultural factors of greater exposure, the higher case fatality in men may be related to the delay to seek health services, as well as the difficulty in adhering to treatment<sup>16</sup>. The hormonal action has also been investigated, highlighting

the potential of testosterone to cause immunosuppression in men, given its association with greater susceptibility and poor control of the parasite load, in addition to inducing cell apoptosis and attenuating the pro-inflammatory process<sup>19</sup>.

Older people also presented a higher risk of death in this study, which may be related to the greater susceptibility to complications caused by the disease itself. A similar result was obtained in national and state contexts. In Brazil, from 2007 to 2018, there was a more expressive risk in the age group over 60 years old<sup>16</sup>; and in an evaluation of prognostic factors for death from HVL in the Sao Paulo State, Brazil, between 1999 and 2005, the mean age of individuals who died from it was 44 years old, but with a stronger association for death in those over 50 years old<sup>20</sup>.

A high association with HVL case fatality was observed in the black-skin population. It is known that HVL is a neglected disease that mainly affects individuals in unfavorable socioeconomic conditions; and in Brazil, people of African descent are mostly black and of mixed race<sup>21,22</sup>. In the Ceara State, these population groups concentrate individuals with less education as well as lower socioeconomic status, thus being a reflection of racial inequality<sup>23</sup>.

In this study, the case fatality was more expressive among illiterate people, indicating that lack of information, hygiene standards and disease prevention are aspects to be considered. Similarly to skin color, little education is a marker of low socioeconomic status, and therefore, it limits access to the health system; consequently, it contributes to a higher risk of comorbidities associated with HVL and food insecurity<sup>24</sup>. This fact was also found in the Piaui State, Northeastern Brazil, between 2012 and 2018, which described a number of individuals affected by HVL as having a low level of education, requiring actions to improve quality of life to control the disease and make control measures more effective<sup>21</sup>.

There was a higher case fatality in urban area residents which may suggest that cases are more concentrated in the periphery and, in turn, in the more socioeconomically privileged population; or due to possible late diagnosis, a consequence of a disordered growth of populations in the peripheries or even an inadequate differential diagnosis. The migration of the population to urban areas in Brazil since 1980 was accompanied by a change in the transmission pattern to peri-urban regions of large cities in the Northeast and Southeast regions<sup>16</sup>.

In the HVL epidemic that occurred in the Piaui State from 1980 to 1986, the geographical distribution of the epidemic process and the concomitance of its onset, with prolonged drought, accompanied by the emigration of people and domestic animals from endemic to epidemic

regions, suggests that migratory movements have triggered the epidemic<sup>25</sup>.

Late diagnosis is considered an important factor associated with HVL case fatality which is why the training of doctors in the Family Health Program should be prioritized by the basic network<sup>26</sup>. Timely diagnosis is considered a challenge in Brazil, where the disease is still often treated only based on clinical manifestations<sup>11</sup>.

According to a research conducted on factors associated with death from HVL in the Sao Paulo State, Brazil, from 1999 to 2005, the initial increase in case fatality rate was caused by a misdiagnosis of the disease by health professionals and, afterwards, the maintenance of its levels came as a result of the occurrence of cases in vulnerable populations, such as those infected with HIV<sup>11</sup>.

In another study carried out in Brazil from 2007 to 2017, in addition to known individual risk factors such as age and low education, the unavailability of emergency beds and healthcare professionals was also identified as possibly related to an increased risk of death from HVL<sup>22</sup>.

In priority municipalities of Ceara, the peri-urbanization and urbanization processes of HVL are expanding<sup>27</sup>. This is due to several factors, such as: deforestation and environmental changes, increased population migration, and especially, the adaptation of the main vector (*L. longipalpis*) to the urban environment, making its control a challenge for the National Program for the Control and Prophylaxis of Visceral Leishmaniasis<sup>20</sup>. The precarious living conditions of the populations in the peripheries (underprivileged urban areas), which grow rapidly in a disorderly manner and without infrastructure, such as garbage collection and sewage treatment<sup>28</sup>, are also directly associated with the incidence and case fatality rates of HVL<sup>26</sup>.

In multivariate analysis, the case fatality of HVL remained associated with HIV infection. The VL-HIV coinfection requires characterization, identification and resolution of the difficulties to restrain the progression of both diseases. Previous studies have detected an increased case fatality rate, ranging from 4.6% to 16.6% in coinfecting patients in the Northeast region, specifically in the states of Rio Grande do Norte<sup>4</sup> and Pernambuco<sup>29</sup>; as well as in the Minas Gerais State (13.0%), in the Southeastern region<sup>14</sup>. This is explained by the fact that both diseases cause infection and multiply in the lymphoid cells. In addition, HVL may act as an opportunistic disease in immunosuppressed patients<sup>7</sup>.

Immunosuppression in coinfecting patients has the consequences of reduced therapeutic response, limitations in diagnosis, high mortality, and increased possibility of relapse<sup>14</sup>. The presence of HIV leads to severe forms of HVL which are difficult to control and manage. Therefore,

this coinfection requires characterization, identification and resolution of the difficulties to restrain the progression of both diseases<sup>13</sup>. The classic symptoms such as fever and hepatosplenomegaly were not statistically significant in this study, because although they are considered diagnostic criteria, they do not influence the prognosis of the disease whose characteristics are also identified in other state capitals in Brazil, such as Sao Paulo/SP<sup>11</sup>, Campo Grande/MS<sup>30</sup> and Teresina/PI<sup>31</sup>.

In this study, variables that indicate the severity of the case were identified, which lead to the choice of medication for the treatment. Weakness, infectious condition, edema, hemorrhagic phenomena and jaundice were symptoms associated with LVH lethality, the latter was also present in the multivariate analysis. The same symptoms (except weakness) were also present in the multivariate analysis. It is worth noting that from 2010 to 2019, one of the main risk factors for lethality in Brazil was infectious and hemorrhagic complications<sup>4,20</sup>.

The occurrence of hemorrhagic phenomena, jaundice and edema as important risk factors for death from HVL demonstrates the involvement of the liver in the severity of the disease. It has been shown that in humans with active infection by *Leishmania* spp. there is also increased production of Th2 cytokines, such as IL-10, IL-4 and TNF as well as IL-6, IL-8, IL-12 and IFN- $\gamma$ . This phenomenon of exaggerated production configures a process known as cytokine storm and is part of the intense inflammatory process described in HVL<sup>32</sup>.

The hepatic dysfunction associated with thrombocytopenia can cause severe bleeding and increase the risk of death<sup>18</sup>. In the earliest diagnosis or during the course of treatment, the presence of bleeding signals the identification of disease severity<sup>20,33</sup>.

Along with hemorrhagic phenomena, the presence of secondary bacterial infections represents a strong predictor of death among individuals with HVL<sup>31</sup>. It is known that there is a high casuistry of individuals who enter the Brazilian Unified Health System with opportunistic infections associated with HVL in advanced stages<sup>18</sup>. These findings support the importance of preventing infectious conditions and treating patients with HVL affected by bacterial infections<sup>3,34</sup>.

In the bivariate analysis of this study, amphotericin B showed a 5.18% higher risk of death. It is considered the only option for the treatment of stroke patients who already have a prognosis with a high possibility of worsening, such as pregnant women, adults over 50 years old, people with previous impairment of cardiac, renal and/or hepatic functions, and individuals with HIV-HIV coinfection<sup>20</sup>. However, pentavalent antimony was observed to be a

protective factor, since it has been considered the first choice treatment in Brazil since 1950<sup>16,20,35</sup>. Similarly, the same drug was the most prescribed in countries of the African continent, such as Sudan, Kenya, Uganda, and Ethiopia; and also in India, where it was not associated with serious adverse events<sup>36-38</sup>.

It is noteworthy that the choice of drug for treatment is based on the presence of comorbidities, clinical severity and side effect profile<sup>39</sup>. In addition to the criteria for the limited use of amphotericin B, the lack of adherence of prescribers to the recommendations of the Brazilian MH is also suggested<sup>24,34</sup>. The choice of amphotericin B as treatment may be due to a possible inconsistency in filling out the notification form since the liposomal formulation is the most widely used in the Ceara State.

Patients who did not take any drug for treatment were over four times more likely to die from HVL in the Ceara State. This fact leads us to observe that timely and specific treatment is necessary to reduce the case fatality of this disease and prove the fact that, when untreated, HVL is highly lethal.

Despite the efforts made in the surveillance of HVL in the Ceara State, the main goal to reduce its case fatality by 50% has not yet been achieved. Therefore, there is a need to intensify the epidemiological surveillance actions and, with that, the urgency of promoting refresher courses for healthcare professionals to recognize early symptoms of the disease and improve the monitoring of patients under treatment, in order to identify early possible complications, reduce the degree of morbidity, case fatality rates and risks of local transmission. Knowing the factors associated with HVL case fatality can help to improve the recommended public policies, enable the refinement of the epidemiological surveillance program and, consequently, prevent deaths related to the disease in the of Ceara State.

The research had limitations related to the use of secondary data, including notification forms with fields containing some missing or incomplete information, and fillings considered inadequate. However, these difficulties did not provide loss of information due to a large amount of data.

## CONCLUSION

The data points to a high case fatality rate for HVL in the state, which was more expressive in men, over 60 years old, black skin color, illiterate and urban residents. People coinfecting with HIV who manifested symptoms of weakness, infectious condition, edema, jaundice, pallor and hemorrhagic phenomena; treated with liposomal amphotericin B and those who did not take any

prescription drug had a higher risk of dying from HVL. In multivariate analysis, the risk factors for case fatality were age group, black skin color, symptoms of jaundice, edema, hemorrhagic phenomena, and no prescription drug intake. On the other hand, the case fatality was lower in individuals who received the pentavalent antimonial drug as the initial treatment.

Knowing the factors associated with the lethality of HVL can help to improve public policies, making it possible to refine the epidemiological surveillance program and, consequently, prevent deaths related to the disease in Ceara. Early detection of cases, adequate treatment and continued education of healthcare professionals are recommended, thus avoiding the evolution to death.

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