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ORIGINAL ARTICLE

Human Visceral Leishmaniasis: lethality and time from suspicion to treatment in an endemic area in Brazil

Leishmaniose visceral humana: letalidade e tempo da suspeição ao tratamento em área endêmica no Brasil

Leishmaniasis visceral humana: letalidad y tiempo desde la sospecha hasta el tratamiento en un área endémica de Brasil

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ABSTRACT

Background and objectives: human visceral leishmaniasis (HVL) are a persistent public health problem, configuring a challenge to reduce its lethality. In order to evaluate the factors associated with lethality, this study emphasizes the time elapsed from suspicion to treatment of HVL, in the years 2015 to 2019, in the municipality of Araguaína-TO, an area of intense transmission. **Methods**: an epidemiological study of case series with longitudinal follow-up with information extracted from HVL notification and investigation forms. The relative risk (RR) was used as a measure of the strength of association for death, being calculated with confidence intervals (95% CI) estimated by the Wald test. Time intervals were represented in days by box plot as medians (Md). **Results:** of the 191 cases of HVL, 179 (93.72%) were cured and 12 (6.28%) had a fatal outcome. There was no association of risk of death by sex, education, race, being significant only by age in the age groups of young (RR= 16.09) and older adults (RR=7.08). The time from suspicion to treatment in children was shorter (0-35 days, Md=12) than that of older patients (4-44 days, Md=18) and in those who died (7-65 days, Md=20) highlighting greater inopportunity of healing in these last two groups. **Conclusion:** late diagnosis was a determining indicator for worse outcomes, five days made the difference between the group with an outcome for cure with the group of those who died, highlighting the need to shorten the wait for treatment.

Keywords*: Visceral leishmaniasis. Delayed Diagnosis. Mortality.*

RESUMO

Justificativa e objetivos: a leishmaniose visceral humana (LVH) constitui-se em persistente problema de saúde pública, configurando-se um desafio à redução de sua letalidade. Para avaliação dos fatores associados à letalidade, este estudo tem ênfase no tempo decorrido da suspeição ao tratamento de LVH, nos anos de 2015 a 2019, no munici-

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pio de Araguaína-TO, área de transmissão intensa. **Métodos:** estudo epidemiológico de série de casos com acompanhamento longitudinal, com informações extraídas das fichas de notificação e investigação de LVH. Utilizou-se o risco relativo (RR) como medida de força de associação para o óbito, sendo calculado com intervalos de confiança (IC 95%) estimados pelo Teste de Wald. Os intervalos de tempo foram representados em dias por *box plot* em medianas (Md). **Resultados:** dos 191 casos de LVH, 179 (93,72%) obtiveram cura e 12 (6,28%) apresentaram desfecho fatal. Não houve associação de risco de morte por sexo, escolaridade, raça ou cor, sendo significativa apenas por idade nas faixas etárias de adultos jovens (RR= 16,09) e idosos (RR=7,08). O tempo da suspeição ao tratamento em crianças foi mais curto (0-35 dias, Md= 12) que o de pacientes mais velhos (4-44 dias, Md=18) e naqueles que evoluíram ao óbito (7-65 dias, Md=20), realçando maior inoportunidade de cura nesses dois últimos grupos. **Conclusão:** o diagnóstico tardio foi um indicador determinante para piores desfechos, e cinco dias fizeram a diferença entre o grupo com desfecho para cura e o grupo dos que vieram a óbito, destacando a necessidade de encurtamento da espera para tratamento.

Descritores: *Leishmaniose visceral. Diagnóstico tardio. Mortalidade.*

RESUMEN

Justificación y objetivos: la leishmaniasis visceral humana (HVI) constituye un problema persistente de salud pública, configurando un desafío para reducir su letalidad. Con el objetivo de evaluar los factores asociados a la letalidad, este estudio enfatiza el tiempo transcurrido desde la sospecha hasta el tratamiento de la VLH, en los años 2015 a 2019, en el municipio de Araguaína-TO, zona de transmisión intensa. **Métodos:** estudio epidemiológico de serie de casos con seguimiento longitudinal con información extraída de los formularios de notificación e investigación LVH. Se utilizó el riesgo relativo (RR) como medida de la fuerza de asociación para muerte, siendo calculado con intervalos de confianza (IC 95%) estimados por la prueba de Wald. Los intervalos de tiempo se representaron en días mediante diagrama de caja como medianas (Md). **Resultados:** los 191 casos de LVH, 179 (93,72%) se curaron y 12 (6,28%) tuvieron un desenlace fatal. No hubo asociación de riesgo de muerte por sexo, educación, raza o color, siendo significativo solo por edad en los grupos de edad de adultos jóvenes (RR= 16,09) y ancianos (RR=7,08). El tiempo desde la sospecha hasta el tratamiento en los niños fue menor (0-35 días, Md=12) que en los pacientes mayores (4-44 días, Md=18) y en los que fallecieron (7-65 días, Md=20) destacando mayor inoportunidad de curación en estos dos últimos grupos. **Conclusión**: el diagnóstico tardío fue un indicador determinante de peor desenlace, los cinco días marcaron la diferencia entre el grupo con resultado de curación con el grupo de los que fallecieron, destacando la necesidad de reducir la espera para el tratamiento.

Palabras clave: *Leishmaniasis visceral. Diagnóstico Tardío. Mortalidad.*

INTRODUCTION

Leishmaniasis is a chronic, sometimes debilitating and lethal disease that affects humans and different species of wild and domestic animals. The phenotypes of the disease are divided into four different modalities of pathogenic manifestations: cutaneous, mucocutaneous, diffuse and visceral leishmaniasis, the most severe form.[1–3]

They are caused by a variety of protozoa transmitted by female sandflies and have a complex biological cycle. The parasites involved in human visceral leishmaniasis (HVL) are the protozoa of the *Leishmania spp* complex. bringing together two species: *L. (Leishmania) infantum* [*sin. L. (L) chagasi*] and *L. (L) donovani*, the former being the species responsible for cases in the Americas.[2,4]

L. (L) infantum infection is characterized by a broad clinical spectrum, with an insidious character and nonspecific symptomatology, a fact that can make its diagnosis difficult. The classic form of the disease is marked by irregular or remitting fever, cutaneous-mucous pallor, weight loss and hepatosplenomegaly.[2,3]

Progressively, in the course of the disease, patients can suffer complications with the continuous fever leading to a more intense impairment of the general condition. More severe malnutrition sets in, increasing susceptibility to secondary infections, edema and significant hematological disorders.[2,3,5]

The World Health Organization emphasizes the seriousness of this disease by informing that if not treated, it can progress to death in more than 90% of cases. Its lethality rate continues to represent a major challenge for health systems, as it requires adequate management and a rapid and accurate diagnosis.[2,3]

Research that addresses the pattern of occurrence of HVL can contribute to a better understanding the behavior of the disease, and may constitute a valuable tool for planning and executing health surveillance activities.

Thus, this study sought to evaluate the epidemiological characteristics and factors associated with HVL lethality, with emphasis on the time elapsed from suspicion to treatment, in the municipality of Araguaína-TO, considered an area of intense transmission, from 2015 to 2019.

METHODS

This is an epidemiological study of a case series

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with longitudinal follow-up of autochthonous HVL in the municipality of Araguaína-TO, according to sociodemographic and clinical variables and the temporal evolution from January 2015 to December 2019, excluding entries due to relapses.

The municipality of Araguaína is located in the state of Tocantins (Figure 1), northern region of Brazil, has a territory of 4,004.646 km², located in the geographic extension of MATOPIBA, acronym formed with the initials of the states of Maranhão, Tocantins, Piauí and Bahia. The state borders Pará, to the northwest, Goiás, to the south, and Mato Grosso, to the southwest, being considered an important region of agricultural frontier expansion.[6]

Tocantins in the last ten years totaled 2,909 notified cases of HVL, taking sixth place in a ranking of Brazilian states that most confirmed cases, behind only Maranhão, Minas Gerais, Ceará, Pará and Bahia.[7]

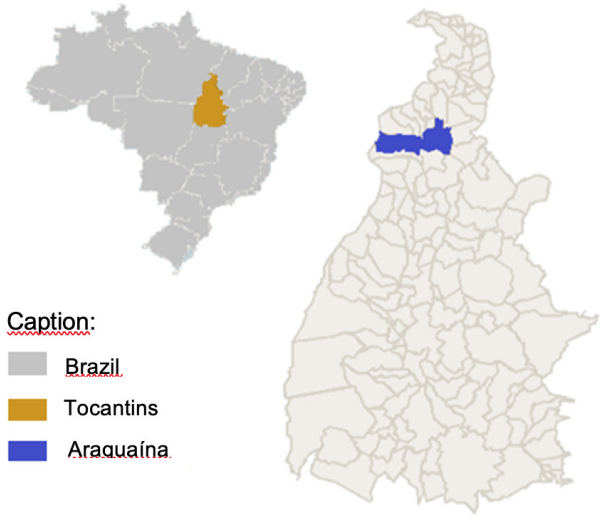

Figure 1. Geographic location of the municipality of Araguaína-TO.

In northern state, the municipality of Araguaína stands out, as it presents an endemic-epidemic process of HVL since 2006, when there was an alarming increase in the number of human cases, going from 56 to the expressive quantitative of 287 cases in 2007, when it reached the highest number of records of the disease in Brazil. It remained, since then, among the five Brazilian municipalities with the highest absolute number of annual records of HVL.[7]

The research used information from the Araguaína Municipal Health Department database, which is composed of sociodemographic and clinical epidemiological variables from the notification and investigation forms sent to the Department of Epidemiological Surveillance.

After extracting the data, sociodemographic variable tabulations with their respective frequencies and calculations of lethality were performed. For the inferential statistics of risk association for death, relative risk (RR) was used, since its design allows calculating the ratio between the absolute risk of becoming ill or dying both in individuals with the exposure of interest and in those without exposure, considering a p-value of <0.05 for statistical significance.

The RR was calculated with the respective confidence intervals (95% CI) estimated by the Wald test, using the riskratio.wald() function of the epitools package in the R© software version 3.6.1 to infer which variable presented a significant association of risk of death.[8,9]

In the temporal analysis, the cases were divided into five groups, namely: group with all records, which is represented by the term "general population"; group of children aged less than or equal to 5 years; group of adults 50 years of age or older; group of patients who were cured, represented by the term "cure outcome"; and finally, the group of those who died from HVL, represented by the term "death-outcome".

Calculations of intervals in days were performed, considering the dates of suspicion (notification), date of onset of symptoms, date of start of treatment and date of completion of the case (outcome), as shown in figure 2.

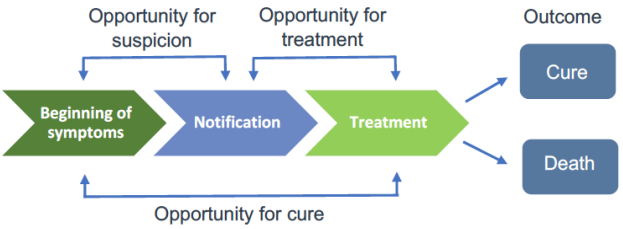

Figure 2. Temporal analysis with their respective intervals.

Due to the high dispersion presented by the time intervals, it was decided to use the box plot to represent the data, since these exhibit measures of non-parametric central tendencies (median), with sample distribution or symmetry that also highlight outliers.

This study complies with Resolution 466/2012, of the Brazilian National Health Council for Research on Human Beings, and Resolution 196 of October 10, 1996, of the Brazilian National Health Council, in compliance with the criteria of the Research Ethics Committee (REC), under Opinion 4,843,317 of July 13, 2021, CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration)29617320.9.0000.5519.

RESULTS

A total of 191 autochthonous cases of HVL were registered, of which 179 (93.7%) evolved to cure and 12 (6.3%) had a fatal outcome. Among the deaths, four of them did not start treatment, the youngest being a one-month-old infant, and the oldest, an 86-year-older adult.

Cases were concentrated in males (58%), children under 10 years old (57.6%) and brown individuals (88.5%).

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Table 1. Sociodemographic characterization of human visceral leishmaniasis cases by risk association for death, Araguaína-TO, 2015-2019.

Variable	Cases		Deaths	Lethality	RR#	95%CI	*p-value*
	N	%	N	N			
Sex							
Male	110	57.6	9	8.18	2.12	0.59-7.59	0.366
Female	81	42.4	3	3.7	0.47	0.13-1.69	
Age group							
<1- 09 years	110	57.6	4	3.64	1	-	-
10-19 years	10	5.2	0	-	0.14	2.11e-05- 921.27	1.000
20-29 years	18	9.4	1	5.56	1.55	1.91e-01-12.53	0.543
30-39 years*	15	7.9	2	13.33	16.09	5.93 - 43.68	<0.001
40-49 years	15	7.9	0	-	0.09	1.40e-05 - 620.63	1.000
50-59 years	8	4.2	0	-	0.17	2.65e-05 - 1.142.63	1.000
≥ 60 years*	15	7.9	5	33.33	7.08	2.09 - 23.94	<0.001
Education							
Illiterate	0	-	-	-	-	-	-
Incomplete 1st-4 th	11	5.8	2	18.18	1	-	-
4th grade	5	2.6	1	20.00	0.981	0.638 - 1.509	1.000
IES	22	11.5	1	4.55	1.132	0.882 - 1.452	0.539
CES	6	3.1	1	16.67	1.01	0.687 - 1.485	1.000
IHS	10	5.2	0	0.00	1.18	0.930 - 1.495	0.486
CHS	19	9.9	2	10.53	1.07	0.815 - 1.405	0.627
IHE	0	-	-	-	-	-	-
CHE	2	1	0	0.00	1.157	0.845 - 1.585	1.000
Ignored	7	3.7	1	14.29	-	-	-
Not applicable	109	57.1	4	3.67	-	-	-
Race/color							
Brown	169	88.5	9	5.33	1	-	-
White	10	5.2	0	0.00	1.05	0.99 - 1.11	1.000
Black	9	4.7	2	22.22	0.86	0.65 - 1.14	0.127
Ignored	3	1.6	1	33.33	0.78	0.44 - 1.38	0.204
Yellow	0	-	-	-	-	-	-

*Caption: *Variables with statistical significance; RR - Relative Risk; e-X: short scientific notation; IES - Incomplete Elementary School; CES - Complete Elementary School; IHS - Incomplete High School; CHS - Complete High School; IHE - Incomplete Higher Education; CHE - Complete Higher Education.*

In the analysis by level of education, 57% of notifications reported the category "not applicable", followed by "Incomplete High School" (11.5%) as represented in table 1.

As for the risk association for death, although men had a high lethality rate (8.18%), there was no significant association of death by gender (p = 0.36) and education (p>0.05) and race/color (p >0.05). However, there was statistical significance for the age variable, observed in the age groups from 30 to 39 years old (p<0.05) and 60 years old and older (p<0.05).

The time elapsed from the onset of symptoms to suspicion in all assessed individuals was 13 days (M_d = 13). The shortest interval for disease suspicion occurred in children younger than 5 years (M_d = 10 days) and in those who had a favorable outcome for cure (M_d = 11 days). Individuals who died had higher medians (M_d = 14) as well as the group of older patients (≥ 50 years), as can be seen in figure 3.

Once HVL suspicion is raised, it takes up to 13 days (higher value without outliers) for diagnostic confirmation and institution of specific pharmacological treatment. In the group of children, there is less dispersion of data and the beginning of treatment is faster when compared to the other groups (Figure 4).

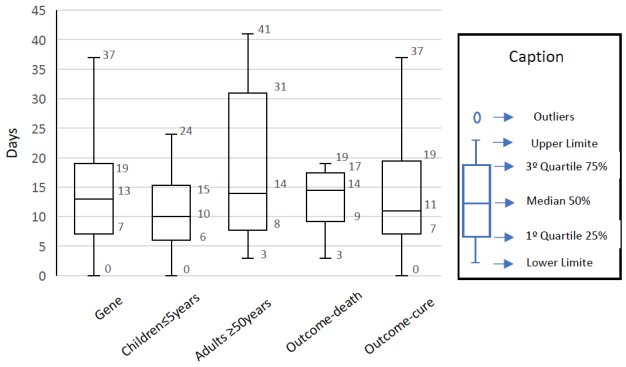

Figure 3. Intervals in days from the onset of symptoms to human visceral leishmaniasis suspicion by assessed groups, Araguaína-TO, 2015-2019.

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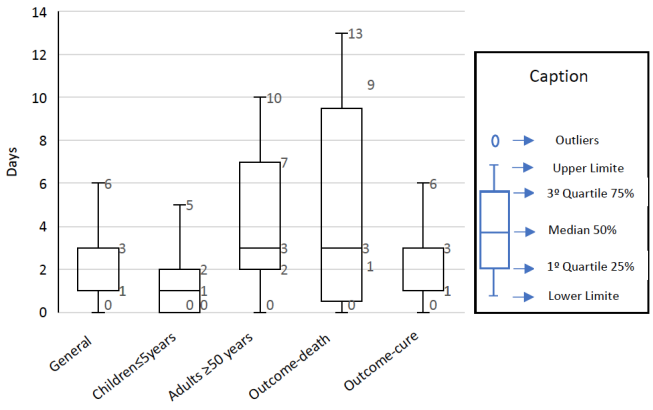

Figure 4. Intervals in days from suspicion to initiation of treatment of human visceral leishmaniasis by evaluated groups, Araguaína-TO, 2015-2019.

The opportunity for cure can be seen in Figure 5, through a broader temporal evaluation, starting from the date of the first symptoms until the start of treatment. In the group with a cure outcome, this occurred within 50 days (M_d=15), the longer intervals were concentrated in the group of older patients (M_d=18) and in those who died (M_d=20).

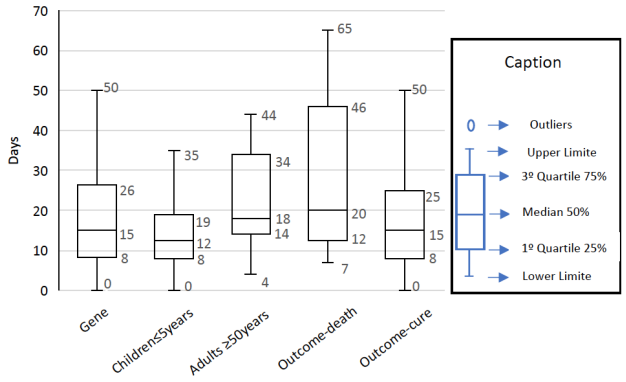

Figure 5. Intervals in days from the onset of symptoms to human visceral leishmaniasis treatment by assessed groups, Araguaína-TO, 2015-2019

DISCUSSION

In epidemiological and clinical studies, there is a tendency for males to be more affected by HVL. The cause remains uncertain, but it is argued that men perform occupational and behavioral activities that facilitate exposure to risky environments. Moreover, under experimental conditions, differences were observed in relation to parasitic load and clinical manifestation according to gender.[10–13]

Low educational level is a frequent feature in epidemiological studies in Brazil and worldwide. It is argued that this population faces situations of vulnerability, mainly due to low socioeconomic conditions, as is the case of many individuals affected by HVL.[10,14–17] In addition to this, these data can be presented in this way, due to the fact that, as in this research, visceral leishmaniasis affected mostly children who are still climbing the initial grades of early childhood education.

The predominance of brown skin color in this study (88.5%) is in agreement with data from Pernambuco and Ceará,[16,17] different from what the study in São Paulo presents, in which 49.3% of cases occurred in white individuals and only 26.8% in brown.[15] It may have contributed to the results found in Araguaína. The 61.6% brown population in Araguaína may have contributed to the results found in Araguaína. This population is also larger in the entire North (72.2%) and Northeast (62.5%) regions of Brazil.[18,19]

As for analysis by age group, children (< 10 years) totaled 110 cases, which corresponds to more than half of all records; however, they maintained low lethality when compared to other age groups, especially those of young adults (30 to 39 years old) and older adults (≥ 60 years old), who showed a statistically significant association (p< 0.001), with a high risk of progressing to death when compared to younger people (RR= 16.09 and 7.08).

Children in the municipality of Araguaína presented greater opportunities for healing than adults, possibly explained by the fact that they are commonly in contact with health services, to meet the vaccination schedule and childcare follow-ups in primary care.

This greater proximity would facilitate access to care and consequent surveillance of this group. Furthermore, it is likely that parents or guardians are more likely to quickly seek care in the face of an illness in children; on the other hand, an adult can seek to palliate their symptoms, postponing their medical assessment, which should be regular.

At the national level, the study carried out from 2017 to 2019 confirms that mortality in Brazilians over 50 years of age is the highest (17.3%), and the lowest occurs in children (4.6%).[20] The age variable, especially if associated with comorbidities, but not gender, has shown relevance for the death outcome from HVL in some studies carried out in Brazil. In Sergipe, for instance, the highest concentration of cases occurs in the first decade of life, but with the lowest lethality, which increases every decade reaching 39.3% in people aged 60 years and older.[3,12,21]

Accordingly, the older adults (≥ 60 years) in this study reached a mortality rate of 33.3%, the highest, followed by young adults (30-39 years) with a percentage of 13.3%. It is conjectured that there is a higher risk of death in older adults due to comorbidities that, in addition to aggravating the condition, may make it difficult to suspect HVL. Data from the Pan American Health Organization (PAHO) for the Americas draws attention to the growing proportion of cases in young adults over the years and relates them to HIV co-infection, precisely when individuals are more susceptible to depression of their immune system.[14,17,20,22,23]

When mortality is analyzed with a focus on the time it takes, from the onset of symptoms to health care for suspicion of the disease, according to studies carried out in Brazil, in the years 2007 to 2014, for individuals who

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had a fatal outcome, this time was from 10 to 61 days (M_d = 25 days).[21] However, in recent years (2017 to 2019), this interval has increased, and national medians reach 40 days. The wider intervals were with four Brazilian states, namely: Piauí, Rio Grande do Sul, Rio de Janeiro and Rio Grande do Norte, equivalent to 80, 76, 69 and 63 days, respectively.[23]

In children under 5 years of age, the national median of those with the outcome of death was 26 days and those who progressed to cure, 24 days. In contrast, in adults over 50 years of age, the median in Brazil was 49 days for those who progressed to cure and 44 days for death, that is, shorter intervals in the death outcome. This result contrasts with the present study and only highlights the hypothesis that lethality is not only inherent to the rapid diagnosis, although extremely important, but that individual factors of patients and specific to each region should be better investigated.[23]

In a study conducted with older adults in Campo Grande-MS, Brazil, from 2000 to 2013, whose lethality rate was 20%, the multivariate analysis revealed that the time between the onset of symptoms and the therapeutic intervention greater than 60 days was associated with up to the highest lethality. Likewise, in the results found in the present study, this temporal margin was conferred exactly on the group of patients who did not achieve cure and died from HVL, reinforcing the hypothesis that more than two months of lack of opportunity for treatment may be a predictor of worse outcomes.[11,24]

It is recommended in Brazil that, based on HVL suspicion, the case must be notified, investigated and closed at Notifiable Diseases Information System (SINAN), within a maximum period of 60 days, with a final diagnosis made accurately and as early as possible. As shown in the data, all suspected cases were investigated in a timely manner, in accordance with what is required by the information systems[3,5]. In addition to this, the opportunity for suspecting HVL in Araguaína is satisfactory when compared to other regions of the country.

The presentation of a shorter time between the onset of symptoms and treatment may suggest users' non-delayed access in search of care and health professionals' ability to list HVL as a suspected disease. This possibly translates into greater contact with these professionals in the service line, since leishmaniasis is endemic in the city.

This has also been made possible thanks to the significant progress in HVL diagnosis in recent decades, with the introduction of technologies such as rapid tests, which have gained prominence for their practicality, allowing the immediate initiation of treatment, serving since 2010 as a confirmatory test methodology in the Unified Health System (SUS).[5,23,25]

Therefore, the delay in starting patient treatment has been associated with risk factors for death,[21] and the results of this research confirm such conditions, in the observation that five days made the difference when comparing the group of patients who concluded the case by cure (M_d=15) with the group of those who evolved to death (M_d=20).

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AUTHORS' CONTRIBUTIONS

Millena Pereira dos Santos and **Jardel Martins Ferreira** contributed to the conception, article design, analysis and writing of the article; **Marco Augusto Giannoccaro da Silva** and **Katyane de Sousa Almeid**a contributed to the planning and design of the article, review and final approval of the article.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.