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Clinical-epidemiological profile of patients with dengue with warning signs and severe dengue in a University Hospital

Perfil clínico-epidemiológico de pacientes com dengue com sinais de alarme e dengue grave em Hospital Universitário

Perfil clínico-epidemiológico de pacientes con dengue con signos de alarma y dengue grave en un Hospital Universitario.

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ABSTRACT

Introduction: Dengue is a public health-relevant arboviral disease that can progress to severe forms. **Objective:** To understand the epidemiological profile of patients hospitalized with a diagnosis of severe dengue at a university hospital in the northern region of Brazil. **Method:** Epidemiological, descriptive, census-based, retrospective study of a population of 400 medical records and a sample of 151 records of patients hospitalized for dengue from January 2019 to April 2024. A semi-structured form was used containing sociodemographic variables, year of diagnosis, preexisting conditions, among others. Variables were processed in the Statistical Package for the Social Sciences (SPSS). Chi-square and/or Fisher's exact tests were performed, a significance level of 5% was adopted, and the study was approved by an ethics committee. **Results**: The patient profile was predominantly female, mixed race (pardo), aged 10-19 years; hospitalization peaked in 2021, and 2022 had the highest number of severe cases. Persistent vomiting, increased hematocrit, and lethargy and/or irritability were associated with greater likelihood of an unfavorable disease course. **Implications:** The profile of patients with severe dengue comprised adolescents, female, mixed race (pardo), students, from the urban area of Araguaína. Collaborative approaches, professional capacity building, and strengthening school-based health education actions are necessary.

KEYWORDS: Dengue; Arboviral Infections; Hospitalization; Health Surveillance; Viral Hemorrhagic Fevers.

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INTRODUCTION

Dengue is a vector-borne viral infection that predominates in warm, tropical regions. Transmission occurs continuously between humans and mosquitoes, with Aedes aegypti as the primary vector and Aedes albopictus serving as a secondary vector in certain areas[1]. Approximately 400 million infections are reported worldwide each year. Its incidence has increased 30-fold over the past five decades, underscoring its growing public health importance[2].

In Brazil, the first half of 2024 saw roughly 6.2 million probable dengue cases, the highest number reported in a single year, corresponding to an incidence exceeding 3,000 cases per 100,000 inhabitants, and resulting in more than four thousand deaths during the period[3].

In the state of Tocantins, located in Brazil's north-central region, the first documented cases of dengue virus transmission occurred in 1991 in the municipality of Araguaína. Since then, the virus has circulated intensely and continuously throughout the state[4]. In 2022, Tocantins experienced a marked increase in dengue cases, which exceeded eighteen thousand and were reported across 124 municipalities. This scenario highlights the need for thorough investigations into viral circulation in the region[5].

The dengue arbovirus comprises four distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4), each capable of causing infection and a wide range of clinical manifestations (6). The disease may be asymptomatic or symptomatic. When symptomatic, presentation can be systemic and dynamic with variable clinical manifestations, ranging from mild forms to severe conditions with risk of progression to death[7].
Severe dengue is characterized by intense plasma leakage, shock syndrome, respiratory failure, and significant bleeding, particularly of gastrointestinal or intracranial origin. In addition, vital organ involvement—such as liver, heart, and brain—can occur and is associated with a higher risk of mortality [1,8].

The World Health Organization (WHO) classification in use since 2009 divides dengue into severe and non-severe forms, the latter being further subdivided into dengue with warning signs and dengue without warning signs. Warning signs include thrombocytopenia, increased hematocrit, abdominal pain, persistent vomiting, hemorrhagic manifestations, lethargy, restlessness, hepatomegaly, and laboratory hemoconcentration[8].

The pathophysiological process underlying severe dengue is complex and incompletely understood. It is postulated to involve genetic and viral factors as well as host immune components. Moreover, despite dengue's long-recognized impact, there is no specific antiviral treatment, and licensed vaccines have shown limited benefit in clinical contexts [8,9].

Accordingly, optimizing care for patients with severe dengue in hospital settings is essential to prevent deterioration and save lives. Therefore, this study aimed to characterize the epidemiological profile of patients hospitalized with a diagnosis of severe dengue at a university hospital in the northern region of Brazil.

METHODS

An epidemiological, quantitative, descriptive, census-based, retrospective study was conductedusing secondary data collected from hospitalization records of patients diagnosed with dengue with warning signs and severe dengue at the university hospital located in the municipality of Araguaína, TO. The study followed the guidance of the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement[10].

For case definition, the still-current WHO 2009[8] criteria were adopted, which classify dengue with warning signs as including severe and continuous abdominal pain; persistent vomiting; mucosal bleeding/other hemorrhages; lethargy or irritability; postural hypotension or syncope; fluid accumulation (ascites, pleural effusion, pericardial effusion); and a progressive increase in hematocrit. Severe dengue is characterized by shock or respiratory distress, severe bleeding, and severe organ involvement.

The study population comprised 400 medical records of patients with suspected dengue. Of these, 249 were excluded for not meeting the inclusion criteria, resulting in a sample of 151 medical records of patients hospitalized for dengue during the period from January 2019 to April 2024.

Data collection was census-based and took place from September 2024 to January 2025; it was conducted by two trained medical students. All medical records of patients hospitalized at the university hospital with a diagnosis of dengue with warning signs and/or severe dengue, and archived in the medical

records and statistics archive service (SAME) for the period January 2019 to April 2024, were included, as these corresponded to the historical series made available by SAME at the start of the research.

Excluded were medical records of patients diagnosed with other arboviral infections, hospitalizations not related to dengue, incomplete records due to patient discharge against medical advice, and records not archived in SAME, those outside the study period, and/or those lacking variables necessary for analysis.

A semi-structured form, adapted by the authors, was used and included the following variables: year of diagnosis, sex, age, city, zone, education level, race/skin color, occupation, preexisting conditions (diabetes mellitus, systemic arterial hypertension, and peptic acid disease), clinical manifestations of warning signs and severe dengue, platelet count, length of hospital stay, and clinical outcome.

Age was grouped into the following ranges: 0–9 years, 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, and ≥60 years. Platelet count was categorized into thrombocytopenia (<150,000/mm3) and normal range (150,000–400,000/mm3)[11]. Data were tabulated and organized using Microsoft Excel® 2024 spreadsheets and subsequently transferred to the *Statistical Package for the Social Sciences* (SPSS), version 20.1 for *Windows*.

The study employed descriptive, exploratory, and inferential statistical analyses. Descriptive statistics were used to describe and quantify demographic characteristics, clinical symptoms, and serological markers divided into two groups: severe dengue and dengue with warning signs. Associations between groups were analyzed using Pearson's chi-square (x2) test of independence or, when necessary, *Fisher* exact test.

For all tests, effect sizes were determined and analyses of adjusted standardized residuals (ASRs) were performed for the purpose of manual calculation of (*Odds ratios* - ORs) within the x^2 framework. Only associations for which tables of adjusted standardized residuals showed cell values greater than two in SPSS (critical value 1.96 on the Z-score) were considered for OR calculation. Tables containing ASRs and ORs are not presented here, as they were described in the Results section. The significance level adopted was an alpha error of 5% with a 95% confidence level.

This research complied with all human subjects research recommendations contained in Resolution Nº. 466/2012 of the National Health Council. The study was approved by the Research Ethics Committee (CEP) of the Tropical Diseases Hospital of the Federal University of Northern Tocantins under opinion number 7.237.401.

RESULTS

The study included 151 medical records of dengue cases with warning signs. Of these, 50 progressed to severe dengue (33.1%). Overall, the year with the most hospitalizations was 2021, accounting for 30.4% (n = 46) of the cases. In addition, 50.3% (n = 46) were female and 32.4% (n = 49) were aged 10–19 years. A predominance of self-declared mixed-race individuals was observed: 84.7% (n = 128).

Table 1. Sociodemographic characteristics of dengue cases with warning signs and severe dengue. Araguaína, Tocantins, Brazil, 2025.

Variables	General (n=151)	Dengue		Dengue (Warning signs; serious)	
		Serious (n=50)	Alarm signals (n=101)	X^2 (gl)	P-value (φ)
Year of hospitalization					
2019	45(29,8%)	7 (14%)	38 (37,6%)		
2020	9(6%)	0(0%)	9(8,9%)		
2021	46(30,5%)	9(18%)	37(36,6%)	39,93 (5)	<0,000** (0.021)
2022	39(25,8%)	27(54%)	12(11,9%)		
2023	5(3,3%)	3(6%)	2(2%)		
2024	7(4,6%)	4(8%)	3(3%)		
Sex					
Feminine	76(50,4%)	31(62%)	45(44,6%)	4,072 (1)	0,044* (0,164)
Masculine	75(49,6%)	19(38%)	56(55,4%)		
Age range (years)					
<9	30(19,9%)	7(14%)	23(22,77%)		
10-19	49(32,5%)	20(40%)	29(28,71%)		
20-29	23(15,2%)	12(24%)	11(10,89%)	11,328 (6)	0,069 (0,277)
30-39	21(13,9%)	3(6%)	18(17,83%)		
40-49	9(6%)	2(4%)	7(6,93%)		
50-59	13(8,6%)	3(6%)	10(9,9%)		
≥ 60	6(4%)	3(6%)	3(2,97%)		
Race/skin color					
Black	4(2,6%)	1(2%)	3(2,9%)	1 (2)	1 (0,032)
Brown	128(84,8)	43(86%)	85(84,2%)		
White	19(12,6%)	6(12%)	13(12,9%)		
Education					
Illiterate	3(2%)	2(4%)	1(1%)		
Maternal	2(1,3%)	0(0%)	2(2%)		
Incomplete primary education	47(31,1%)	13(26%)	34(33,6%)		
Complete elementary education	2(1,3%)	0(0%)	2(2%)	9,89 (8)	0,228 (0,268)
Incomplete secondary education	12(7,9%)	5(10%)	7(7%)		
High school diploma	17(11,3%)	5(10%)	12(11,8%)		
Incomplete higher education	6(4%)	4(8%)	2(2%)		

Completed higher education	14(9,3%)	2(4%)	12(11,8%)		
Not informed	48(31,8%)	19(38%)	29(28,8%)		
Occupation					
Student	59(39%)	20(40%)	39(38,6%)		
From home	4(2,7%)	2(4%)	2(2%)		
Gen.serv. assis.	4(2,7%)	3(6%)	1(1%)	27,99	0,313
Others[a]	40(26,5%)	9(18%)	31(30,7%)	(28)	(0,462)
Not informed	44(29,1%)	16(32%)	28(27,7%)		
Zone					
Urban	148(98%)	50(100%)	98(97%)	1,51	0,551
Rural	3(2%)	0(0%)	3(3%)	(1)	(0,100)
History of comorbidity					
Yes***	25(16,5%)	7(14%)	18(17,8%)	5,83**	0,265**
No	126(83,5)	43(86%)	83(82,2%)	(5)	(0,208)
City					
Araguaína	105(69,5)	32(64%)	73(72,2%)		
Tocantinópolis	7 (4,6%)	4(8%)	3(3%)		
Arapoema	6 (3,9%)	2(4%)	4(4%)	21,79	0,550
Colinas -TO	5 (3,3)	2(4%)	3(3%)	(24)	(0,385)
Others[b]	28 (18,7)	10(20%)	18(17,8%)		

Legend: * p<0.05; ** Fisher's exact test with Cramér's V; *** Systemic arterial hypertension, Diabetes Mellitus, peptic disease; Othersa: domestic worker, cargo checker, merchant, patrol operator, mechanic, pool attendant, cleaning services assistant, commercial manager, teacher, nurse, farmer, lawyer, nursing technician, retiree, carpenter, administrative assistant, butcher, salesperson, truck driver, gas station attendant, foreman, seamstress, prospector, hotelier, inspector; Othersb: Nova Olinda, Xambioá, Darcinópolis, Wanderlândia, Bernardo Sayão, Palmeiras-TO, Colmeia, Araguanã, Pau d'Arco, Aparecida de Goiânia, Aragominas, Estreito, Carmolândia, Guaraí, Itacajá, Campos Lindos, Ananás, Aguiarnópolis, Babaçulândia, Bandeirantes-TO, Santa Terezinha-TO.
Source: prepared by the authors, 2025.

A chi-square test of independence was performed, revealing a significant association between dengue classification and year of hospitalization; however, the effect size was negligible (x2 (5) = 39.93; p < 0.000; φ = 0.021). Analysis of adjusted standardized residuals showed that only 2019, 2021, and 2022 were associated with cases of severe dengue and dengue with warning signs. In 2019, patients had 1.31 and 0.08 times greater odds of progressing to severe dengue than in 2021 and 2022, respectively. Conversely, cases in 2021 showed 0.1 greater odds of progression to severe dengue compared with 2022.

In addition, tests found a significant association between dengue classification and sex, although the effect size was weak (x2 (1) = 4.072; p < 0.044; φ = 0.164). Despite being significant with a weak effect size, in the present study females had 2.027 times greater odds of developing severe dengue compared with males.

Table 2 presents the profile of clinical manifestations in the analyzed population. Persistent vomiting predominated at 56.9% (n = 86), and absence of mucosal bleeding and/or other hemorrhages was 51.6% (n = 78). Additionally, a majority did not present lethargy or irritability (85.5%, n = 129), nor hematocrit elevation (95.5%, n = 144). Compared with cases with warning signs, patients with severe dengue were more likely to have a hematocrit increase of ≥10% (10%, n = 5) and lethargy or irritability (24%, n = 12). Regarding clinical outcome, 94.7% (n = 143) recovered and 0.6% (n = 1) died.

Hemorrhages, lethargy or irritability, and progressive hematocrit increase were associated with dengue and its clinical progression. However, there was no relevant relationship between abdominal pain, postural hypotension or presyncope, fluid accumulation, hepatomegaly ≥2 cm, length of hospital stay, and

platelet range.

When analyzing effect sizes for variables with significant associations, mucosal bleeding/other hemorrhages and clinical outcome demonstrated moderate effect sizes (φ = 0.305; φ = 0.336, respectively), whereas persistent vomiting, lethargy or irritability, and progressive hematocrit increase demonstrated weak effect sizes (φ = 0.185; φ = 0.188; φ = 0.180, respectively).

Thus, odds ratios were calculated for the significant variables, showing that patients with persistent vomiting had 2.29 times greater odds of progressing to severe dengue; individuals with lethargy or irritability had 2.39 times greater odds of severe disease; those with mucosal bleeding/other hemorrhages had 3.88 times greater odds of clinical worsening compared with patients without these signs; and patients with progressive hematocrit increase had 5.5 times greater odds of unfavorable progression.

Table 2. Clinical manifestations of dengue cases with warning signs and severe dengue. Araguaína, Tocantins, Brazil, 2025.

		Dengue		Dengue (Warning signs; serious)	
Variables	**General (n=151)**	**Serious (n=50)**	**Warning signs (n=101)**	**X^2 (gl)**	**P-value (φ)**
Intense and continuous abdominal pain					
yes	103 (68,3%)	39 (78%)	64 (63,3%)	3,303	0,069
no	48 (31,7%)	11 (22%)	37 (36,7%)	(1)	(0,149)
Persistent vomiting					
yes	86 (56,9%)	35 (70%)	51 (50,5%)	5,190	0,023*
no	65 (43,1%)	15 (30%)	50 (49,5%)	(1)	(0,185)
Mucosal bleeding/other hemorrhages					
yes	73 (48,3%)	35 (70%)	38 (37,6%)	14,038	<0,000*
no	78 (51,7%)	15 (30%)	63 (62,4%)	(1)	(0,305)
Lethargy or irritability					
yes	22 (14,6%)	12 (24%)	10 (9,9%)	5,341	0,021*
No	129 (85,4%)	38 (76%)	91 (90,1%)	(1)	(0,188)
Postural hypotension or syncope**					
yes	9 (5,9%)	5 (10%)	4 (3,9%)	2,176	0,158
no	142 (94,1%)	45 (90%)	97 (96,1%)	(1)	(0,120)
Fluid accumulation (ascites, pleural effusion, pericardial effusion)					
yes	27 (17,9%)	12 (24%)	15 (14,8%)	1,906	0,167
no	124 (82,1%)	38 (76%)	86 (85,2%)	(1)	(0,112)
Hepatomegaly ≥2 cm**					
yes	10 (6,6%)	6 (12%)	4 (4%)	3,496	0,083

no	141 (93,4%)	44 (88%)	97 (96%)	(1)	(0,152)
Progressive increase in hematocrit**					
yes	7 (4,6%)	5 (10%)	2 (2%)	4,866	0,040*
no	144 (95,4%)	45 (90%)	99 (98%)	(1)	(0,180)
Hospitalization period					
Up to 5 days	123 (81,5%)	38 (76%)	85 (84,1%)	1,474	0,225
≥6 days	28 (18,5%)	12 (24%)	16 (15,9%)	(1)	(0,099)
Platelet range**					
Thrombocytopenia (<150mil/mm3)	142 (94%)	46 (92%)	96 (95%)		
Normal range (150-400 mil/mm3)	9 (6%)	4 (8%)	5 (5%)	0,555 (1)	0,480 (0,061)
Clinical outcome**					
Cure	143(94,7%)	42(84%)	101(100%)	15,935	0,000*
Death due to complications	1(0,7%) 7(4,6%)	1(2%) 7(14%)	0(0%) 0(0%)	(2)	(0,336)
External transfer due to injury					

Legend: * p<0.05; ** Fisher's exact test.
Source: prepared by the authors, 2025.

DISCUSSION

This study analyzed the clinical-epidemiological profile and factors associated with progression to severe dengue in hospitalized patients. Analysis of demographic, clinical, and laboratory variables allowed identification of characteristics that lead to the severe form and divergences from the current literature.

The year with the highest number of hospitalizations was 2021, while 2022 showed the highest percentage of severe cases. This result differs from another study [12], which reported a reduction in dengue cases in 2021, possibly due to the COVID-19 pandemic, a circumstance that may explain increased severity the following year due to reduced vector-control efforts and restrictions imposed the prior year.

Regarding sex and risk of severe dengue, international studies[1,13] indicate that women are more predisposed. However, other research reports higher incidence among men, attributed to greater engagement in outdoor activities[2].

In this study, individuals identifying as brown (pardo) predominated among cases. Conversely, a national study[14] found higher dengue frequency among White individuals. These discrepancies, taken alone, do not predict dengue risk but relate to factors of movement to endemic areas, increasing exposure to the vector. Socioenvironmental factors associated with social inequality that disproportionately affect Black, brown, and Indigenous populations—who more often reside in housing that favors mosquito proliferation—may explain higher incidence in these groups[15].

Although age group and education did not show significant associations in this study, the literature documents greater risk of severe disease at the extremes of age, such as ≥65 years and in children[13]. In the present analysis, however, adolescents aged 10–19 years showed greater predisposition, possibly due to increased capillary fragility in younger age ranges[1].

Regarding education, individuals with higher educational attainment had lower odds of progressing to the severe form, likely because they are more able to recognize warning signs and seek care early[1]. Furthermore, Brazilian Institute of Geography and Statistics (IBGE) data indicate that Black, brown, and Indigenous populations experience greater educational inequalities compared with Whites, which contributes to delayed recognition of disease signs and symptoms[15].

A predominance of cases from urban areas was observed, consistent with previous studies demonstrating higher dengue incidence in urban compared with rural settings [2]. This pattern is explained by population growth, high population density, unplanned urbanization, and climatic conditions that favor vector proliferation[16].

Concerning preexisting conditions, the comorbidities evaluated (diabetes mellitus, systemic arterial hypertension, and peptic disease) did not show a relevant association with disease severity. This finding contrasts with other publications in which diabetes mellitus and hypertension were notable risk factors for more severe disease[17]. Moreover, because these comorbidities are more frequent in older populations, age-related physiological changes affect the immune response to viral infection, exacerbating disease course[18].

Demographic analysis showed that Araguaína, Tocantins, had the largest number of cases because the municipality houses the reference hospital for this study. This finding is expected, as it is the regional health hub for the northern macro-region of the state. Such centralization allows patients from neighboring municipalities to be referred to the tropical disease reference center, especially in severe cases[19].

Abdominal symptoms, such as abdominal pain and vomiting, are common in dengue. One study that correlated dengue cases with acute abdomen found abdominal pain, nausea, and vomiting in 15%, 20%, and 16% of patients, respectively. These symptoms can be associated with development of acute abdomen in dengue, which may occur for various reasons, including rupture of splenic hematoma, gastrointestinal hemorrhage due to disease-associated coagulopathy, and, more rarely, direct invasion of abdominal organs[20].

The presence of mucosal bleeding and/or other hemorrhages is an indicator of severity. The literature reports that hemorrhagic manifestations carry variable risk, from self-limited episodes such as epistaxis or gingival bleeding to potentially fatal gastrointestinal hemorrhages[1]. In this study, however, thrombocytopenia was not associated with clinical severity, a result that corroborates a cross-sectional study conducted in Colombia[21]. Nevertheless, it is well established that platelet reduction and the consequent risk of bleeding are intrinsically linked to immune dysfunction, in which cytokines and virus-specific antibodies destroy platelets—a mechanism that contributes to the pathogenesis of bleeding[1].

Although orthostatic hypotension or presyncope were less associated with disease severity in the present investigation, the literature indicates these symptoms are linked to dengue severity. These manifestations are common signs of dehydration; rehydration is a core element of treatment for dengue-related events to prevent disease worsening[22].

With respect to fluid accumulation, although not, by itself, a marker associated with greater severity in this study, the literature indicates that pleural effusion is closely associated with severe disease. Pulmonary involvement may reflect multisystem viral involvement, inflammatory response, and the plasma leakage characteristic of dengue[18].

Early identification of plasma leakage is essential to prevent complications, yet no WHO classification fully encompasses this subgroup. Moreover, the definition and refinement of diagnostic criteria for plasma leakage have been persistently neglected, resulting in a scarcity of reports describing this manifestation[1,23].

This study did not demonstrate hepatomegaly as related to unfavorable disease progression, unlike lethargy and/or irritability, which showed association with the severe form. In contrast, the literature suggests that lethargy and hepatomegaly are related to more severe dengue cases[24]. These findings are critical for resource-limited settings, such as border areas; early recognition of warning signs for disease progression will help individuals seek medical care more effectively and in a timely manner.

Regarding progressive hematocrit increase, it was found to be a predictor of progression to the severe form. This finding aligns with other literature indicating that hemoconcentration is significantly associated with dengue hemorrhagic fever, often resulting from changes such as dehydration and increased capillary permeability[25].

A retrospective study in Bangladesh[26] identified a length of hospital stay slightly greater than 5 days, mainly among middle-aged patients who remained hospitalized longer than younger patients. In this study, a similar trend was observed but without association with clinical severity. The discrepancy may relate to the sample's age distribution, which consisted predominantly of children and adolescents. It is important to emphasize that timely hospital admission is fundamental to reduce the likelihood of severe disease, as delays favor progression to more severe presentations[2].

Regarding outcome, an overall reduction in dengue fatality was observed. A study in the Americas suggests this decline may be associated with advances in health surveillance actions, health education, and population awareness. Thus, despite increased case numbers in recent years, a lower proportion of severe forms and, consequently, deaths have been recorded[27].

Dengue mortality is intrinsically associated with symptoms of the severe form, which include coagulopathy with irreversible systemic alterations. Hence, inability to predict warning signs early and inadequate clinical management may be determining factors for a fatal outcome[28].

This research has limitations in the study period analyzed, since the temporal window examined may not capture robust changes in the epidemiology of severe dengue. As secondary data were used, there is reliance on completion of medical records, which may lead to information bias owing to incomplete and nonstandardized entries by the various healthcare professionals involved. In addition, study data were obtained from previously recorded clinical records, making it impossible to fully control for missing or inconsistent clinical and laboratory information, which may limit analysis of possible associations.

CONCLUSION

The profile of hospitalized patients diagnosed with severe dengue consisted predominantly of adolescents, female individuals, of mixed race, students, and residents of urban areas in Araguaína. Symptoms such as bleeding, persistent vomiting, progressive increase in hematocrit, and lethargy or irritability were identified and were associated with a higher likelihood of progression to an unfavorable clinical outcome of dengue. In addition, the studied region is hyperendemic for dengue, making it necessary to strengthen collaborative approaches (One Health) to dengue in school settings and among healthcare teams, in order to promote greater awareness through health education and to enable early recognition of severity symptoms by healthcare professionals, thereby preventing worsening of clinical conditions.

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RESEARCH ETHICS COMMITTEE APPROVAL

This study was approved by the Research Ethics Committee of the Tropical Diseases Hospital of the Federal University of Tocantins (HDT/UFT), under Opinion No. 7,237,401, Certificate of Presentation for Ethical Review (CAAE) No. 83766724.8.0000.8102.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.