

Hospitalization of Pediatric Patients with Oral and Pharyngeal Cancer in Brazil's National Health System from 2008 to 2023

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Hospitalizações de Pacientes Pediátricos com Câncer Oral e Faríngeo no Sistema Único de Saúde entre 2008 e 2023

Hospitalizaciones de Pacientes Pediátricos con Cáncer Oral y Faríngeo en el Sistema Único de Salud Pública del Brasil entre 2008 y 2023

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ABSTRACT

Introduction: Pediatric cancer patients often need inpatient admissions due to treatment or complications, but this variable was not systematically evaluated in Brazil's public health services. **Objective:** To evaluate inpatient admissions of children and adolescents with oral and pharyngeal cancer in the Brazilian public healthcare system. **Method:** Population-based approach study from 2008 to 2023 of the annual hospitalizations recovered and normalized per 1,000,000 inhabitants aged 0-19 years (person-year incidence), in addition to the annual deaths, hospital mortality (%), length of hospital stay (days), costs (R\$), and conditions (elective or urgent). The significance level was adjusted to 5%, according to Prais-Winsten generalized linear regression models. **Results:** From 2008 to 2023, 24,662 inpatient admissions were approved, 50.5% of which classified as urgent. The incidence was 395 per 1,000,000 0-19 aged children. During this period, 626 deaths were reported, representing 2.5% of all hospitalizations. Moreover, the mean length of stay was 5.8 days and the mean cost was R\$ 1,526.87. There was a decreasing time trend in the incidence of hospitalizations of children and adolescents (both $p < 0.001$). The incidence and hospital mortality were significantly lower among children and adolescents compared to other age groups (all $p < 0.001$). **Conclusion:** Over the last 16 years, an important number of inpatient admissions of children and adolescents with oral and pharyngeal cancer in the Brazilian public healthcare system was recorded, revealing specific patterns of hospital morbidity.

Key words: Oral Neoplasms; Pharyngeal Neoplasms; Child; Adolescent; hospitalization.

RESUMO

Introdução: Pacientes pediátricos com câncer frequentemente necessitam de internações por causa do tratamento ou complicações, mas essa variável não foi sistematicamente avaliada nos serviços públicos de saúde do Brasil. **Objetivo:** Avaliar as internações de crianças e adolescentes em razão do câncer oral e faríngeo no sistema público de saúde brasileiro. **Método:** Em uma abordagem populacional entre 2008 e 2023, os números anuais das hospitalizações foram recuperados e normalizados por 1.000.000 de habitantes com idades entre 0 e 19 anos (incidência por pessoa-ano). Além disso, foram recuperados os números anuais de óbitos, mortalidade hospitalar (%), duração (dias), custos (R\$) e circunstâncias (eletiva ou urgente). O nível de significância foi ajustado para 5%, considerando modelos de regressão linear generalizada de Prais-Winsten. **Resultados:** De 2008 a 2023, 24.662 internações foram aprovadas, considerando 50,5% como internações urgentes. A incidência foi de 395 por 1.000.000 de crianças de 0 a 19 anos. Nesse período, foram relatados 626 óbitos, representando 2,5% de todas as internações. Além disso, as internações duravam em média 5,8 dias e custaram em média R\$ 1.526,87. Houve uma tendência temporal decrescente na incidência de internações entre crianças e adolescentes (ambos $p < 0,001$). A incidência e a mortalidade hospitalar foram significativamente menores entre crianças e adolescentes em comparação com outras faixas etárias (todos $p < 0,001$). **Conclusão:** Nos últimos 16 anos, foi registrado um número importante de internações de crianças e adolescentes por conta do câncer oral e faríngeo no sistema público de saúde brasileiro, revelando padrões específicos de morbidade hospitalar. **Palavras-chave:** Neoplasias Buciais; Neoplasias Faríngeas; Criança; Adolescente; Hospitalização.

RESUMEN

Introducción: Los pacientes pediátricos con cáncer a menudo necesitan hospitalización debido al tratamiento o a complicaciones, pero esta variable no se ha evaluado sistemáticamente en los servicios de salud pública del Brasil. **Objetivo:** Evaluar las hospitalizaciones de niños y adolescentes debido al cáncer oral y faríngeo en el sistema público de salud brasileño. **Método:** En un enfoque a nivel poblacional entre 2008 y 2023, se recuperaron los números anuales de las hospitalizaciones y se normalizaron por cada millón de habitantes de entre 0 y 19 años (incidencia por persona-año). Además, se recuperaron los números anuales de muertes, mortalidad hospitalaria (%), duración (días), costos (R\$) y circunstancias (electiva o urgente). El nivel de significación se ajustó al 5%, considerando modelos de regresión lineal generalizada de Prais-Winsten. **Resultados:** De 2008 a 2023, se aprobaron 24.662 hospitalizaciones, considerando el 50,5% como hospitalizaciones urgentes. La incidencia fue de 395 por cada millón de niños de 0 a 19 años. En este período, se reportaron 626 muertes, lo que representa el 2,5% de todas las hospitalizaciones. Además, las hospitalizaciones duraron en promedio 5,8 días y costaron en promedio R\$ 1.526,87. Hubo una tendencia temporal decreciente en la incidencia de hospitalizaciones entre niños y adolescentes (ambos $p < 0,001$). La incidencia y la mortalidad hospitalaria fueron significativamente menores entre niños y adolescentes en comparación con otros grupos de edad (todos $p < 0,001$). **Conclusión:** En los últimos 16 años, se registró un número importante de hospitalizaciones de niños y adolescentes debido al cáncer oral y faríngeo en el sistema público de salud brasileño, revelando patrones específicos de morbilidad hospitalaria. **Palabras clave:** Neoplasias de la Boca; Neoplasias Faríngeas; Niño; Adolescente; Hospitalización.

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INTRODUCTION

Worldwide, oral and pharyngeal cancer are frequently diagnosed in adults and older individuals. In fact, the incidence of these types of cancer in children and adolescents is significantly lower when compared to other age groups, primarily due to the limited exposure to risk factors as alcohol and tobacco¹. Less than 10% of all tumors affect pediatric patients, nevertheless², the occurrence and health-related impacts of these malignancies cannot be underestimated, as quality of life and morbimortality^{1,2}. A meta-analysis estimated the prevalence of malignant neoplastic oral lesions among children and adolescents accounting for 1.9% of 64,522 biopsies³.

A 30-year study at a Brazilian reference center for oral and maxillofacial cancer provided valuable insights about the matter. Despite the low occurrence of oral and maxillofacial cancer in pediatric patients at this center (0.8%), the majority of the cases were highly aggressive tumors, as lymphomas (52.7%) and sarcomas (27.3%) and oropharynx was the most predominant anatomical site (38.2%)⁴. This type of malignant tumor depends on the population investigated (*e.g.*, genetic variations and exposure to risk factors)^{1,5}, but the impact of cancer and its treatment in this age group can trigger significant health complications that require immediate and complex care, in addition to routine diagnostic and therapeutic approaches^{6,7}.

It is known that patients with head and neck cancer, including oral and pharyngeal malignant tumors require planned and unplanned hospitalizations. The treatment of these types of malignant tumors may require inpatient admissions due to clinical exams, procedures, or bedside care for treatment-related complications, as chemotherapy and radiotherapy toxicities. In addition to the clinical procedures, healthcare costs impact the patient and the institutions alike^{8,9}.

Although there are studies describing clinical and histopathological characteristics of oral and pharyngeal cancer in pediatric patients in Brazil^{4,10,11}, hospital morbidity and its impacts are a significant gap in the state of the art. To date, there is no study evaluating the inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil. The objective of this study was to evaluate inpatient admissions of children and adolescents with oral and pharyngeal cancer in the Brazilian public healthcare system.

METHOD

A nation-wide investigation with data from all public health services connected to the Brazilian National Health System (SUS) was outlined. Longitudinal, retrospective,

quantitative time series (ecological study)¹² design for a 16-years period from 2008 to 2023, encompassing the entirety of public health service productivity (without restrictions of the type of service).

The primary outcome of the study was the person-year incidence of inpatient admissions of children and adolescents (aged 0-19 years) with oral and pharyngeal cancer. Eligible admissions refer to malignant tumors, regardless of their objectives (diagnostic, therapeutic, or disease and its treatment related complications). This variable was measured by the annual number of Hospital Admission Authorizations (AIHs) approved by SUS, adjusted per 1,000,000 inhabitants, registered by the Hospital Information System (SIH/SUS)¹³, and the estimated population of individuals aged 0-19 years during the period investigated was retrieved from the intercensal projections of “*Instituto Brasileiro de Geografia e Estatística*” (IBGE)¹⁴. As secondary variables, the annual number of deaths, hospital mortality (percentage of deaths per inpatient admissions), mean length of stay (days), mean cost (in Brazilian currency, R\$), and conditions (elective or urgent). In addition, the primary and all secondary variables were also collected for individuals aged 20 or older for comparative purposes.

The data were collected in April 2024 by a sole researcher. The TABNET¹⁵ (Computer Department of the National Health System – DATASUS) was utilized to access the data, following the same stages described in a previous study¹², sequentially selecting the options “*epidemiological information and morbidity*” and “*hospital morbidity*” offered by the tool. The inpatient admissions were filtered by the location of hospitalization (Brazil). The period (2008-2023) and content (primary and secondary variables) were adjusted in their respective boxes. Furthermore, the age group filter was used to adjust for children (0-9 years old), adolescents (10-19 years old) and other age groups (20 years or older). Ultimately, all AIHs requested for malignant tumors of the oral cavity and pharynx were filtered by the list of morbidities, according to the International Statistical Classification of Diseases and Related Health Problems¹⁶ 10th version (ICD-10/C00-C14). The data collected were exported to spreadsheets for further processing and statistical analysis.

For all statistical analyses, Jamovi¹⁷ (version 2.4.11) and PAST¹⁸ (version 4.03) packages were utilized. The significance level was 5% ($\alpha = 0.05$) for all inferential approaches and *p* lower than 0.05 was considered a statistically significant outcome. The person-year incidence for the period was presented along with the median (annual), including the interquartile range (IQR) and the minimum and maximum values. The values were rounded to integers (count data). The correlation

among the incidences was verified with the Spearman correlation matrix, highlighting the coefficient ρ (ρ). The comparisons among the incidences (incidence ratio) were checked with generalized linear models, utilizing a flexible model for under and overdispersion (non-robust or robust variance, respectively), considering negative binomial regression (quasi-Poisson distributions) and maximum likelihood estimation (Log-likelihood ratio).

For temporal trends, autocorrelation was checked using the Durbin-Watson test, and the Prais-Winsten regression was adopted¹⁹. After a logarithmic transformation (\log_{10}) of datasets, the angular coefficients (β_1) were estimated, including their 95% confidence interval (95% CI) [$(\beta_1) \pm \{t\text{-critical value} \times \beta_1\text{-standard error}\}$]. The Annual Percent Change (APC - %) was obtained using the values of β_1 , including its limits [$\{-1+10^{(\beta_1)}\} \times 100$]. When p was not statistically significant, the trend was defined as stationary. When significant, if the value of β_1 was positive or negative, it was defined as increasing or decreasing, respectively. In this analysis, the costs (R\$) of inpatient admissions were annually adjusted by the IPCA (National Consumer Price Index) according to IBGE¹⁴ to mitigate the impact of inflation over time.

The review and approval by the Ethics Committee was waived because only deidentified, anonymized, open access data were utilized (public domain) in compliance with Directive 510/2016 of the National Health Council (CNS)²⁰.

RESULTS

Over the last 16 years in Brazil's public health services, 414,339 inpatient admissions of individuals with oral and pharyngeal cancer were approved, including 24,662 (5.9%) 0-19 years old children and adolescents. Among those, oral and pharyngeal cancer represented 39.6% of all malignant neoplasms of the digestive organs, 11,560 (46.9%) inpatient admissions were for 0-9 age children and 13,102 (53.1%) for adolescents in the 10-19 age group. The median number of inpatient admissions during this timeframe was 722 and 819 per year, respectively, 12,557 (52.1%) were urgent and 12,105 (47.9%) were elective.

Table 1 shows the person-year incidence of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health services (per 1,000,000 inhabitants). The incidence between 2008 and 2023 converged among the age groups, with pronounced variability (IQR) in both, suggesting temporal variations. A pattern emerged in the minimum and maximum values, as the highest ones were observed in the first quartile of the time series (2008 and 2010), while the lowest were observed in the third and fourth quartiles (2019 and 2020), also suggesting temporal variations.

Table 2 shows the characteristics of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health services, including hospital

Table 1. Person-year incidence of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health services from 2008 to 2023 per 1,000,000 inhabitants (2024)

Age group	Person-year incidence	Median (annual)	IQR	Minimum (year)	Maximum (year)
Children (0-9 years old)	393	18.0	25.0	9 (2020)	51 (2010)
Adolescents (10-19 years old)	398	21.5	18.5	13 (2019)	43 (2008)
Overall (0-19 years old)	395	19.5	22.0	11 (2020)	47 (2008)

Caption: IQR = interquartile range.

Table 2. Characteristics of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health services from 2008 to 2023 (2024)

Characteristics	Children (0-9 years old)	Adolescents (10-19 years old)	Overall (0-19 years old)
Deaths	290	336	626
Hospital mortality (%)	2.5	2.6	2.5
Mean length of stay (days)	6.1	5.7	5.8
Mean cost (R\$) per hospitalization	1,686.89	1,432.86	1,526.87
Urgent hospitalization (%)	51.5	49.7	50.5



mortality rate, length of hospital stay, and mean cost of each hospitalization. Adolescents (53.7%) and children (46.3%) died during hospitalization revealing similar hospital mortality for both age groups. Overall, 141,816 hospitalization days were recorded, 46.8% (66,337 days) for children and 53.2% (75,479 days) for adolescents. The costs of inpatient admissions of children and adolescents with oral and pharyngeal cancer between 2008 and 2023 were R\$ 33,003,906.93, R\$ 17,403,467.21 (52.7%) for children and R\$ 15,600,439.72 (47.3%) for adolescents.

From 2008 to 2023, the person-year incidence of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health service was significantly, positively and very strongly correlated ($p < 0.001$ and $\rho = 0.944$), indicating a similar pattern of temporal variation. Table 3 shows the temporal trends of the person-year incidence and other characteristics of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health service. A decreasing temporal trend of the incidence of inpatient admissions for both age groups was observed over the past 16 years, as well as stationary temporal trends of the hospital mortality and of the proportion of urgent hospitalizations. However, an increasing temporal trend in the length (days) and mean costs (R\$) of each inpatient admission of children was observed, contrary to adolescents (both stationary).

Ultimately, Table 4 shows the comparison of the person-year incidence and other characteristics of inpatient admissions among children, adolescents and other age groups with oral and pharyngeal cancer in Brazil's public health services. There was no difference of mean length of stay (days), mean cost (R\$) per hospitalization, and proportion of urgent hospitalizations. However, the incidence per 1,000,000 inhabitants was 86.2% lower (95% CI = 81.8 - 89.5%) in children, and 85.7% lower (95% CI = 81.2 - 89.1%) in adolescents than other age groups. Likewise, the hospital mortality (%) was 79.2% lower (95% CI = 71.1 - 85.4%) for children, and 78.6% lower (95% CI = 70.4 - 85.0%) for adolescents than other age groups.

DISCUSSION

This study evaluated inpatient admissions of children and adolescents with oral and pharyngeal cancer in the Brazilian public healthcare system with similar pattern of hospital morbidity for both age groups. Since children and adolescents are less affected by these types of cancer compared to other age groups^{1,2}, it is possible to understand the low frequency of inpatient admissions (5.9%). However, despite lower when compared to the other age groups (20 years or older individuals), the number of inpatient admissions still reflect to some

Table 3. Temporal trends of the person-year incidence and other characteristics of inpatient admissions of children and adolescents with oral and pharyngeal cancer in Brazil's public health services from 2008 to 2023 (2024)

Variable	β_1	R ²	p	APC (%)	Trend
Children (0-9 years old)					
Incidence (per 1,000,000)	-0.054 [-0.066, -0.045]	0.920	<0.001*	-11.7 [-9.8, -14.1]	Decreasing
Hospital mortality (%)	0.008 [-0.010, 0.020]	0.015	0.646	N/A	Stationary
Mean length of stay (days)	0.010 [0.004, 0.016]	0.504	0.002*	2.3 [0.9, 3.8]	Increasing
Mean cost (R\$) per hospitalization	0.035 [0.021, 0.051]	0.534	0.002*	8.4 [5.0, 12.5]	Increasing
Urgent hospitalization (%)	0.002 [-0.006, 0.009]	0.002	0.841	N/A	Stationary
Adolescents (10-19 years old)					
Incidence (per 1,000,000)	-0.033 [-0.043, -0.026]	0.862	<0.001*	-7.3 [-5.8, -9.4]	Decreasing
Hospital mortality (%)	0.004 [-0.005, 0.012]	0.048	0.403	N/A	Stationary
Mean length of stay (days)	0.003 [-0.001, 0.007]	0.242	0.161	N/A	Stationary
Mean cost (R\$) per hospitalization	0.018 [-0.001, 0.031]	0.295	0.054	N/A	Stationary
Urgent hospitalization (%)	0.001 [-0.001, 0.004]	0.019	0.595	N/A	Stationary

Captions: β_1 = angular coefficient; R² = coefficient of determination; APC = Annual Percent Change (%); * = $p < 0.05$ (statistically significant outcome); [] = 95% confidence interval; N/A = not applicable.

Table 4. Comparison of the person-year incidence and other characteristics of inpatient admissions of children, adolescents and other age groups with oral or pharyngeal cancer in Brazil's public health services from 2008 to 2023 (2024)

Comparison	Incidence ratio	Limits		p
		Lower	Upper	
Incidence (per 1,000,000)				
Intercept	46.7	41.7	52.3	<0.001*
Other age groups		ref		
Children	0.138	0.105	0.182	<0.001*
Adolescents	0.143	0.109	0.188	<0.001*
Hospital mortality (%)				
Intercept	4.25	3.63	4.93	<0.001*
Other age groups		ref		
Children	0.208	0.146	0.289	<0.001*
Adolescents	0.214	0.150	0.296	<0.001*
Mean length of stay (days)				
Intercept	5.91	5.25	6.63	<0.001*
Other age groups		ref		
Children	1.010	0.762	1.341	0.943
Adolescents	0.948	0.711	1.263	0.715
Mean cost (R\$) per hospitalization				
Intercept	1,854	1,647	2,097	<0.001*
Other age groups		ref		
Children	0.903	0.671	1.214	0.497
Adolescents	0.752	0.559	1.011	0.059
Urgent hospitalization (%)				
Intercept	51.6	49.6	53.7	<0.001*
Other age groups		ref		
Children	0.955	0.869	1.050	0.342
Adolescents	0.921	0.836	1.014	0.095

Captions: * = $p < 0.05$ (statistically significant outcome); *ref.*: reference level (incidence ratio = 1).

extent the necessity for hospitalizations in this age group, especially considering the frequency of aggressive malignant tumors involving head and neck^{4,21}.

A decreasing incidence of inpatient admissions among children and adolescents over the last 16 years was observed. This may reflect the progress achieved in oncology diagnosis and therapies in recent years, including the refinement of chemotherapy and radiotherapy strategies, which significantly reduce the need for hospitalizations due to toxicities^{22,23}. In addition, with the exception of human papillomavirus (HPV) exposure, there has been a shift in patterns of exposure to key risk factors (*e.g.*, decreasing in tobacco and alcohol use), which has reduced the incidence of oral and pharyngeal cancer in many countries (general population studies)^{24,25}.

Consequently, it is reasonable to understand that lower therapeutic toxicity may corroborate the declining hospitalizations of children and adolescents with oral and pharyngeal cancer. However, the overall lower incidence due to changes in population exposure to risk factors (alcohol and tobacco) is not directly associated with children and adolescents, as previously mentioned¹. Thus, other non-addressed factors may contribute to this outcome and require further investigation.

On the other hand, it is important to acknowledge that despite their lower frequency, tumors involving head and neck often cause significant anatomical alterations that are associated with functional changes as voice/speech, hearing, breathing and swallowing⁷. It is also possible that the initial signs and symptoms may not be easily perceived



or misdiagnosed as inflammatory/infectious processes (e.g. tonsillitis, otitis and abscess) and delay the diagnosis²⁶. Furthermore, these tumors may also require surgical procedures for resection and subsequent rehabilitation in pediatric patients, requiring tertiary care (inpatient admissions)⁷. In addition, some protocols may advocate multidisciplinary approaches to achieve diagnosis and propose appropriate therapies for pediatric patients with head and neck cancer, which may occur in a hospital setting⁶. Therefore, it is expected that children and adolescents with oral and pharyngeal cancer may require inpatient admissions at some point. This perspective should be added to the context of toxicities and adverse events related to not entirely avoidable chemotherapy and radiotherapy^{22,23}.

In this study, a hospital mortality of 2.5% was observed among pediatric patients with oral and pharyngeal cancer, significantly lower than other age groups, a specific parameter that does not reflect mortality by cancer itself (regardless of the type), only the number of patients who died after inpatient admissions^{12,27}. The literature emphasizes differences related to hospitalizations of patients with cancer, including oral and pharyngeal, especially related to the type of tumor and the therapeutic modalities, including signs and symptoms, staging and general health status^{28,29}. Given that these variables were not available at the data sources utilized, they were not addressed herein. Additionally, to date, studies with similar approaches for comparisons purposes are scarce in the literature.

Nevertheless, oropharyngeal cancer has contributed to the increase of head and neck cancer cases in recent years worldwide³⁰, although the survival among pediatric patients remains stable in some epidemiological scenarios³¹. A study of pediatric patients aged between 0-14 and 15-19 years with mouth or pharynx cancer evaluated 167 deaths in Brazil between 1999 and 2005, representing 0.5% of all deaths by this type of cancer³². These findings are consistent with the low hospital mortality observed over the past 16 years in this study, including the stationary trend of this parameter, whether children or adolescents.

Eventually, this study showed a rising trend of costs and length of hospital stay for children with oral and pharyngeal cancer. A scoping review corroborated these findings, indicating that healthcare costs are substantial among pediatric patients (0-14 years) with any type of cancer and hospitalizations responding for one third of these costs³³. Another study reported that pediatric patients (0-14 years) with cancer require high-cost treatments in the first year post-diagnosis, higher than for adolescents and young adults (15-19 years)³⁴. Cancer public costs are crucial to understand the care

provided and outcomes related to pediatric patients, as vulnerable economic conditions can impact the course of the disease, reinforcing the need to track hospitalization-related expenses to guide public policies^{33,34}.

A major achievement of the present study is the investigation of hospital morbidity of children and adolescents with oral and pharyngeal cancer over a 16-years period in Brazil. Comparisons with other age groups contributed positively to the state of the art, demonstrating the impact caused in different age groups. The main limitations of inpatient admission records refer to poor specificity of oral and pharyngeal malignant tumors or the objectives of each hospitalization, which limits the possibilities of this approach. In addition to being an ecological study, it is a registry-based approach where the data entry did not involve the researchers, potentially leading to some degree of misreporting or delays, which could result in variations of the parameters (information bias).

New studies could explore other characteristics related to hospital morbidity on-site in these age groups, focusing on patient-related variables as socioeconomic, demographic and cancer-related factors (type of tumor, staging, and complications). It would also be useful to investigate the underlying causes of inpatient admissions. This thorough approach would allow a comprehensive understanding of the factors influencing morbidity and could inform more targeted and effective interventions to improve patient outcomes.

CONCLUSION

Over the last 16 years, from 2008 to 2023, specific patterns of hospital morbidity were observed, and the number of inpatient admissions of pediatric patients with oral and pharyngeal cancer decreased in Brazil's public health services, with slight differences between children and adolescents. The person-year incidence and hospital mortality were lower compared to other age groups, but the length of stay and costs were comparable. There was no predominance among elective or urgent cases in both age groups.

CONTRIBUTIONS

Ricardo Barbosa Lima contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review; Aquiles Sales Craveiro Sarmiento and Silas Zambaldi Garcia contributed to the study design, wording and critical review; Stefany Santana Bispo, Nathan Henrique de Santana Fontes, Everton Guilherme Jesus dos Santos, Talita Silva Sobral

and Breno Gustavo do Nascimento Gomes contributed to the acquisition, analysis and interpretation of the data, wording and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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