

Trends in Oral Cancer Mortality in Brazil by Region and Main Risk Factors

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Tendências de Mortalidade por Câncer Bucal no Brasil por Regiões e Principais Fatores de Risco

Tendencias de la Mortalidad por Cáncer Bucal en Brasil por Región y Principales Factores de Riesgo

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ABSTRACT

Introduction: Oral cancer still stands out as a concerning public health issue. **Objective:** Verify the trend of oral cancer mortality by Brazilian regions and risk factors, evaluating the time interval between diagnosis and treatment. **Method:** Study with secondary data from DATASUS (mortality rate and time to treatment) and Vigitel (alcohol and cigarette use). Time series analyzes and correlations were performed among mortality rates (2010-2019) and alcohol and cigarette use (2010-2019) for over 40 years of age. Descriptive analysis of the time between diagnosis and treatment was also performed. **Results:** There was an increase in the trend to oral cancer by region and sex, with a predominance of males. The annual percentage change (APC) of alcohol intake and cigarette use was considered stationary in most regions analyzed. When correlating the variables, there was a statistically significant correlation for mortality rate (2010-2019) and percentage of alcohol use ($p=0.011$; $r=0.957$), percentage of cigarette use ($p=0.019$; $r=0.936$) and crude mortality rate in men (2019) ($p=0.005$; $r=0.97$). It was found that most cases (74%) take more than 60 days to start treatment. **Conclusion:** Although alcohol and tobacco use are risk factors for oral cancer, the present study showed an increase in cancer mortality and stationary for the risk factors analyzed. The beginning of the treatment was over 60 days after diagnosis.

Key words: mouth neoplasms/mortality; tobacco use disorder; alcohol drinking; time series studies; public health.

RESUMO

Introdução: O câncer bucal ainda é destacado como preocupante problema de saúde pública. **Objetivo:** Verificar a tendência de mortalidade por câncer bucal por Região brasileira e fatores de risco, avaliando o intervalo de tempo entre o diagnóstico e o tratamento. **Método:** Estudo com dados secundários do DATASUS (taxa de mortalidade e tempo para tratamento) e do Vigitel (consumo de álcool e cigarro); análises de séries temporais e correlações entre taxas de mortalidade (2010-2019) e consumo de álcool e cigarro (2010-2019), para idade superior a 40 anos, e análise descritiva do tempo entre diagnóstico e tratamento. **Resultados:** Houve aumento da tendência de câncer bucal por Regiões e sexo, com predominância para o sexo masculino. A variação percentual anual (VPA) da ingestão de álcool e o uso de cigarro foram considerados estacionários na maioria das Regiões analisadas. Ao correlacionar as variáveis, verificou-se correlação estatisticamente significativa entre taxa de mortalidade (2010-2019) e percentual de consumo de álcool ($p=0,011$; $r=0,957$), percentual de consumo de cigarro ($p=0,019$; $r=0,936$) e taxa bruta de mortalidade em homens (2019) ($p=0,005$; $r=0,97$). Verificou-se que, na maioria dos casos (74%), o tempo para início do tratamento é de mais de 60 dias. **Conclusão:** Embora o consumo de álcool e o tabagismo sejam fatores de risco para o câncer bucal, o presente estudo concluiu que houve aumento da mortalidade por câncer e os fatores de risco analisados permaneceram estacionários. O início de tratamento foi maior do que 60 dias a partir do diagnóstico.

Palavras-chave: neoplasias bucais/mortalidade; tabagismo; consumo de bebida alcoólica; estudos de séries temporais; saúde pública.

RESUMEN

Introducción: El cáncer oral todavía se destaca como un problema de salud pública preocupante. **Objetivo:** Verificar la tendencia de la mortalidad por cáncer bucal por región brasileña y factores de riesgo, evaluando el intervalo de tiempo entre el diagnóstico y el tratamiento. **Método:** Estudio con datos secundarios de DATASUS (tasa de mortalidad y tiempo de tratamiento) y Vigitel (consumo de alcohol y cigarrillos). Se realizaron análisis de series de tiempo y correlaciones entre las tasas de mortalidad (2010-2019) y el consumo de alcohol y cigarrillos (2010-2019) para los mayores de 40 años. También se realizó un análisis descriptivo del tiempo transcurrido entre el diagnóstico y el tratamiento. **Resultados:** Hubo un incremento en la tendencia al cáncer bucal por región y sexo, con predominio del sexo masculino. El cambio porcentual anual (APV) de la ingesta de alcohol y el consumo de cigarrillos se consideró estacionario en la mayoría de las regiones analizadas. Al correlacionar las variables, hubo una correlación estadísticamente significativa para tasa de mortalidad en hombres (2010-2019) y porcentaje de consumo de alcohol para hombres ($p=0,011$; $r=0,957$), porcentaje de consumo de cigarrillos en hombres ($p=0,019$; $r=0,936$) y tasa bruta de mortalidad en hombres (2019) ($p=0,005$; $r=0,97$). Se encontró que la mayoría de los casos (74%) demoran más de 60 días en comenzar el tratamiento. **Conclusión:** Aunque el consumo de alcohol y el tabaquismo son factores de riesgo para el cáncer oral, el presente estudio mostró un aumento en la mortalidad por cáncer y estacionario para los factores de riesgo analizados. Hubo un alto porcentaje de inicio del tratamiento durante 60 días después del diagnóstico.

Palabras clave: neoplasias de la boca/mortalidad; tabaquismo; consumo de bebidas alcohólicas; estudios de series temporales; salud pública.

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INTRODUCTION

Oral cancer is a malignant tumor affecting lips, its internal lining and surrounding structures as well as the buccal mucosa, palate, gingiva, oropharynx and tongue. It is more prevalent in men older than 40 years of age. It is a concerning problem of public health¹ with most of the cases diagnosed at advanced stages and eventually death for many of them.

There were reports of 377,713 new cases (lips and oral cavity) in the whole world in 2020 (264,211 men and 113,502 women), with rate of mortality of up to 50%². In Brazil, data of the Atlas of Mortality by Cancer³ showed that in 2019 alone, mortality by oral cancer (lips, base of the tongue, other parts of the tongue, gingiva, floor of the mouth and palate) recorded 2,661 cases (2,062 men and 599 women) based in the population of 2010/100 thousand inhabitants. The highest specific rate was found for 80 years or older (10%), followed by 70 to 79 years (6.92%). Brazil's standard rate (1.21) was greater than the world's level (1.16)³.

The most prevalent oral cancer is squamous cell carcinoma (SCC), its etiology is multifactorial, and the most relevant risk factors are tobacco and alcohol. However, excessive solar exposure, human papilloma virus (HPV), diet and occupation have also been associated with risk factors of the disease⁴⁻⁹.

Because it is a public health issue in Brazil, organization of health services and systems for prevention are in place, including campaigns and protective laws, diagnosis and treatment.

The National Program of Tobacco Use Control (PNCT) was implemented in the decade of 1980 as a preventive framework which promoted effectiveness of individual and collective actions aimed to prevent the initiation of tobacco use, mainly in children, adolescents and youngsters; promote the cessation of smoking and divulge tobacco-free and its by-product environments. The National Policy of Tobacco Control entered into force in 2005 as a result of the WHO Framework Convention on Tobacco Control (WHO FCTC)¹⁰. These initiatives allowed Brazil to join WHO's program MPOWER (monitor tobacco use and prevention policies; protect people from tobacco smoke; offer help to quit; warn about the dangers of tobacco; enforce bans on advertising, promotion and sponsorship, raise taxes on tobacco products), aimed to monitor tobacco use through taxes raise to protect the population from smoking, offer help to quit and determine bans. Eventually, these actions led to the decline of tobacco use^{10,11}.

Brazil has laws in place as "*Lei Seca*" to control the use of alcohol and driving. In 2015, Law number 13.106/2015

criminalized the offer of alcohol beverages to minors which previously was categorized as a misdemeanor¹³. However, according to data of Vigitel¹⁴ about the abusive use of alcohol (four or more doses for women and five or more doses for men), women's use increased from 11% in 2018 to 13.3% in 2019 but is more prevalent in men with 25.3% in 2019.

For curative or diagnostic purposes, oncologic patients can seek consultations at Basic Attention (BA) with clinicians or family doctors. In addition, depending on the type of cancer, it can be screened at Dental Clinics (CEO) and referred for treatment of the most common types of cancer in Brazil at High Complexity Dental Care Clinics (Unacon), or High Complexity Oncologic Clinic (Cacon) for any type of cancer¹⁵.

The Law of the 60 days determines that the patient is entitled to the first treatment at SUS (National Health System) in until 60 days counted from the confirmed pathology diagnosis. In addition, the Law of the 30 days ensures the maximum limit of up to 30 days for the required tests to elucidate the head clinician's suspicion of malignant neoplasm¹⁵.

The aim of this study was to analyze the trend of mortality by oral cancer per Brazilian regions and risk factors as alcohol and tobacco use and evaluate the time between the diagnosis and beginning of treatment of oral cancer.

METHOD

Data of the Atlas of Mortality by Cancer³ were utilized to analyze the time trend of crude death rate (100 thousand inhabitants) involving lips, base of the tongue, other parts of the tongue, gingiva, floor of the mouth, palate and other parts of the mouth, according to each region from 2010 to 2019, for the age range of 40 years or older when oral cancer becomes more prevalent^{16,17}.

These data were compared with the main known risk factors as tobacco and alcohol use utilizing the System of Information of Vigitel¹⁴, which includes the capitals of the States and older than 18 years old individuals. Vigitel's sampling procedures try to obtain for each capital of the 26 Brazilian states and Federal District all the probabilistic samples of the adult population (≥ 18 years) living in domiciles with at least one land line. The data were collected by sex and type of use – alcohol and/or tobacco – per region (capitals and adults older than 40 years of age) according to Vigitel¹⁴. For alcohol use, the response yes for alcohol ingestion is considered and for tobacco use, whether it is a smoker and daily and whether it is a smoker but not daily. The percentage of abusive use of alcohol was calculated (equal or more than

three times a week) for both sexes in 2019. According to Vigitel, between 2010 and 2019, adult women and men with 40 years or older of all the regions living in the capitals of the States were interviewed. The number of interviewees was divided by Regions: Midwest, 1,900 (± 271.6) men and 7,020 ($\pm 1,286.3$) women; Northeast, 3,434 (± 422) men and 13,843.2 ($\pm 2,366.8$) women; North, 3,247.7 (± 361.5) men and 11,121.4 ($\pm 1,480.1$) women; Southeast, 1,930.5 (± 247.9) men and 7,193.4 ($\pm 1,071.2$) women; South, 1,512.4 (± 193.2) men and 5,837.8 (± 889.7) women.

Further to the diagnosis, early treatment is required. It was attempted to analyze the mean time between the diagnosis and beginning of the treatment of oral cancer with data extracted from DATASUS' "PAINEL-Oncologia"¹⁸. The data were collected by year as: malignant neoplasm of the lip, malignant neoplasm of the tongue, malignant neoplasm of other and unspecified parts of the tongue, malignant neoplasm of the gingiva, malignant neoplasm of the floor of the mouth, malignant neoplasm of the palate, malignant neoplasm of other and unspecified parts of the mouth, malignant neoplasms of other and ill-defined parts of the lip and oral cavity. It has been decided to analyze the period of the diagnosis, the beginning of the treatment and the year 2019 separately since because of the pandemic, the collection of the data could be jeopardized and discrepancies from 2013 to 2021 could potentially be encountered. Also, the rates of mortality and the percentage of abusive use of alcohol for 2019 were analyzed separately to check whether the percentage variation of the rates from 2010 to 2019 were similar if compared with a specific year, because the trend of the years was analyzed.

To calculate the Annual Percent Change (APC) of the crude death rates, it was utilized the Prais-Wisten regression which estimates correction of autocorrelation of first order according to Antunes et al.¹⁹: $-1 + 10b = \Delta(1)$.

To calculate confidence intervals:

$$\Delta 95\text{ CI} = -1 + 10(b \pm t^* se)$$

In this formula, b corresponds to the annual growth rate. The values of b and standard deviation (se) were extracted from the regression analysis and the value of t , from the test of distribution t . The trend of increase, decrease or stagnation was expressed as APC with respective confidence intervals (95%) and the trend whose coefficient of regression was not different from zero was categorized as stationary ($p > 0.05$). The statistical package Stata 14 was utilized for the analyzes.

The analyzes of the rate of mortality were correlated with alcohol and tobacco use and rates of mortality by sex (Pearson's correlation). For such, the Statistical Package for the Social Sciences (SPSS) version 21.0 was utilized with level of significance of 5%. Descriptive analyzes were utilized to analyze the time from the beginning of the diagnosis and treatment in Microsoft Excel.

RESULTS

The results of the study show that there is an overall trend of increase of oral cancer per regions and sex. There was raising trend for all the regions evaluated for males and females of the Southeast and South regions (Table 1). The highest APC of mortality was found for men in the North region followed by the Northeast region. For females, the highest APC was found in the South Region followed by the North region.

The analysis of alcohol and tobacco use per sex along the years revealed that tobacco use has presented a stationary trend either for men or women, except in the North region for women and North, Midwest and South regions for men (Table 2).

While analyzing the variables rate of mortality by sex and alcohol and tobacco use (Table 3), it was found a statistically significant correlation (Pearson's correlation) for the rate of mortality in men (2010-2019) and the percentage of alcohol use in men ($p=0.011$; $r=0.957$),

Table 1. Annual Percent Change of mortality by cancer in lip, base of the tongue, other parts of the tongue, gingiva, floor of the mouth and other parts of the mouth according to the Brazilian regions and sex for older than 40 years of age , 2010-2019

Regions	Man (APC)	CI				Woman (APC)	CI			
		2010-2019	Min.	Max.	Trend		2000-2019	Min.	Max.	Trend
Midwest	2.30	0.01	0.04	Increase	2.68	-0.02	0.07	Stationary		
Northeast	3.25	0.01	0.05	Increase	0.58	-0.00	0.01	Stationary		
North	6.67	0.04	0.09	Increase	3.00	-0.01	0.07	Stationary		
Southeast	1.12	0.01	0.01	Increase	2.94	0.01	0.04	Increase		
South	1.21	0.00	0.02	Increase	3.38	0.01	0.05	Increase		

Captions: APC – Annual Percent Change; Min. = Minimum value; Max. = Maximum value; CI = Confidence interval.

Table 2. Annual percent change of alcohol and tobacco use according to regions for older than 40 years of age

		% Alcohol use			% Tobacco use				
		CI				CI			
		APC (2010- 2019)	Min.	Max.	Trend	APC (2010- 2019)	Min.	Max.	Trend
Man	Midwest	3.90	0.00	0.08	Increase	-0.70	-0.02	0.01	Stationary
	Northeast	1.81	-0.01	0.05	Stationary	-2.16	-0.05	0.00	Stationary
	North	0.98	-0.01	0.03	Stationary	-5.44	-0.08	-0.03	Decrease
	Southeast	2.32	-0.03	0.08	Stationary	-1.03	-0.04	0.02	Stationary
	South	3.28	0.01	0.06	Increase	-1.24	-0.03	0.01	Stationary
	Midwest	3.56	-0.03	0.10	Stationary	-2.23	-0.05	0.01	Stationary
Woman	Northeast	1.11	-0.07	0.10	Stationary	-3.09	-0.07	0.00	Stationary
	North	0.82	-0.05	0.07	Stationary	-6.39	-0.10	-0.03	Decrease
	Southeast	2.19	-0.05	0.10	Stationary	-0.69	-0.04	0.02	Stationary
	South	2.24	-0.04	0.09	Stationary	-1.95	-0.04	0.00	Stationary

Captions: APC = Annual Percent Change; Min. = Minimum value; Max. = Maximum value; CI = Confidence Interval.

Table 3. Mortality rate (raw) by neoplasms (lip, base of the tongue, other parts of the tongue, floor of the mouth, palate and other parts of the mouth), alcohol and tobacco use per sex, older than 40 years, Brazil

Regions	2010-2019		2010-2019		2010-2019		2019 (alcohol)		2019	
	Mortality rate M	Mortality rate W	% alcohol M	% alcohol W	% tobacco M	% tobacco W	% abusive use** M	% abusive use** W	Mortality rate M	Mortality rate W
Midwest	6.37	1.72	48.01	11.88	12.75	4.53	30.84	11.76	6.27	1.46
Northeast	7.09	2.7	49.45	11.16	10.62	3.41	20.04	4.79	7.96	2.71
North	4.21	1.77	47.27	10.2	11.5	3.84	15.30	4.27	4.86	2.04
Southeast	8.43	2.14	50.23	13.76	15.46	5.4	36.62	11.28	8.86	2.54
South	8.69	1.83	51.01	13.4	14.99	5.99	41.77	18.06	9.89	2.15

Captions: M = Man; W = Woman.

(**) More than three times a week.

the percentage of tobacco use in men ($p=0.019$; $r=0.936$) and the mortality crude rate in men (2019) ($p=0.005$; $r=0.97$). The correlation was statistically significant still for the percentage of alcohol use (2010-2019) and the rate of mortality in men (2019) ($p=0.001$; $r=0.99$), the percentage of tobacco use in men (2010-2019) and the percentage of abusive use of alcohol in men ($p=0.05$; $r=0.87$) – abusive percentage is when the frequency of use is three-fold greater than three times a week. The statistically significant percentage of abusive use of alcohol in men was correlated with the percentage of abusive use of alcohol in women ($p=0.012$; $r=0.95$).

For most of the cases (74%), it takes more than 60 days to initiate the treatment when the timeline from 2013 to 2021 (Table 4) is analyzed.

After evaluating the period from 2013 to 2021 per Brazilian Region and States, it was found that the State of Roraima (North Region) had the highest percentage of cases (80.77%) with more than 60 days from diagnosis and beginning of the treatment. In 2019, the State of Paraíba (Northeast Region) had the highest percentage of cases (75.21%).

DISCUSSION

The present study revealed that mortality by oral cancer increased in several Brazilian regions, although the exposure to risk factors has remained stationary. Additionally, it was demonstrated that males presented higher rates of oral cancer than women.

Table 4. Number of individuals with time to begin the treatment of neoplasms of the lip and oral cavity* according to time intervals defined and percentage of cases treated in until 60 days. Brazilian regions, 2013-2021 and 2019

Regions	2013 to 2021				2019			
	Less than 30 days	31 to 60 days	More than 60 days	% higher than 60 days	Less than 30 days	31 to 60 days	More than 60 days	% higher than 60 days
Southeast								
São Paulo	2,879	1,851	7,066	59.90	604	89	861	55.41
Rio de Janeiro	437	380	1,748	68.15	102	46	227	60.53
Minas Gerais	1,559	1,415	3,358	53.03	313	164	438	47.87
Espírito Santo	249	274	862	62.24	59	121	95	34.55
Northeast								
Ceará	618	513	1,021	47.44	104	36	146	51.05
Rio Grande do Norte	457	231	411	37.40	129	10	70	33.49
Paraíba	120	159	775	73.53	25	8	102	75.56
Pernambuco	324	311	1,426	69.19	75	61	141	50.90
Alagoas	116	133	475	65.61	19	149	46	21.50
Sergipe	55	52	218	67.08	11	32	29	40.28
Bahia	410	468	1,771	66.86	79	28	244	69.52
Maranhão	158	78	282	54.44	28	31	30	33.71
Piauí	140	159	225	42.94	30	12	39	48.15
South								
Paraná	1,566	903	1,471	37.34	342	10	207	37.03
Santa Catarina	575	382	1,192	55.47	112	13	144	53.53
Rio Grande do Sul	1,218	591	1,755	49.24	279	25	229	42.96
North								
Rondônia	88	57	120	45.28	10	4	20	58.82
Acre	9	9	33	64.71	2	2	4	50.00
Amazonas	71	30	180	64.06	24	12	29	44.62
Roraima	2	3	21	80.77	2	8	2	16.67
Pará	104	78	447	71.07	27	5	67	67.68
Amapá	8	2	20	66.67	1	13	3	17.65
Tocantins	29	33	76	55.07	6	58	12	15.79
Midwest								
Mato Grosso do Sul	191	101	308	51.33	29	7	56	60.87
Mato Grosso	188	139	277	45.86	34	34	30	30.61
Goiás	280	222	813	61.83	71	51	117	48.95
Distrito Federal	66	35	227	69.21	11	14	28	52.83

(*)C00. Malignant neoplasm of the lip; C01. Malignant neoplasm of the base of the tongue; C02. Malignant neoplasm of other parts and unspecified parts of the tongue; C03. Malignant neoplasm of the gingiva; C04. Malignant neoplasm of the mouth floor; C05. Malignant neoplasm of the palate; C06. Malignant neoplasm of other parts and unspecified parts of the mouth.

In a study conducted by Perea et al.²⁰, the authors evaluated the mortality by mouth and larynx cancer from 2002 to 2013 in Brazil and found that oral cancer had a raising trend in the Northeast regions and decreasing trend in the Southeast, South and Midwest regions. The data from 2010 to 2019 were analyzed in

the present study and showed a raising trend for most of the regions for males and stationary for women (Table 1).

Some authors described risk factors for oral cancer as tobacco and alcohol use, HPV infection and unhealthy diet (few fruits and vegetables)²¹⁻²⁴. Herein, only tobacco

and alcohol use were analyzed, both with widely disclosed control policies in Brazil.

Since 1986, some laws addressing the use of tobacco and alcohol have been enforced in Brazil, one of them FCTC/WHO¹⁰. This Convention specifically determined tax raise on tobacco products and strong sanitary warns. Because of these actions, tobacco consumption dropped between 1989 and 2008 in individuals in the age range of 15-34 years of age and those with more than nine years of education²²⁻²⁴. Considering that older than 40 years of age is a risk factor according to the National Institute of Cancer José Alencar Gomes da Silva (INCA)¹⁶ this study found decrease of use only in the North Region for both sexes.

Because of alcohol consumption, the Pan American Health Organization – PAHO approved the Plan of Action to Reduce the Harmful Use of Alcohol in 2011²⁵. Its objective is to prevent persons to drive under the influence of alcohol and implement actions to modify the context of use, in addition to restrictions to offer alcohol beverages and tax raise¹¹⁻¹². This study found that the trends of alcohol use were stationary or increasing (Midwest and South regions for men).

Despite the actions of control of risk factors as tobacco and alcohol use, decreasing data were not detected based in the analyzes of the trend from 2020 to 2019 but stationary instead for the majority, revealing that the use did not have many significant oscillations along the years. However, the database Vigitel¹⁴ was utilized to evaluate the alcohol and tobacco use through telephone interviews with the population living only in the Brazilian capitals. Another remarkable aspect is that 70% of the sample consisted of women who had lower exposure to alcohol and tobacco than men and for a more representative sample, more men exposed to risk factors would have to be included. DATASUS database did not include the habits of the patients with tumor (rate of mortality), which is a limitation of the study, possibly some patients who died by oral cancer did not use alcohol or tobacco.

According to Serna et al.²¹, the proportion of oral cancer among men and women is 2.6, the third highest when compared to other Latin American countries with raising rates for men and women. The present study tried to correlate raw mortality rates by oral cancer with the risk factors analyzed (alcohol and tobacco use). It was found statistically significant correlation among risk factors and mortality rates for men because of the high prevalence in this population.

Some authors affirm that the inequality of access to health services is a barrier to the diagnosis across different Brazilian regions and that late diagnosis leads to still worse outcomes^{22,25}. Diagnosis at advanced stages of the disease

has been a factor associated with high mortality caused by oral cancer²⁵. Once diagnosed and after determining location, stage and other characteristics of the patient, conventional treatments include surgery, chemotherapy and radiotherapy²⁴ with potential 5-year survivorship in almost 50% of the cases if initiated soon after the diagnosis^{24,25}. Nevertheless, some studies suggest that Latin countries present unsatisfactory response to radiation treatment offered to the patients, potentially influencing the rates of mortality by cancer²⁷.

The results of the present study (Table 4) show that it is necessary to investigate which obstacles of the health system are able to cause more delays between the diagnosis and beginning of the oncologic treatment. The delay may be related to sub-notification of cases and/or poor access of the patient to health services. Studies report that the organization of public health system in Brazil and patients' profile with cancer most likely lead to vulnerable prognosis for these patients²⁸⁻³².

CONCLUSION

Brazil has a policy of surveillance of oral health, tobacco and alcohol use which present stationary trend in most of the country regions, nevertheless, the mortality rate has presented raising trend for the majority of the regions evaluated and time between diagnosis and beginning of the treatment for most of the regions compromises the prognosis of the patients.

CONTRIBUTIONS

Regiane Cristina do Amaral contributed substantially to the study design and/or concept. Rosana Apolonio Reis Andrade and Graziene Ribeiro Couto contributed to the acquisition, analysis and/or interpretation of the data. Brenda Yuliana Herrera Serna, Erika Rezende-Silva e Mônica Christine Alves Cabral Cardoso contributed to the wording and/or critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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