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ORIGINAL ARTICLE

Tooth loss is associated with atherosclerosis and a poorer functional outcome among stroke patients

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Abstract

Objectives The purpose of the study was twofold: (1) to test the hypothesis that tooth loss is independently associated with carotid atherosclerotic burden (CAB) among individuals with ischemic stroke (IS) or transient ischemic attack (TIA) and (2) to test the association between tooth loss and disability following the occurrence of cerebral ischemia.

Materials and methods This observational study included 418 patients with IS or TIA. Tooth loss and the CAB were measured through a head and neck multidetector computed tomography angiography. CAB was analyzed in both common, internal, and external carotid arteries and classified in five levels of vascular occlusion. The modified Rankin Scale (mRS) was used to evaluate the functional outcome at patient discharge. Health records provided information on sociodemographic and medical covariates. The association between CAB and tooth loss, as well as between tooth loss and subtypes of cerebral ischemia were estimated through Poisson regression. Cox regression was carried out to evaluate the association between tooth loss and the mRS, with $\alpha = 5\%$.

Results Mean age was 65.6 ± 13.8 years, with 52.4% males. Multivariate analyses revealed that severe tooth loss (> 23 missing teeth) was independently associated with CAB ≥ 50% (PR = 2.86, 95% CI = 1.19–6.89) and mRS scores (> 2) (HR = 1.97, 95% CI = 1.10–3.75).

Conclusion Tooth loss was independently associated with CAB and predicted a poorer functional outcome among IS and TIA patients.

Clinical relevance Clinical assessment of tooth loss may provide important information on risk for CAB and poorer functional outcome among stroke patients.

Keywords Oral health · Atheroma · Disability evaluation · Risk factor · Epidemiology

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Introduction

Recent medical and dental research has focused on the relationship between chronic oral infections and noncommunicable diseases, especially atherosclerosis and cardiovascular disease [1, 2]. Stroke is a vascular disease that affects the brain arteries, and is the 5th cause of death and a leading cause of disability in the USA [3]. Previous findings suggest that oral health may affect the risk of stroke [4].

The global prevalence of oral diseases has risen in the last 20 years, with a 64% increase in the disability-adjusted life years due to oral conditions [5]. The biological plausibility underlying the association between oral infections and AVD was previously detailed and is related to (1) transient bacteremia and translocation of oral bacterial pathogens and (2) elevations in circulating levels of inflammatory mediators [6].

Tooth loss is a valid and strong surrogate measure of past oral diseases [7]. The main causes for tooth loss are periodontitis and apical periodontitis (secondary to advanced caries) [5]. Even though there is evidence of an association between tooth loss and AVD [7], no previous studies have tested this relationship in a specific population of patients with ischemic stroke (IS). Importantly, few studies evaluated the association between oral health and the functional outcome following IS, using the modified Rankin Scale (mRS) [8].

Currently, 3 to 4% of total health care is spent on the management of stroke, including hospital treatments, rehabilitation, and follow-up care, in Western countries [9]. In patients that had a severe disability (mRS 4 and mRS 5) [10], the cost increases up to eight-fold. Identifying new risk factors for transient ischemic attack (TIA) and IS as well as finding new secondary prevention strategies to improve a patient's quality of life after a stroke benefits not only the individual but also contributes to improved public health.

Thus, the purpose of this study was to test the following hypotheses: (1) tooth loss is independently associated with carotid atherosclerotic burden (CAB) and (2) tooth loss can predict disability (poorer mRS scores) among patients with IS or TIA.

Methods

Study design and ethical issues

The research protocol of this observational study was approved by the Ethics and Research Committee of the Pontifical Catholic University of Rio Grande do Sul (CAAE#66511417.4.1001.5336). Participants signed a consent form following admission to the São Lucas Hospital (Porto Alegre, Brazil). Before the analyses, all data were de-identified to protect the anonymity of participants. This observational study is based on both retrospective cross-sectional and longitudinal data analyses and conforms to the STROBE guidelines.

Study population

A total of 459 consecutive hospital patients diagnosed with IS (acute ischemic lesion on brain and/or neurological deficits lasting > 24 h) or TIA (neurological deficit < 24 h without new ischemic lesions) were recruited, from January 2015 to December 2017. Forty-one potentially qualifying patients were excluded due to incomplete acquisition of oral images on multidetector computed tomography angiography (MDTCA), leaving a total of 418 subjects (IS $n = 324$ and TIA $n = 94$). Patients diagnosed with hemorrhagic stroke were not considered for inclusion in the study, because hemorrhagic stroke is attributable primarily to hypertensive peaks and rupture of a cerebral aneurysm (i.e., noninfectious/inflammatory mechanisms) (Fig. 1).

Diagnostic imaging

All participants had undergone a head and neck MDCTA and a magnetic resonance imaging of the brain prior to enrollment in this study.

CVD risk factors

Socio-demographic and medical variables were collected from hospital health records. Hypertension was defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg [11]. The body mass index (BMI) was calculated, dividing the weight by the height squared [12]. Diabetes was defined as the use of insulin or hypoglycemic medication, or fasting plasma glucose ≥ 100 mg/dl, or history of diagnosed diabetes [13]. Low-density lipoprotein cholesterol (LDL-c) was computed from the Friedewald equation [14]. Smoking was assessed as current, former, or never smoker.

Measurement of CAB

MDCTA images were analyzed by an experienced radiologist masked regarding the objective of the study. MDCTA was performed with a 64-slice CT scanner (Philips iCT, Amsterdam, Netherlands). All participants had received an iodinated contrast injection (Ultravist 300 (623 mg/ml); Bayer, Pharma AG Berlin, Germany) prior to imaging. The protocol parameters for image acquisition were as follows: spiral mode, 0.8 rotation time; pitch, 0.8; slice thickness, 0.6–1.0 mm; collimation, 120 × 0.6 mm; acquisition parameters, 110 Kv, 200 mA. The images were visualized using the Arya software (PACS Aurora v.3.3). This neurologic scan protocol is performed on all patients at São Lucas Hospital

(Neurology Department) and generally allows visualization of the maxillary and mandibular teeth.

The carotid system was explored in transverse and longitudinal scans. Both common, internal and external carotid arteries were examined for the presence of atherosclerotic plaque. CAB was classified in five levels, 0%, < 50%, 50–75%, > 75%, and 100%, according to the vessels occlusion [15]. Based on the threshold value for vascular therapy [16] and according to the distribution of this sample, CAB was dichotomized in low (CAB < 50% in all carotid arteries) or high (CAB ≥ 50% in one or more carotid arteries) [15].

Measurement of functional outcome and etiology of cerebral ischemia

The modified Rankin Scale (mRS) is validated and widely used to assess the functional outcome, or disability, after IS. The mRS comprises six scores and death, indicating the level of disability and consequent assistance that the patient will need after an IS. In this study, mRS scoring was performed by a neurologist, following the structured interview [17] at time of patient discharge. For analysis, mRS score were dichotomized in ≤ 2 or > 2, given that a score ≥ 3 indicates a disability outcome (moderate to severe) requiring assistance to perform simple activities 2 [8].

The etiology of the stroke subtype was measured according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [18]. Medical records of patients classified as undetermined were re-evaluated after the discharge, and cases defined as a non-lacunar brain infarct, without arterial stenosis or cardioembolic sources, were classified as Embolic Stroke of Undetermined Source (ESUS) [19].

Measurement of dental status

The MDCTA was used to measure the number of natural teeth. This exposure variable was evaluated by a trained dentist masked to the other variables. Impacted teeth, deciduous teeth, and the 3rd molars were not assessed; hence, participants had a potential to have between zero and 28 permanent natural teeth. Tooth loss was categorized as none (0 missing teeth), slight (1–8 missing teeth), moderate (9–22 missing teeth), and severe (23–28 missing teeth). Slight tooth loss was determined by the functional dentition (≥ 20 teeth) [20]; the other cutoffs conformed to a balanced distribution of the sample across missing teeth.

Statistical analysis

Statistical analyses were carried out using SPSS Statistics v.25 (IBM, Chicago, USA). The independent variable was tooth loss, categorized as none (no missing teeth), slight (1–8 missing teeth), moderate (9–22 missing teeth), and severe (23–28 missing teeth). The dependent variables were CAB, mRS, and the TOAST classification. Descriptive statistics (*N* and %) according to CAB and mRS were calculated. Univariate and multivariate Poisson regressions with robust variance were carried out to estimate the association (prevalence ratios (PR)) between the main exposure (tooth loss) and the outcomes (CAB and TOAST classification). Stroke subtypes (cardioembolic and ESUS) were evaluated in the same group.

Cox proportional hazards (HR) regression was used to evaluate the association between the main exposure, tooth loss, and the outcome, mRS score, considering the time to patient discharge or time to hospital death (when death occurred previously to the discharge). The sociodemographic and medical covariables were used in the adjusted models, with $\alpha \leq 5\%$.

Results

After exclusions, a total of 418 patients were included in the study. The characteristics of the sample (*N*/%) in relation to the CAB and mRS are expressed in Table 1. The mean age was 65.6 ± 13.8 years (20–96 years), and 52.4% were men.

Table 2 shows the results of the univariate and multivariate analyses evaluating the association between tooth loss and CAB. Model 1 is the unadjusted analysis, model 2 is adjusted for sociodemographic variables, and model 3 is adjusted for sociodemographic and medical variables. In model 3, severe tooth loss (23 to 28 missing teeth) (PR = 2.84, 95% CI = 1.18–

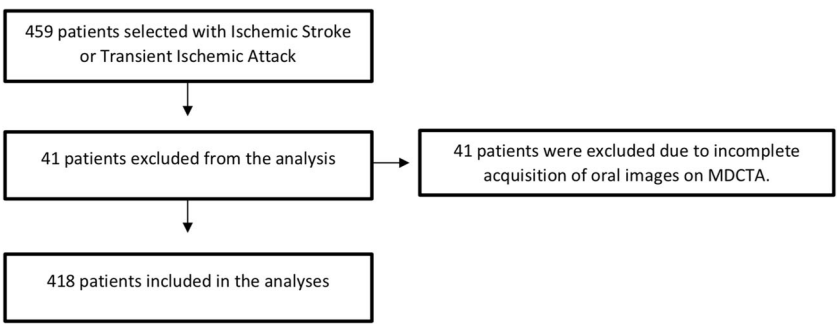

Fig. 1 Flowchart of the study sample

Table 1 Sociodemographic, medical, and dental characteristic of the sample in relation to CAB ($N = 418$) and mRS ($N = 411$)

Variable	CAB		mRS score	
	< 50% *N* (%)	≥ 50% *N* (%)	≤ 2 *N* (%)	> 2 *N* (%)
Socio-demographic				
Age, mean (SD), years	64.5 ± 14.0	70.63 ± 11.24	64.38 ± 13.31	69.52 ± 14.50
Age (≥ 60 years)	219 (63.7)	59 (80.8)	198 (63.5)	76 (77.6)
Male	180 (82.3)	39 (52.7)	170 (54.5)	46 (46.5)
Medical				
BMI (> 25)	209 (62)	38 (51.4)	193 (63.3)	50 (50.5)
Hypertension	258 (75)	66 (89.2)	237 (76)	82 (82.8)
Diabetes	63 (18.3)	19 (25.7)	61 (19.6)	20 (20.2)
LDL-c (≥ 130 mg/dL)	66 (23.8)	25 (37.3)	70 (26.3)	18 (24.7)
Smoking (current and former)	120 (34.9)	33 (44.6)	118 (37.8)	33 (33.3)
Previous IS or TIA	63 (18.4)	8 (10.8)	49 (15.7)	20 (20.4)
Dental				
Tooth loss				
• None & Slight (0–8 MT)	81 (23.5)	8 (10.8)	76 (24.4)	13 (13.1)
• Moderate (9–22 MT)	137 (39.8)	27 (36.5)	122 (39.1)	38 (38.4)
• Severe (23–28 MT)	126 (36.6)	39 (52.7)	114 (36.5)	48 (48.5)

CAB carotid atherosclerotic burden, *mRS* modified Rankin Scale, *BMI* body mass index, *LDL-c* low-density lipoprotein cholesterol, *IS* ischemic stroke, *TIA* transient ischemic attack, *MT* missing teeth

6.81), hypertension (PR = 2.42, 95% CI = 1.16–5.06), and LDL-c (≥ 130 mg/dl) (PR = 2.01, 95% CI = 1.30–3.09) were independently associated with CAB ≥ 50%. These three variables presented the highest strength of association with the CAB (Wald chi-square values of 5.48, 5.55, and 9.94, respectively).

Table 3 shows the results of the univariate and multivariate analyses evaluating the association between tooth loss and

Table 2 Univariate and multivariate regression analyses for the association between tooth loss and CAB. Prevalence ratios (PR) and Wald chi-square values. Model 1: unadjusted analyses; model 2: adjusted for sociodemographic variables; model 3: adjusted for sociodemographic and medical variables

Variables	Model 1			Model 2			Model 3		
	95% CI			95% CI			95% CI		
	Wald	PR	*p*	Wald	PR	*p*	Wald	PR	*p*
Tooth loss None and slight (0–8 MT)		1			1			1	
Moderate (9–22 MT)	2.53	1.83 (0.87–3.86)	0.11	3.96	1.53 (0.73–3.19)	0.26	3.45	2.27 (0.95–5.38)	0.06
Severe (23–28 MT)	*7.01*	*2.63 (1.28–5.38)*	*< 0.01*	*1.28*	*2.07 (1.01–4.23)*	*0.04*	*5.48*	*2.84 (1.18–6.81)*	*0.01*
Age (≥ 60 years)				3.36	1.68 (0.96–2.92)	0.06	1.98	1.45 (0.85–2.61)	0.15
Sex (male)				0.22	0.91 (0.61–1.37)	0.63	0.01	0.99 (0.64–1.54)	0.98
BMI (> 25)							2.27	0.71 (0.46–1.11)	0.13
Hypertension							*5.55*	*2.42 (1.16–5.06)*	*0.01*
Diabetes							1.17	1.32 (0.80–2.17)	0.28
LDL-c (≥ 130 mg/dL)							*9.94*	*2.01 (1.30–3.09)*	*< 0.01*
Smoking							0.97	1.25 (0.80–1.94)	0.32
Previous IS or TIA							1.39	0.67 (0.35–1.30)	0.24

Numbers in italicized represent statistical differences

p value, *BMI* body mass index, *LDL-c* low-density lipoprotein cholesterol, *IS* ischemic stroke, *TIA* transient ischemic stroke, *MT* missing teeth. Numbers in italicized represent statistical differences

Table 3 Univariate and multivariate regression analyses for the association between TL and mRS score. Hazard ratio (HR) and Wald Cox regression. Model 1: unadjusted analyses; model 2: adjusted for sociodemographic variables; model 3: adjusted for sociodemographic and medical variables

Variables	Model 1			Model 2			Model 3		
	95% CI			95% CI			95% CI		
	Wald	HR	*p*	Wald	HR	*p*	Wald	HR	*p*
Tooth loss									
None and slight (0–8 MT)		1			1			1	
Moderate (9–22 MT)	3.29	1.79 (0.95–3.37)	0.07	1.82	1.56 (0.82–3.00)	0.18	0.73	1.42 (0.63–3.20)	0.39
Severe (23–28 MT)	*7.39*	*2.34 (1.27–4.32)*	*< 0.01*	*3.99*	*1.94 (1.01–3.73)*	*0.04*	*4.35*	*2.40 (1.05–5.46)*	*0.03*
Age (≥ 60 years)				1.79	1.40 (0.85–2.31)	0.18	< 0.01	0.98 (0.51–1.90)	0.96
Sex (male)				0.70	1.19 (0.79–1.79)	0.40	0.39	1.17 (0.72–1.91)	0.53
BMI (> 25)							*4.11*	*0.60 (0.36–0.98)*	*0.04*
Hypertension							1.33	1.48 (0.76–2.88)	0.25
Diabetes							0.13	0.96 (0.52–1.80)	0.91
LDL-c (≥ 130 mg/dL)							0.18	1.13 (0.65–1.94)	0.67
Smoking							0.16	0.90 (0.53–1.52)	0.69
Previous IS or TIA							0.06	1.09 (0.56–2.11)	0.80

Numbers in italicized represent statistical differences

p value, *BMI* body mass index, *LDL-c* low-density lipoprotein cholesterol, *IS* ischemic stroke, *TIA* transient ischemic stroke. Numbers in italicized represent statistical differences

mRS scores. Model 1 is the unadjusted analysis, model 2 is adjusted for sociodemographic variables, and model 3 is adjusted for sociodemographic and medical variables. Model 3 reveals that severe tooth loss (23 to 28 missing teeth) (PR = 2.40, 95% CI = 1.05–5.46) and higher BMI (> 0.25) (PR = 0.60, 95% CI = 0.36–0.98) were independently associated with more severe mRS scores (> 2), presenting the highest strengths of association (Wald chi-square values of 4.35 and 4.11, respectively).

Table 4 shows the multivariate analysis for the relationship between tooth loss and the subtypes of cerebral ischemia (TOAST classification), adjusted for the socioeconomic and medical variables. Moderate tooth loss (9 to 22 missing teeth) was independently associated with cardioembolism or ESUS etiology (PR = 1.90, 95% CI = 1.01–3.57).

Discussion

Dental caries and periodontitis are highly prevalent diseases and the major reasons for tooth loss [5]. As a consequence, tooth loss serves as a strong surrogate measure of a history of oral disease [7]. Present results support the hypothesis that tooth loss is independently associated with higher levels of CAB among patients with cerebral ischemic events. Noteworthily, a poorer score of mRS was also independently

Table 4 Multivariate regression analyses for the association between tooth loss and TOAST classification. Prevalence ratios (PR) and 95% CI

Etiology of cerebral ischemia[a]	PR[d] by tooth loss			
	N	None and slight	Moderate	Severe
Large-artery atherosclerosis	94	1	0.72 (0.41–1.28)	0.95 (0.54–1.67)
Cardioembolism or ESUS[b]	107	1	*1.90 (1.01–3.57)*[c]	1.22 (0.61–2.45)
Small-vessel occlusion	67	1	0.57 (0.31–1.03)	0.53 (0.27–1.03)
Cryptogenic	131	1	1.03 (0.67–1.58)	1.26 (0.81–1.96)

Numbers in italicized represent statistical differences

[a] Ten patients had other determined etiology and were not analyzed

[b] A total *N* = 107, 74 are cardioembolic and 33 are ESUS

[c] *p* value significant ($p < .05$)

[d] Adjusted for age, sex, BMI, hypertension, diabetes, LDL-c, smoking, and previous IS or TIA

associated with tooth loss. To our knowledge, this study is novel on reporting an association between CAB, disability (mRS), and tooth loss among IS or TIA patients.

In the present study, CAB was evaluated using MDCTA, in contrast to other investigations that used ultrasound [21]. Even though ultrasound is a noninvasive, affordable, and safe method, MDCTA is more accurate in quantifying the intensity of the stenosis [22, 23].

Severe tooth loss was associated with high levels of CAB, independent of age, sex, and other potential medical confounders. Interestingly, the strength of the association of severe tooth loss (Wald chi-square = 5.48) and hypertension (Wald chi-square = 5.55) was similar, and the latter is a classic risk factor related to carotid stenosis. Thus, based on present findings, the number of remaining permanent teeth may improve the prediction of the occurrence of cardiovascular events, especially those of atherosclerotic origin.

Previous studies evaluated the association between oral health and AVD among patients with no history of ischemic events, with similar results [24]. Noteworthy, present findings measured this association in an "unhealthy" population, which reinforces the possible impact of chronic oral disease on general health. To date, only two studies evaluated the relation between periodontitis and vascular events in patients with history of IS or TIA. In both studies, severe periodontitis was significantly associated with recurrent vascular events and an increase of aortic arch atheroma plaque thickness [25, 26].

The independent association between moderate tooth loss and cerebral ischemia of embolic origin supports the hypothesis that bacteria from periodontitis and apical periodontitis may contribute to a prothrombotic state, presumably by activating or stimulating the coagulation system. A study by Loubakos *et al.* [27] linked the main molecular mechanism between *Porphyromonas gingivalis*, the pathogen with high prevalence in periodontitis and apical periodontitis, and the activation of coagulation factors, promoting platted aggregation and clot development.

Given the high prevalence of periodontists in adults, it is likely that the group with moderate tooth loss presented with periodontally affected teeth, thus enabling the occurrence of transitory bacteria, and the activation of the coagulation cascade leading to the formation of blood clots. In contrast, the group with severe tooth loss, even with presumptive evidence of past dental infection, presumably had a lower burden of oral microbial pathogens than in the other groups at time of the examination.

Although several patients in this study presented cerebral ischemia caused by large-artery atherosclerosis, when the association between tooth loss and IS subtype was adjusted for medical covariates in the analysis, tooth loss did not exhibit a significant relationship with IS due to large-artery atherosclerosis. Possible factors attributed to this result may be the strength of other traditional risk factors for lacunar and atherothrombotic stroke, such as age, hypertension, and diabetes [28].

Tooth loss was assessed as the main oral health exposure, which may be a limitation of the present study. Although tooth loss has been widely accepted as a strong surrogate of the history of oral infectious-inflammatory diseases in epidemiological investigations [7], present results must be interpreted with caution, since no direct evaluations of oral infection and oral inflammation were available. Moreover, due to the retrospective design of this study, it was not possible to discriminate tooth loss attributable to caries, periodontitis, and endodontic infection. On the other hand, the association observed in the present investigation between tooth loss and high levels of CAB and mRS scores seems to be of high clinical relevance, considering that the number of permanent natural teeth can be easily assessed and can be accurately self-reported [29], with no need of specific equipment or trained staff.

In addition, the present findings must be interpreted with the understanding that oral diseases are associated with noncommunicable major chronic conditions that share common risk factors, such as age, general lifestyle, smoking, eating behavior, and socioeconomic status. Hence, there is evidence [30] that the adjustment for these traditional risk factors may weaken the relationship between oral health and cardiovascular diseases. Nevertheless, adjusted models revealed an independent association between tooth loss, CAB, and mRS in this sample.

Another limitation of the present study is the lack of sociodemographic variables such as education and income, which were not available. However, the classic medical risk factors for CVD were included in the analysis. Another consideration is the relatively small sample size ($N = 418$). Nonetheless, the post hoc power of the present sample was 99%, with $\alpha = 5\%$, given the distribution of the main exposure (tooth loss) and the main outcome (CAB), where 23.5% of the individuals with none or slight tooth loss had CAB < 50%, and 52.7% of the participants with severe tooth loss had CAB ≥ 50%.

Aging, diabetes, and hypertension have been recognized as predictors to a poor outcome after IS [31]. In the present study, only severe tooth loss and BMI < 25 were independently associated with poorer mRS scores. We have to be cautious when interpreting these results: BMI is an accepted method to evaluate the nutritional status. However, this method presents some limitations, especially when evaluating an older population [32]. Through the years, changes occur in the body composition, and older people lose muscle mass and generally increase the intramuscular fat mass [33]. The BMI does not accurately measure the quantity of fat and muscle present since an individual with low BMI does not necessarily present a good nutritional condition.

Severe tooth loss was also independently associated with a poorer mRS score in this study, which is in accordance with previous studies [8]. There is strong evidence that the elevation of the systemic levels of inflammatory marks, especially interleukin-6 and C-reactive protein, is independently related

to the severity of the stroke and poor outcome after stroke [34]. Nevertheless, parallel to the transitory bacteremia of oral origin, periodontitis and apical periodontitis can also contribute to the increasing levels of systemic pro-inflammatory mediators such as CPR and interleukins [35, 36].

Due to the observational nature of this study, we cannot assign causality to our findings. Nevertheless, chronic infection and inflammation are considered important risk factors for atherosclerotic disease and functional outcomes. The result of this study, which captures surrogate information on the history of oral infection, is consistent with current knowledge of infection, inflammation, and atherosclerosis. Discovery of novel potential risk factors such as tooth loss, related to the early stage and progression of CAB, could ultimately lead to new approaches for prevention in the general population and further reduction in morbidity and mortality from cardiovascular diseases. Furthermore, these results encourage future laboratory and clinical interventional research related to this association, which may contribute to a better understanding of the oral-systemic relationship.

In conclusion, tooth loss was independently associated with CAB and predicted a poorer functional outcome among IS and TIA patients. Clinical assessment of tooth loss, or history of oral infection, may provide important information on risk for CAB and poorer functional outcome among patients with IS or TIA.

Author contributions Leão TS contributed to the study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, drafting of the manuscript, and approval of the final version of the manuscript. Tomasi G contributed to acquisition of data, analysis and interpretation of data, and approval of the final version of the manuscript. Ibrahim MS contributed to statistical analysis, analysis and interpretation of data, and approval of the final version of the manuscript. Conzatti L contributed to acquisition of data, statistical analysis, and approval of the final version of the manuscript. Marrone LP contributed to the study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. Reynolds MA contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. Gomes MS contributed to the study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final version of the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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