RESEARCH ARTICLE

Editorial Process: Submission:02/14/2025 Acceptance:09/08/2025 Published:09/12/2025

Risk Factors for Oral Mucositis in Pediatric Oncology Patients Undergoing Chemotherapy: A Prospective Cohort

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Abstract

Objective: To verify the risk factors for incidence and severity of oral mucositis (OM) in children and adolescents during anticancer treatment. **Methods:** A prospective cohort was carried out with 105 patients under 19 years, followed for ten consecutive weeks and submitted to chemotherapy (CT) with or without another treatment modality. Sociodemographic variables were collected using a specific form, with CT regimens obtained from medical records and the oral cavity evaluated by Oral Modified Assessment Guide (OAG). Bivariate comparison tests were used to summarize data and test within- and between-group differences. The longitudinal changes in the participants' condition were modeled by mixed-model regression, using generalized estimating equations. **Results:** The incidence of mild/moderate and severe OM (SOM) ranged from 43.8% to 64.8% and 16.2% to 31.4%, respectively. The sex, age, type of tumor, treatment modality did not statistically influence the severity of OM. The longer the time since the chemotherapy session, the lower the risk of presenting OM and SOM. However, the chances of OM or SOM not occurring at longer intervals between chemotherapy sessions were very low. In most patients who developed OM, the mild/moderate condition persisted for ten weeks and the severe form for three weeks. *Conclusion:* Children and adolescents with cancer showed oscillations in the severity of OM during antineoplastic treatment and only the time since the last chemotherapy was statistically significant for severity of OM and OAG score.

Keywords: Mucositis- Risk Factors- Child- Pediatrics

Asian Pac J Cancer Prev, **26 (9)**, 3319-3329

Introduction

Childhood cancers differ from adult cancers in terms of etiology (which is not related to lifestyle, and only a few types are paternally inherited); lower rate of genetic mutation, and metabolic response to chemotherapeutic drugs [1]. Their treatment can be through surgery, chemotherapy, radiotherapy, immunotherapy, and stem cell transplantation, depending on the type of tumor and stage [2]. However, chemotherapy alone is the standard treatment for major cancers that affect children and adolescents or in combination with surgery or radiotherapy [3].

Several chemotherapy protocols are used in the treatment of children and adolescents, which may include a single or multiple highly toxic drugs due to their lack of specificity [4]. Non-specific chemotherapeutic agents can cause cumulative systemic toxicity, worsened by the duration of treatment [5]. Generally, the dose capable of killing cancer cells and causing toxicity in healthy tissues is borderline [4].

Oral mucositis (OM) is the most frequent toxicity in children and adolescents undergoing chemotherapy [6]. They may develop OM in approximately 43% [7] to 64% [4] of cases. Meanwhile, the incidence of the severe form of oral mucositis (SOM) can range from approximately 9% [4] to 36% [8]. Risk factors for the occurrence and severity of OM may be related to the patient (age, sex, nutritional and oral health status) or to the treatment (treatment modality, chemotherapy agent, dose, among others) [9].

The management of the patient during cancer treatment, with emphasis on OM, should be focused on the prevention and rapid treatment of ulcerations of the oral mucosa, since they predispose the patient to secondary infections by viruses, fungi, and bacteria. In addition, OM affects basic functions (such as eating, talking, drinking, and swallowing), impacts hospitalization time and cost, nutritional status, and quality of life [10].

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In this scenario, children and adolescents undergoing anticancer treatment need to more carefully look at oral healthcare, seeking individualized care, which may reflect in improved quality of life and have a positive impact in cancer therapy, reducing situations related to the increase in hospitalization time and an increase in treatment costs [11].

Although there are several studies that evaluate the possible risk factors for the occurrence of OM in children and adolescents with cancer, they differ from each other. They do not present strong scientific evidence of their role in the development of OM [6,12,13]. De Farias Gabriel et al. [12] conducted a systematic review and meta-analysis to identify the risk factors associated with the development of OM in pediatric oncology patients and, as a limitation, they did not take into account the risks for the severe form of OM. Therefore, the primary objective of this study was to verify the incidence and severity of OM in pediatric patients undergoing chemotherapy for 10 consecutive weeks, as well as the factors associated with its occurrence. The study hypotheses are that the incidence of OM and SOM differ during the follow-up and that the factors associated with the occurrence of OM are different from SOM.

Materials and Methods

Study design

This study consists of a short-term prospective cohort, where subjects (oncopediatric patients) were identified, followed up and risk factors for the occurrence of the outcome (OM and SOM) were evaluated. It followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guideline for Reporting cohort studies" [14].

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was received by the Ethics Committee on Human Research under Presentation Certificate for Ethics Assessment number 12922113.8.0000.5188. All patients or legal guardians signed informed consent to be included in this study.

Setting

Children and adolescents with cancer were recruited from the pediatric oncology sector in Napoleão Laureano Hospital, located in João Pessoa, Paraiba, Northeast Brazil. This hospital is a reference center for prevention, diagnosis, and cancer treatment. Approximately 392,278 outpatient visits and 5,509 outpatients are performed annually at this location. The pediatric ward has 21 beds and the pediatric ICU has six beds [11]. The participants were selected and followed up for 10 consecutive weeks.

Participants

An accessible sample of inpatients and outpatients, both genders, between 0 to 19 years old, assisted by the Pediatric Oncology Service of the hospital was included in this study. The eligibility criteria were diagnosed and treated for some type of malignancy; did not start cancer treatment; were programmed to receive chemotherapeutic treatment for the first 10 weeks; did not received radiotherapy in the head and neck region; did not have inflammation of the oral mucosa before starting chemotherapy; and the caregiver gave consent for the child/adolescent to participate in the study.

The number of patients admitted in the pediatric oncology sector during the research period and who met the eligibility criteria determined the sample size.

Variables of the study

The dependent variables were obtained coded in an ordinal scale as without OM (score 0); mild or moderate OM (score 1); or SOM (score 2), in addition to the modified Oral Assessment Guide (OAG) score [15].

The independent variables of interest for this investigation were: sex ("male" / "female"), age ("0 to 12 years old"/ "13 to 19 years old"), local of residence ("capital city" / "Interior of State" / "Other State"), ethnicity ("White" / "Black" / "Brown" / "Indigenous"), baseline disease, type of tumor ("hematological" / "solid"), treatment modality ("Chemotherapy" / "Chemotherapy + surgery" / "Chemotherapy + radiotherapy" / "Chemotherapy + radiotherapy + surgery"), number of chemotherapy sessions (in days), period since the last chemotherapy (in weeks), death ("yes"/ "no"), oral assessment guide per site ("voice", "swallow", "lips", "tongue", "saliva", "palate", "labial mucosal", "gingiva"), leukocytes and platelets counts and creatinine blood level ("normal", "altered"), granulokine administration ("yes" / "no"), platelet concentrate infusion ("yes" / "no"), laser therapy ("yes" / "no"), and treatment interruption ("yes" / "no").

Data source/measurement

The sociodemographic and clinical variables were collected from the medical records at the beginning of the research. The laboratory data were collected from the medical records once a week. The outcomes Oral Mucositis (OM) and Severe Oral Mucositis (SOM) were evaluated weekly, during a 10-week period, using the modified OAG [15] by one researcher calibrated (kappa>0.85).

The OAG scale was based on the assessment of eight items (voice, swallowing, lips, tongue, saliva, palate, labial mucosa, and gingiva) through scores of 1 to 3, which scores 1 indicates normal status, score 2 represents slight changes of oral structures and functions without lesions, and score 3 represents severe alterations. Each item is given a score (from 1 to 3), producing individual scores ranging from 8 to 24. If the total OAG value equals 9 or greater, it means that the patient has OM. If any of the eight items scores 3, then the patient was diagnosed with SOM [15].

At each follow-up week, all patients and caregivers were clinically evaluated and instructed to perform strict oral hygiene care. If OM was diagnosed (OAG score greater than or equal to nine, indicating at least one change in the oral mucosa), low-level laser therapy was performed according to the protocol: wavelength of 660nm, power

of 40mW, and dose of 4J/cm2, applied locally for 30 s on reddish, erosive and/or ulcerated regions (ECCO Fibras e Dispositivos/Brazil – Model BM0004A).

Thus, all the patients received oral health surveillance and were treated for OM and other oral problems. For this reason, this factor was controlled and the variables "oral hygiene", "dental treatments" and "treatment of oral mucositis" were not included in the statistical analysis with the other variables. The leukocyte, platelet and creatinine counts were considered normal whose values were between 3,500 and 10,000mm3, 150,000 and 450,000mm3, 0.5 to 1.0mg/dl; respectively. Values above or below normal were classified as "altered".

Statistical methods

Descriptive statistics and bivariate comparison tests were used to summarize data and test within- and between-group differences. Incidence rates were calculated for longitudinal data, including weekly cumulative incidences for each occurrence of OM or SOM during the 10-week follow-up.

The Poisson regression with robust error variance was used to model the recurrent data (the number of times the participant was diagnosed as having OM or SOM). Since different individuals had different numbers of recurrent events, the Poisson regression assumes that the outcome (i.e., the number of events of interest that happen in a given interval) follows a Poisson distribution with a fixed rate of event occurrence over time. The effects of independent clinical variables (age, gender, and clinical factors) were expressed as incidence rate ratios (IRR and 95% confidence intervals) and tested for statistical significance.

Then, as the repeated longitudinal assessments were clustered among the participants, there was a violation of the assumption of independence of data. Hence, the longitudinal changes in the participants' condition were modeled by mixed-model regression, using generalized estimating equations (GEE). First, the original database was changed to a format that rearranges the groups of related columns (10-week assessments) into groups of rows in the new data file. The analysis was specified as binomial distribution, and Logit as the link function, in order to run the GEE model for the binary outcomes (OM and SOM), while for the OAG score a Gamma as the distribution and Log as the link function were used. GEE regression parameters were expressed as the odds ratio, at 95% confidence intervals, and the significance of the model effects was tested using Wald chi-square statistics.

All statistical analyses were performed using Microsoft Excel and IBM-SPSS 24.0 software, and statistical significance was set at $p<0.05$ to reject the null hypotheses.

Results

Were admitted to the hospital 115 new patients who met the eligibility criteria for the study. During this period, seven patients died, two were transferred to another hospital and one started radiotherapy in the head and neck region. A total of 105 children were included in this cohort study, 57 (54.3%) male and 48 (45.7%) female. Age ranged from 0 to 18 years (mean ± DP = 7.3 ± 5.2). Most of the children were of black or brown race (n=72; 68.6%), and residents in the countryside or other States (n=68; 64.8%). The main clinical features of the study sample are depicted in Table 1.

Concerning dental status, median (and interquartile range) values for DMFT and dmft indexes were 1.0 (2.0) and 0.5 (2.0) for children with permanent and primary teeth, respectively. The number of chemotherapy sessions during the 10-week follow-up ranged from 3 to 10 sessions (mean ± DP = 5.9 ± 1.7). The occurrence of OM and SOM was assessed at all ten consecutive weeks, and data were expressed as incidence rates. Summary data on OM is detailed in Table 2, showing that the incidences of OM ranged from 43.8% to 64.8%., and SOM ranged from 16.2% to 31.4% throughout the weekly assessments. When the participants' statuses were considered according to their weekly changes, a significant difference was only found between the first and second weeks (p=0.014) – 31 (29.5%) worsened their status.

From a total of 1050 assessments during the 10-week period, 252 (24.0%) observations were free from OM, in 547 assessments (52.1%) participants had OM, and in 251 assessments (23.9%) participants were diagnosed as having SOM. Therefore, the mean (and 95% confidence

Table 1. Main Demographic and Clinical Characteristics of the Study Sample (n=105)

Variables	Categories	n (%)
Sex	Male	57 (54.3)
	Female	48 (45.7)
Age groups	0 – 12 years-old	81 (77.1)
	13 – 19 years-old	24 (22.9)
Race	Brown	50 (47.6)
	White	32 (30.5)
	Black	22 (21.0)
	Indigenous	1 (1.0)
Local of residence	Countryside	66 (62.9)
	Capital city	37 (35.2)
	Other State	02 (1.9)
Baseline disease	Acute Lymphoblastic Leukemia	42 (40.0)
	Wilms Tumor	18 (17.1)
	Osteosarcoma	13 (12.4)
	Others	32 (30.5)
Type of tumor	Hematologic	54 (51.4)
	Solid	51 (48.6)
Treatment	Chemotherapy	69 (65.7)
	Chemotherapy + surgery	26 (24.8)
	Chemotherapy + radiotherapy	5 (4.8)
	Chemotherapy + radiotherapy + surgery	5 (4.8)
Number of chemotherapy sessions	3 – 4	22 (21.0)
	5 – 6	48 (45.7)
	7 – 8	29 (27.6)
	9 – 10	6 (5.7)
Death	No	91 (86.7)
	Yes	14 (13.3)

Table 2. Incidence Rates of OM and SOM, Severity Scores, and Changes in Status According to the Follow-up Week

Week	OM (%)	SOM (%)	OM+SOM (%)	Severity score mean (95%CI)	Unchanged status	p-value*
1st week	60 (57.1)	19 (18.1)	79 (75.2)	0.93 (0.81 – 1.06)	–	–
2nd week	54 (51.4)	33 (31.4)	87 (82.9)	1.14 (1.01 – 1.28)	57 (54.3)	0.014
3rd week	46 (43.8)	29 (27.6)	75 (71.4)	0.99 (0.84 – 1.14)	43 (41.0)	0.158
4th week	56 (53.3)	28 (26.7)	84 (80.0)	1.07 (0.93 – 1.20)	52 (49.5)	0.314
5th week	62 (59.0)	21 (20.0)	83 (79.0)	0.99 (0.87 – 1.11)	45 (42.9)	0.391
6th week	46 (43.8)	31 (29.5)	77 (73.3)	1.03 (0.88 – 1.17)	52 (49.5)	0.702
7th week	56 (53.3)	22 (21.0)	78 (74.3)	0.95 (0.82 – 1.08)	75 (71.4)	0.214
8th week	46 (43.8)	33 (31.4)	79 (75.2)	1.07 (0.92 – 1.21)	62 (59.0)	0.107
9th week	68 (64.8)	17 (16.2)	85 (81.0)	0.97 (0.86 – 1.09)	72 (68.6)	0.096
10th week	53 (50.5)	18 (17.1)	71 (67.6)	0.85 (0.71 – 0.98)	63 (60.0)	0.056

* Changes compared to the previous week; OM, oral mucositis; SOM, severe oral mucositis; Bivariate comparison tests.

Table 3. Frequency of the Scores of the Modified Oral Assessment Guide (OAG), According to Assessed Categories, throughout the 10-Week Period (% in Parenthesis)

Categories	Normal (score 1)	Slight changes (score 2)	Severe changes (score 3)	Mean (SD) score
Saliva	292 (27.8)	647 (61.6)	111 (10.6)	1.83 (0.60)
Lips	716 (68.2)	216 (20.6)	118 (11.2)	1.43 (0.69)
Labial mucosa	927 (88.3)	48 (4.6)	75 (7.1)	1.19 (0.54)
Tongue	983 (93.6)	38 (3.6)	29 (2.8)	1.09 (0.37)
Palate	986 (93.9)	43 (4.1)	21 (2.0)	1.08 (0.34)
Gingiva	990 (94.3)	35 (3.3)	25 (2.4)	1.08 (0.35)
Swallow	999 (95.1)	31 (3.0)	20 (1.9)	1.07 (0.32)
Voice	1022 (97.3)	16 (1.5)	12 (1.1)	1.04 (0.25)
Overall score	6915 (82.3)	1074 (12.8)	411 (4.9)	1.23 (0.52)
Summative score	–	–	–	9.76 (0.96)

intervals) of the number of weeks with OM or SOM were 7.6 (7.1 – 8.1) and 2.4 (2.0 – 2.8), respectively. The distribution of the number of cumulative weeks of participants with OM or SOM is shown in Figure 1.

The number of weeks with OM was significantly higher (p=0.002) for younger participants (age range 1 – 12 years old) compared to older participants (age 13 – 19 years old). No influence of age was observed on the cumulative incidence of SOM (p=0.606). Moreover, the association between the number of weeks with OM or SOM and other independent variables (age, sex, tumor type, metastasis, and treatment modality) were tested using Poisson regression. No significant effect was found, except for the participant's age group (IRR = 1.26; 95%CI

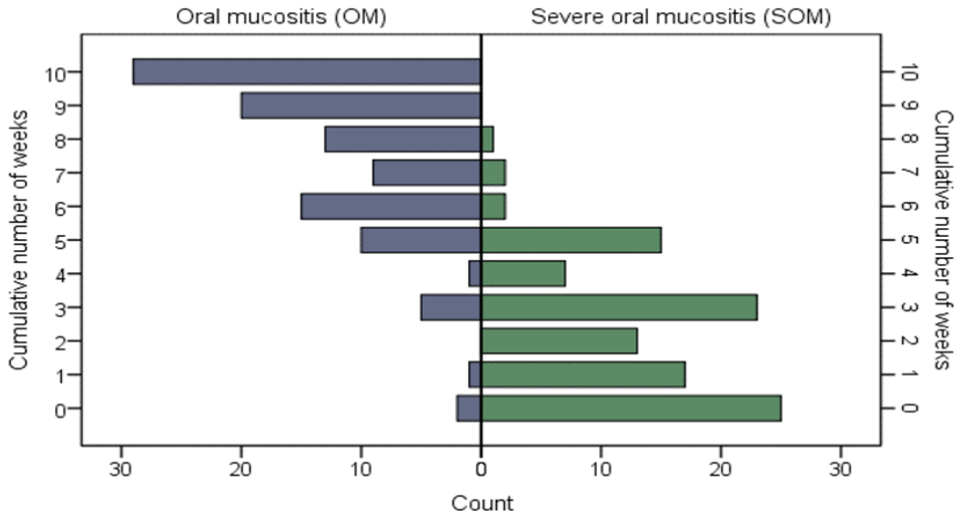

Figure 1. Cumulative Number of Weeks the Participants (n=105) had OM or SOM during the 10-week weekly assessment (n=1050).

Table 4. The Estimated Regression Parameters of Variables on the Changes in the Incidence of Oral Mucositis (OM), Severe Oral Mucositis (SOM), and Oral Assessment Guide (OAG) scores.

Dependent variable	OM[a] Exp B (95% CI)	p-value[a]	SOM[b] Exp B (95% CI)	p-value[b]	OAG score[c] Exp B (95% CI)	p-value[c]
Intercept	2.30 (1.51; 3.51)	0.000	0.31 (0.20; 0.48)	0.000	9.29 (9.02; 9.57)	0.000
Sex (male)	1.63 (1.00; 2.64)	0.048	1.23 (0.82; 1.85)	0.314	1.03 (0.99; 1.06)	0.152
Age (older)	3.38 (1.68; 6.76)	0.001	1.25 (0.77; 2.04)	0.363	1.07 (1.03; 1.12)	0.001
Time after chemotherapy (weeks)	0.97 (0.95; 0.99)	0.038	0.98 (0.96; 0.99)	0.009	0.998 (0.996; 0.999)	0.000
Hematologic tumor	1.26 (0,77; 2.04)	0.349	1.16 (0.76; 1.77)	0.474	1.04 (1.00; 1.07)	0.024
Treatment (combined CTP + RT and/or surgery)	1.20 (0.47; 3.02)	0.696	0.71 (0.39; 1.30)	0.276	1.01 (0.95; 1.08)	0.675

[a,b,c], Columns with the same superscript letters are related.

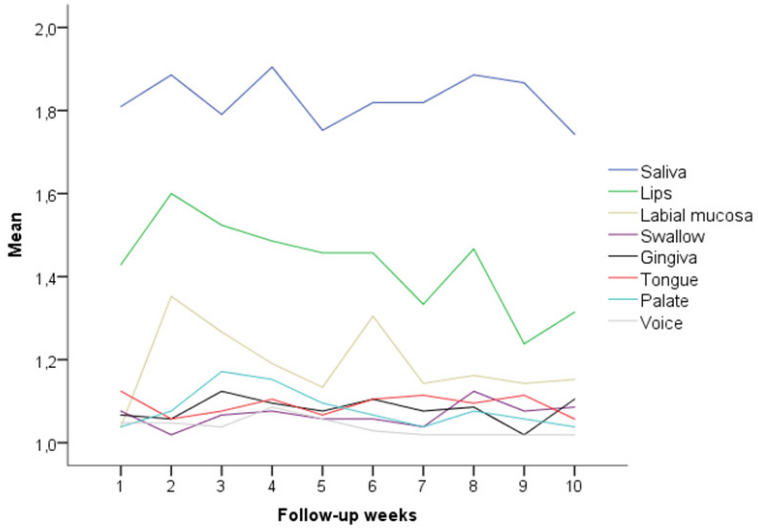

Figure 2. Changes in the Mean Score Values of the OAG Categories throughout the 10-Week Follow-up

= 1.11 – 1.43; p<0.001).

Regarding the Oral Assessment Guide (OAG) assessment, Figure 2 shows the changes in the mean score values of the OAG categories throughout the 10-week follow-up. Summary data are detailed in Table 3, showing a higher number of scores 2 and 3 were observed for "saliva" (mean ± DP = 1.83 ± 0.60) and "lips" (mean ± DP = 1.43 ± 0.69). The mean score of the overall categories was 1.23 (± 0.52). When the scores of all eight categories were summed, the summative score for the 105 participants ranged from 8.0 to 18.0 (mean ± DP = 9.76 ± 0.96). A slight significant increase in the summative OAG score was observed between the first (9.62 ± 1.6) and the second week (10.1 ± 1.9) (p=0.040), and no further changes were observed in the following weeks compared to the first week (p>0.05).

Then, multiple regression models for longitudinal dependent data were constructed to assess the influence of independent variables on the changes in the incidence of OM and SOM, and OAG scores. The final regression models using Generalized Estimating Equation are detailed in Table 4.

Only the time since the last chemotherapy was associated with the occurrence of OM (p=0.038; 95% CI: 0.95; 0.99), SOM (p=0.009; 95% CI: 0.96; 0.99) and OAG score (p=0.000; 95% CI: 0.996; 0.999).

Discussion

Despite being a short-term cohort, studies with children with cancer with a follow-up of ten weeks or more are rare in the literature. The present study analyzed the sociodemographic, clinical and laboratory (hematological) aspects and cancer treatment-related characteristics that may influence the incidence and severity of OM in children and adolescents followed during the induction phase of cancer remission.

The therapeutic regimen of most protocols instituted at this stage is quite aggressive and, therefore, there is a greater susceptibility to adverse effects such as, for example, OM [16]. The time since the last chemotherapy was shown to be a risk factor for OM (regardless of severity). While age, sex, tumor type and treatment modality did not influence the incidence and severity of OM.

To the best of our knowledge, the literature is scarce of studies that have observed temporal relationships between chemotherapy sessions and mucosal toxicity, specifically in pediatric oncology patients. This reinforces the need for oral health surveillance in order to adopt timely preventive measures, especially in patients with a history of oral mucositis and short intervals between chemotherapy cycles.

It is observed in the present study that with each additional day since the last chemotherapy, the chances of

both oral mucositis (in general) and, specifically, severe oral mucositis occurring are reduced. According to the literature, this is due to the time required for the release of chemotherapy agents by the body. The long the time between doses, the more the body reduces the amount of toxic agents to healthy tissues [17]. The fact that it is time dependent makes these effects potentially reversible and, nutritional and/or chemical therapies can contribute to reduce the toxicity during therapies [18].

In Brazil, it is estimated 7,930 new cases of childhood cancers per year in the triennium 2023-2025 being more prevalent in males and in the southern region of the country [19]. In line with the epidemiological profile of Brazil, in the present study there was a predominance of male individuals. There is still no explanation in the literature for the greater propensity of males in the occurrence of childhood cancer however the presence of congenital defects may mediate the hypothetical causal association between them, especially in children under one year of age [20].

The patient's gender was not a variable that statistically influenced the incidence and severity of OM. Most studies in the literature do not present the frequency of OM according to sex in their results but Allen et al. [7], Attina et al. [21], and Carreón-Burciaga et al. (2018) [22] also found no statistically significant association between sex and OM, although it is more common among boys [22, 23].

In general, antineoplastic treatment acts on the direct or indirect destruction of cells with high mitotic activity, so, in addition to cancer cells, it causes damage to oral mucosa cells, especially in younger individuals whose cell renewal is more accelerated [24-26]. Attina et al. [21] found a higher prevalence of OM in individuals older than ten years, however the sample consisted only of patients with solid tumors. In the study by Pratiwi, Ismawati and Ruslin [23], the prevalence was higher in patients with ALL younger than seven years. In addition to the higher frequency, Carreón-Burciaga et al. [22] observed greater severity in patients aged 2 to 5 years compared to those aged 6 to 12. In contrast, Allen et al. [7] did not find statistical significance between OM and age. In our study, although older children and adolescents were 3.38 more likely to have mild/moderate OM (p=0.001), it was not possible to accept the alternative hypothesis (CI 95%:1.68; 6.76). This result may reside in the fact that the sample was mostly composed of younger individuals (0 to 12 years old).

As for the type of tumor, in the regional and local scenario, solid tumors correspond to 56.9% of cases in the Northeast region of Brazil and 57.3% in the state of Paraíba [27,28]. In the present study, the prevalence of hematological tumors was higher, since only Acute Lymphoblastic Leukemia (ALL) represented 40% of the sample. Damascena et al. [29] found that the frequency of OM was higher in children and adolescents with hematological tumors and in those patients the appearance of lesions was twice as fast compared to solid tumors. Allen et al. [7] concluded that the chance of developing OM in cases of hematological tumors was seven times greater than in solid and central nervous system tumors. In the multivariable GEE analysis, the type of tumor (hematological or solid) did not statistically influence the incidence and severity of OM and OAG score.

It is important to note that there is no cut-off point in the OAG total score to determine the severity of OM. For this study, it was adopted that if the patient presented code 3 in at least one category of the instrument, the diagnosis of SOM would be established. A patient who scored 16, for example, could add code 2 to all eight items (diagnosis: mild/moderate OM) or code 1 to one item, code 2 to six items, and code 3 to another item (diagnosis: MOG). Therefore, the total value of the OAG can be useful in identifying one or more items in the oral cavity that need dental care.

The incidence, survival and mortality rate of childhood cancer has been poorly documented, especially in low- and middle-income countries due to the scarcity of vital statistical data and quality records [30]. About 80% of children and adolescents with cancer are cured in high-income countries, while in other countries this rate is less than 30% [19]. The survival rate of the sample was higher than expected for high-income countries, however, the follow-up of patients was only two years. It is noteworthy that for cases of leukemia, kidney and liver tumors, the survival rate reduces to 73% among adolescents [3]. ALL, Wilms Tumor and Osteosarcoma represented 60% of the sample in the present study.

Only a few types of childhood cancers are caused by environmental or lifestyle factors, most with no known cause. Therefore, prevention should focus on early diagnosis of injuries. However, in low- and middle-income countries, the survival rate was lower and is associated with delayed or imprecise diagnosis, unavailability of adequate treatment, treatment abandonment, death due to adverse effects and preventable disease recurrence [19].

Hospital Napoleão Laureano is in the capital of Paraíba (Northeastern Brazil) and is a reference in the state for cancer treatment. The implementation of the Health Care Network in oncology has favored early diagnosis and treatment of cancer through professional training and improved resources [27]. However, in Brazil, large hospitals that perform more complex procedures perform better in health services and they are located in the South and Southeast regions, evidencing regional inequalities [31]. In addition, the distance and cost of moving patients to specialized health centers are associated with delays in cancer diagnosis [32]. About 64% of the sample resided in the countryside or in another state. Such variable may be indicative of a population whose access to health services is not adequate and contributes to a lower survival rate. However, the impact of place of residence and survival rate were not part of the scope of the present study and were included only for sample characterization.

Most of the study participants declared themselves as black or mixed race. The distribution of childhood cancer according to the skin color of the sample corroborates the hospital records of cancer in Brazil from 2000 to 2022, where the prevalence is higher in brown individuals in the Northeast, North and Center-West regions [33]. It is likely that genetic factors contribute to the risk of developing cancer in certain races/ethnicities.

Oral mucositis, Candida and herpes simplex infections, dry lips, xerostomia/ hyposalivation, neuropathic pain, gingivitis, and caries are the main oral complications of cancer treatment in the infant population [34,35].

The incidence of caries in both dentitions in children and adolescents during chemotherapy is higher than in healthy patients, being associated with changes in the quantity and quality of saliva and poor oral hygiene due to pain caused by OM, as well as emotional/psychological disorders [36]. The oral condition of the patients, assessed at baseline using the DMFT and dmft indexes, showed a low experience of dental caries and was important to verify the oral health status before starting cancer treatment and designing a dental treatment plan. However, the study did not set out to verify its incidence, as the follow-up period was short to evaluate clinically detectable cavitations.

Regarding the risk factors for OM in children, nowadays, evidence is dispersed and particularities associated with this population should be considered [12]. In addition to the risk factors analyzed in this study, others need to be taken into account. Among them, oral health care, genetic profile and nutritional status deserve to be highlighted. However, few studies have been conducted to determine their association with the occurrence and severity of OM in children and adolescents.

Specifically, in our study population, although not in the same sample, it is implemented a permanent oral health care for oncopediatric patients. The oral health-promoting strategies adopted in pediatric oncology sector in Napoleão Laureano Hospital were effective to reduce the incidence of OM in pediatric cancer patients. This finding being explained by improvement of patient's oral condition, reduction of biofilm accumulation, and promotion of periodontal health [37]. Furthermore, your parents/guardians improved knowledge and attitudes related to oral health, as provided increased surveillance in relation to the appearance of oral changes resulting from antineoplastic treatment [11]. In this respect, the Multinational Association of Supportive Care in Cancer/ International Society of Oral Oncology (MASCC/ISSO) advises the implementation of a basic oral care protocol, amid lack of high level of evidence studies about the management of OM in pediatric patients [38].

In addition, individual variants within a gene may directly interfere with the course of OM pediatric oncology patients [12]. Previous studies in the same cohort, but not in the same patients, showed that genetic variations increase the likelihood of OM [39] and also the occurrence of severe OM in oncopediatric patients [40]. Thus, the risk factors related to genetic diversity are potential important factors contributing to OM prediction.

Regarding the nutritional status, descriptions of nutritional imbalances and the potential risk for OM in children are lacking. However, lower body weight was significantly associated with a greater risk of OM [41], since the undernutrition results in loss of mucosal barrier integrity and poor wound healing which increases this risk [42]. OM is a common and significant adverse effect of QT, RT and hematopoietic stem cell transplantation (HSCT), with prevalence varying according to regimen and type of treatment [38, 43]. In children and adolescents undergoing chemotherapy the prevalence of OM can reach 90% in the mild/moderate form and 35% in the more severe form [13], being more frequent in this age group compared to adults due to the highest rate of cellular proliferation of the oral mucosal epithelium [26].

The incidence of OM was high during all follow-up weeks, being higher in the second week after the start of cancer treatment. SOM was observed in the first week and reached its highest incidence in the second and eighth weeks. There was a statistically significant difference in the incidence of OM only in the second week. The first signs of OM occur about three to five days after the start of chemotherapy, and then ulcers appear, reaching the maximum intensity of the lesions between seven and 14 days and resolution after a week [44].

Over ten consecutive weeks, patients underwent three to ten sessions of anticancer treatment. The initiation phase of OM begins immediately after the administration of QT or RT and a cascade of events is activated with each dose, being amplified and potentiated by molecular and cellular signals that result in tissue damage, prolonging the damage for days after the beginning of the antineoplastic treatment [45]. Therefore, the incidence observed in patients can be explained by the cumulative effect of chemotherapy in the oral cavity.

The longer the time since the chemotherapy session, the lower the risk of presenting OM, SOM and higher values of OAG. However, the chances of OM or SOM not occurring at longer intervals between chemotherapy sessions are very low. The risk of OM occurrence in children and adolescents has been related to the type of treatment (QT and/or RT), the therapeutic regimen (drug, dose, frequency of administration), patient-related factors (sociodemographic characteristics, genetic and epigenetic factors), systemic health parameters, oral health status, and tumor-related factors [12, 46]. In this context, a recent retrospective cohort study found that clinical variables, such as neutropenia, diagnosis of leukemia, and high-dose MTX protocols increase the chance of OM new cases [47].

In relation to this last clinical variable, the dose of the chemotherapeutic agent and the combination of some chemotherapeutic agents are important risk factors to OM [12]. In a previous study performed in the same oncological center, natural-type pharmaceutical products (44.8% to 57.1%) and antimetabolites (40.0% to 54.3%) were the most antineoplastic compounds administered to pediatric patients [48]. This last class of chemotherapeutic agents includes methotrexate and cytarabine, drugs identified as a potential risk factor to OM [49]. However, the dosage of chemotherapeutic drugs was not considered, being a limitation in the present study.

Saliva was the OAG category that presented the most alterations (codes 2 and 3). Chemotherapy and radiotherapy can trigger acute or late effects on the salivary glands, leading to changes in saliva composition, reduced salivary flow, or xerostomia/ hyposalivation in cancer patients [50]. Saliva plays an important role in maintaining oral health by lubricating the mucosa, controlling dental demineralization, assisting in the composition of the resident microbiota, having antimicrobial action, and assisting in chewing, swallowing, and speaking, among

other functions [51]. It is not clear in the literature whether salivary changes influence the severity of OM [52, 53] or whether saliva stimulation works to prevent OM [54]. However, from the clinical perspective of cancer patients, who are often physically and emotionally weakened, especially children, the multidisciplinary team must be aware of the repercussions of salivary changes on the patient's well-being during treatment.

Children and adolescents undergoing chemotherapy or stem cell transplantation have reported difficulty eating, swallowing, drinking, talking, and sleeping due to OM [55, 56]. Therefore, the OAG is an excellent instrument for evaluating the oral cavity of patients with cancer since, besides identifying erythema and ulcers, are evaluated saliva and patient's ability to speak and swallow.

The lip was the second category that most presented OAG codes 2 or 3. It is known that the lining mucosa of the oral cavity is more prone to develop OM lesions when compared to the keratinized oral mucosa [57]. However, few studies report the occurrence of OM according to the affected region [58]. According to Costa et al. [52], the cheek/palate mucosa was the most affected site by SOM. Guimarães et al. [8] found that the cheek/palate mucosa, lips and labial mucosa were the sites most affected by SOM. Although there are no explanations for the higher occurrence of OM in these sites, the knowledge of most affected sites by lesions are of paramount importance in preventing or controlling severity.

Given the heterogeneity in studies with children and adolescents with cancer, current scientific evidence does not allow conclusions about the effectiveness of interventions for OM in this population. Therefore, intervention protocols can be based on extrapolation of evidence of the adult population [38]. The use of substances that act as a physical barrier to protect the oral mucosa from irritation caused by cancer therapy were recommended in the prevention and treatment of OM [59]. In addition, honey and vitamin E have also been used in the lip or oral mucosa hydration, but it was not possible to establish a guideline [38].

Cryotherapy and photobiomodulation have been highly recommended for the prevention of oral and oropharyngeal mucositis in pediatric cancer and hematopoietic stem cell transplant patients [60]. In a recent systematic review investigating therapies for the prevention and treatment of oral mucositis in pediatric patients, laser therapy, palifermin, honey, and zinc demonstrated reductions in oral mucositis incidence, duration, severity, and pain reported by the patient. However, evidence of their efficacy is still inconclusive to establish accurate clinical protocols [61].

Currently, basic oral care has been suggested in the management of OM in cancer patients [62]. Furthermore, children and adolescents undergoing anticancer treatment need to more carefully look at oral healthcare, seeking individualized care. Therefore, it is important to expand the knowledge of patients and their parents/guardians about possible changes in the oral cavity resulting from cancer therapy [11].

Moreover, mucositis may have profound impacts on children and adolescents' quality of life and levels of psychological distress [55], becoming a constant concern for parents/caregivers [11]. In this sense, a study carry out in the same cancer center shows that dentists working with an oncology team positively impact the quality of life of patients (by the Health-Related Quality Of Life questionnaire - HRQOL) once patient's hospital stay may be long, being exposed to different chemotherapy protocols, frequently [63]. Corroborating these findings, in our study, pediatric patients were most commonly subjected to of 5-6 (45.7%) and 7-8 (27.6%) chemotherapy sessions, and it is important to highlight that the risk of OM is high in cases where the time since the last chemotherapy is shorter.

It is worth mentioning that, during the period in which the data from this study were collected, the hospital where the research was carried out does not have a dental team to monitor the oral health condition of hospitalized patients, and oral hygiene instructions and photobiomodulation were performed only once a week, according to the availability of the researcher who conducted the study.

Among the study limitations are the sample size and the absence of a control/comparison group. However, it should be noted that few studies have a sample of more than 100 patients, especially those followed for ten consecutive weeks and that cancer in children and adolescents is a rare condition. In addition, OM is an adverse effect that may occur concomitantly with other local and systemic changes in cancer patients, making it difficult to control confounding variables. However, such factors are controversial in the literature and, therefore, further studies are needed with children and adolescents with cancer with a low risk of bias and high scientific evidence. It is hard to conduct a study design that includes the various factors associated with the occurrence of OM described in the literature. Another limitation of the study was non-inclusion of the dose of chemotherapeutic agents.

Although, through a more robust statistical analysis, it was possible to identify the risk factors according to the severity of OM, taking into account the cumulative effect of the antineoplastic treatment on the oral cavity over ten weeks of follow-up. Still, no study in the literature evaluated the impact on the interval between chemotherapy cycles and the occurrence of OM.

The findings of this study suggest that close monitoring of the interval between chemotherapy sessions may be a key strategy for reducing the risk of oral mucositis (OM) in pediatric oncology patients. Given that shorter intervals were associated with a higher incidence and severity of OM, multidisciplinary teams should consider this variable when planning treatment support protocols, intensifying oral care practices and prophylactic interventions. Additionally, the results highlight the importance of integrating regular oral assessments into weekly clinical routines, particularly during the first weeks of treatment, when the risk of OM is highest. This proactive approach may help reduce the duration and severity of OM, improving patients' comfort, nutritional intake, and adherence to cancer therapy. The use of structured tools like the Oral Assessment Guide (OAG) also offers a practical method to guide early interventions and tailor individualized oral health support. In low-resource

settings, these insights can inform cost-effective measures focused on treatment timing, clinical surveillance, and preventive oral care education.

In summary, children and adolescents with cancer undergoing antineoplastic treatment had a high incidence of oral mucositis during ten weeks of follow-up. However, only the time since the last chemotherapy session are associated with the appearance of these lesions and OAG score.

Author Contribution Statement

Conceptualization: FGS, ILAR, AMGV; Methodology: FGS, ILAR, AMGV, CRL; Investigation and Formal analysis: FGS, ILAR, CRL; Writing - original draft preparation: FGS, PMMB, CRL, ILAR, SAS, AMGV; Funding acquisition: ILAR Supervision: ILAR, AMGV.

Acknowledgements

Funding statement

Authors are thankful to Coordination for the Improvement of Personnel Higher Education - Brazil (CAPES) - Funding Code 001. This manuscript is part of an approved first author's PhD study.

Ethics Committee Approval

The study protocol was approved by the Research Ethics Committee of the Federal University of Paraíba (Protocol number 12922113.8.0000.5188).

Availability of data

The data that support the findings of this study are available from the corresponding author upon request.

Conflict of interest

The authors have no conflicts of interest to declare.

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