



# Oral Mucositis in Children with Cancer in Southeast of Iran: A Single Center Study

Ghasem Miri-Aliabad <sup>1</sup>, Zahra Shahraki Ghadimi <sup>2,\*</sup>, Behnam Soltani<sup>3</sup>, Zeynab Nasri Nasrabadi<sup>3</sup>

<sup>1</sup> Department of Pediatrics, Ali Asghar Children Hospital, Iran University of Medical Sciences, Tehran, Iran

<sup>2</sup> Clinical Immunology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran

<sup>3</sup> General Physician, Zahedan University of Medical Sciences, Zahedan, Iran

\*Corresponding Author: Department of Pediatrics, Zahedan University of Medical Sciences, Zahedan, Iran. Email: hosnie.sh@gmail.com

Received: 13 October, 2024; Revised: 16 November, 2024; Accepted: 24 November, 2024

## Abstract

**Background:** Oral mucositis is a significant side effect in patients undergoing chemotherapy or radiotherapy, particularly in pediatric oncology.

**Objectives:** This study aimed to investigate the prevalence of chemotherapy-induced oral mucositis and its associated factors in children with malignancies.

**Methods:** This descriptive, prospective study included 100 children under 16 years of age with lymphohematopoietic malignancies, solid tumors, or central nervous system tumors admitted to the pediatric oncology department due to mucositis. Patients were categorized into three age groups: Zero - 5 years, 6 - 10 years, and 11 - 16 years. Data collected included demographic details such as age, sex, type of malignancy, and mucositis severity. The chi-square statistical test was used for data analysis.

**Results:** The average age of participants was  $7.84 \pm 3.93$  years. Sixty-one percent of the patients were boys, and 39% were girls. The age group 0 - 5 years had the highest prevalence of mucositis, while the 11 - 16 years age group had the lowest. The majority of mucositis cases (64%) were observed in children with acute lymphoblastic leukemia (ALL), followed by acute myeloblastic leukemia (AML) patients (12%), and other malignancies (24%). Grade II mucositis was the most common, affecting 34% of patients, while grade IV mucositis was the least common, affecting 13% of patients.

**Conclusions:** Chemotherapy-induced oral mucositis was most prevalent among children with acute leukemia, constituting three-quarters of the cases. Grade II mucositis was the most frequently observed severity level, while grade IV mucositis was the least frequent. These findings underscore the need for targeted strategies to manage and prevent mucositis, particularly in high-risk groups like pediatric leukemia patients.

**Keywords:** Oral Mucositis, Chemotherapy, Children

## 1. Background

In recent years, advances in the treatment of malignancies have significantly improved patient survival rates. However, these therapeutic advancements have brought new challenges, particularly regarding the side effects that impact the quality of life of cancer patients (1). Among these complications, oral mucositis is one of the most severe side effects encountered by patients undergoing radiotherapy or chemotherapy.

Studies indicate that approximately 5 - 15% of patients receiving standard chemotherapy protocols, and all patients undergoing radiotherapy with cumulative

doses exceeding 50 Gy, develop oral mucositis (2). The occurrence of oral mucositis is influenced by various factors, including the type of treatment and the sensitivity of individual patients (3). Patients receiving combined chemotherapy and radiotherapy for head and neck tumors, or those undergoing high-dose chemotherapy before bone marrow transplantation, are at a higher risk of developing severe oral mucositis.

The primary biological cause of mucositis is the direct toxicity of chemotherapy or radiotherapy, although secondary factors such as salivary gland dysfunction, local trauma, infections (both local and systemic), and other disruptions also play a role (4, 5).

Oral mucositis leads to severe, debilitating pain that significantly increases the morbidity associated with cancer treatments. The pain caused by mucositis often necessitates opioid pain management and, due to difficulties with oral intake, can require intravenous or enteral feeding. Severe mucositis can also disrupt treatment plans, sometimes leading to the suspension of therapy and a subsequent reduction in patient survival.

In addition to the physical discomfort, mucositis is associated with secondary complications such as nausea, vomiting, diarrhea, and significant quality-of-life decline, including sleep disturbances, anorexia, and weight loss. It also increases the length of hospital stays and the need for specialized interventions (4).

Oral mucositis is observed in 40% of adult patients receiving standard chemotherapy doses but is even more common in children, with a prevalence of 65% among pediatric cancer patients undergoing chemotherapy (6, 7).

## 2. Objectives

Given the prevalence of oral mucositis as a common complication of chemotherapy, this study investigates its prevalence and associated factors in children with malignancies undergoing chemotherapy.

## 3. Methods

This descriptive study was prospective, and all children aged 1 to 16 years with lymphohematopoietic malignancy, solid tumors, and central nervous system tumors who were admitted to the Pediatric Oncology Department of Aliebnabatab Hospital of Zahedan University of Medical Science in one year due to mucositis were included in the study. This hospital is the central and referral hospital for pediatric cancer patients in Southeast Iran. Patients with acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, Wilms' tumor, neuroblastoma, and brain tumor in the age range of 1 to 16 years were included in the study. The University Ethics Committee, with the code IR.ZAUMS.REC.1397.044, approved this study.

Patients with oral mucositis before chemotherapy and radiotherapy and older than 16 years were excluded from the study, and 100 patients were included in the study. Demographic information, including age, gender, height, weight, and Body Mass Index, was collected. Also, the type of malignancy and grade of mucositis were recorded based on the World Health Organization

(WHO) Scale. Mucositis can be measured by clinical toxicity scales such as Mucositis General Assessment Scales, several Mucositis Variable Scales, and Treatment-Specific Scales. From the most frequently used scale is the WHO, which classifies the severity of lesions into 4 degrees (8).

Before starting chemotherapy and radiotherapy, all patients were examined by a physician, and their condition was evaluated according to the WHO grading of oral mucositis.

Therefore, a score of 0 was considered for people without mucositis, and a score of 1 was considered for erythema without ulceration. Also, for the cases of erythema with ulcers, where the patient was able to eat solids, a score of 2 was given; a score of 3 was given for ulcer patients, where the patient was only able to eat liquids; and a score of 4 was considered for patients who were unable to eat food (Table 1) (8).

The patients were subjected to chemotherapy with the standard protocol, and after completion of chemotherapy and radiotherapy, they were examined for mucositis.

After completing the data collection, descriptive statistics, including percentage, frequency, mean, and standard deviation, were used to describe the data. All data were analyzed by SPSS version 21 software. Chi-square statistical test was used to check the significant relationship. (Figure 1).

## 4. Results

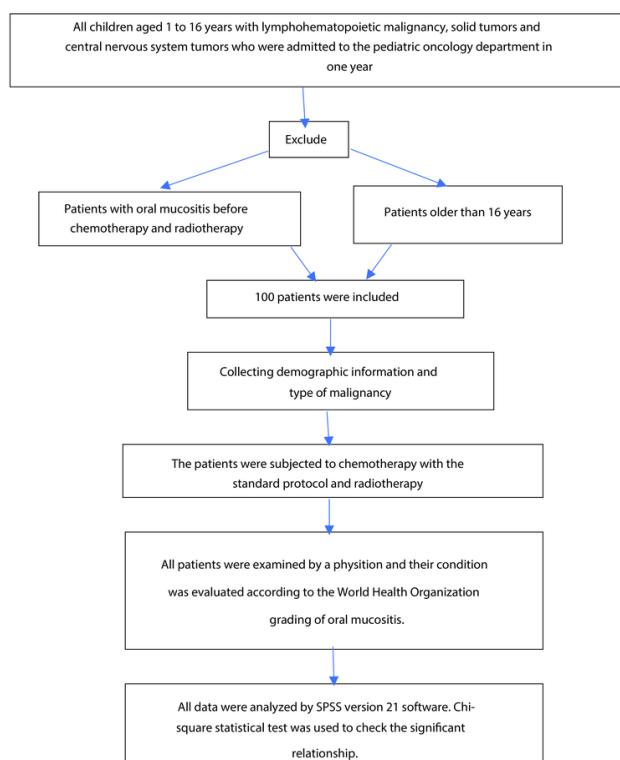
Out of 100 patients with mucositis, 61 (61%) were boys and 39 (39%) were girls. The mean age of the studied patients was  $7.84 \pm 3.93$  years. The largest number of patients with mucositis were ALL patients, comprising 64 patients (64%). Twelve patients (12%) with mucositis were AML, and 24 patients (24%) had other malignancies, such as Hodgkin's lymphoma, non-Hodgkin's lymphoma, neuroblastoma, and central nervous system tumors.

Thirty-four patients (34%) had grade II mucositis, which included the largest number of cases of mucositis caused by chemotherapy. The lowest number of patients with mucositis caused by chemotherapy was observed in grade IV disease (13 patients), and grade II mucositis was the most common (Table 2). Although there was no statistically significant relationship between the severity of mucositis and the gender of patients ( $P$ -value = 0.115), the number of male patients was four times that of female patients in grade III mucositis (Table 2).

In this study, patients were included in three age ranges: Zero to five years, 5 - 10 years, and 10 - 16 years.

**Table 1.** The World Health Organization Grades of Oral Mucositis (8)

Variable	Description
Grade	The World Health Organization grades of oral mucositis
0	No changes
I	Soreness/erythema
II	Soreness/erythema + ulceration + ability to eat solid foods
III	Soreness/erythema + ulceration + ability to use a liquid diet only
IV	Soreness/erythema + ulceration + no possible oral alimentation

**Figure 1.** The study flowchart

The second age group had the highest number of mucositis patients, and the third age group had the lowest number. Based on the chi-square statistical test, there was no significant relationship between age and severity of mucositis in patients ( $P$ -value = 0.543) (Table 3).

The highest number of patients with mucositis was observed in ALL malignancy (64 patients), with 26 patients in the second age group (6 - 10 years), 23

patients in the third age group (11 - 16 years), and 14 patients in the first age group (0 - 5 years) (Table 4).

The lowest number of patients with mucositis caused by chemotherapy was observed in AML malignancy, with 12 patients. No significant relationship was found between the types of mucositis caused by chemotherapy and the type of malignancy ( $P$ -value = 0.252).

Although chemotherapy protocols included several drugs, high-dose methotrexate, high-dose cytarabine, and anthracyclines were more likely to cause mucositis

**Table 2.** Mucositis Frequency According to Mucositis Grade and Sex

Variable	Grade I	Grade II	Grade III	Grade IV	Total
Sex					
Male	17	18	20	6	61
Female	11	16	5	7	39
Total	28	34	25	13	100

**Table 3.** Severity of Mucositis According to Age Group

Variable	Grade I	Grade II	Grade III	Grade IV	Total
Age group (y)					
0 - 5	10	11	11	2	34
6 - 10	9	16	8	7	40
11 - 16	9	7	6	4	26
Total	28	34	25	13	100

than other drugs. Mucositis following radiotherapy occurred only in three patients with nasopharyngeal rhabdomyosarcoma and medulloblastoma who underwent head and neck radiotherapy.

## 5. Discussion

In the present study, the highest number of patients with mucositis caused by chemotherapy had grade II mucositis, while the least number of patients had grade IV mucositis. The second age group (6 - 10 years) had the highest number of mucositis patients, and the third age group (11 - 16 years) had the lowest number. There was no significant relationship between age and the severity of mucositis in patients. Although the relationship between the severity of mucositis and the gender of patients did not show a statistically significant difference, in grade III mucositis, the number of male patients was four times that of female patients.

In the study by Allen et al., which aimed to investigate the prevalence and risk factors of oral mucositis in patients hospitalized in the oncology department, it was determined that the WHO Index of oral mucositis was 32.6% grade I, 34.9% grade II, 14.0% grade III, and 18.6% grade IV. These findings are consistent with the present study, where the highest percentage of mucositis was observed in grade II (9).

The findings of another study indicated that, unlike adults, in children with cancer undergoing chemotherapy, the incidence of oral mucositis is very low. However, the present study focused exclusively on children (10). The differences observed between the

above studies could be attributed to variations in the type of cancer and the treatment regimens used.

The study by Sonis and Clark showed that the prevalence of mucositis in children is higher than in adults with the same malignancy (11). In the current study, the age range of the patients was between 1.3 and 16 years, whereas the Sonis study compared children with adult patients.

The higher occurrence of mucositis in younger patients may be attributed to the higher rate of mitosis in basal cells. This increased mitotic activity can cause the mucous epithelium to lose its ability to regenerate itself, leading to atrophy, thinning, and ulceration of the tissue.

The study by Cheng et al. examined the risk factors of oral mucositis in children and adults undergoing chemotherapy and found no significant relationship between oral mucositis and age (12).

Similar to the results obtained in the present study, some studies have rejected the existence of a relationship between the gender of patients and the occurrence of oral mucositis. However, Gebri et al. reported female sex as an independent risk factor for the occurrence of oral mucositis (13). In contrast, a study by Atinna et al. found the prevalence of mucositis to be 50%, with no significant statistical difference in terms of gender, although a higher prevalence was observed in patients over 10 years old (3).

Given the differing results across studies, the effect of age and gender on the incidence and severity of oral mucositis in patients undergoing chemotherapy

**Table 4.** Prevalence of Mucositis According to the Type of Cancer and Age Group <sup>a</sup>

Age Ranges	Mucositis				Total
	Grade I	Grade II	Grade III	Grade IV	
<b>AML</b>					12
Second	1	6	4	-	11
Third	1	0	0	-	1
<b>ALL</b>					64
First	7	0	6	1	14
Second	7	9	4	6	26
Third	8	7	5	3	23
<b>Other tumors</b>					24
First	3	10	5	1	19
Second	1	1	0	1	3
Third	0	0	1	1	2

Abbreviations: AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia.

<sup>a</sup> First age group (0-5 years), second age group (6-10 years), third age group (11-16 years).

remains unclear, emphasizing the necessity for further research on the impact of these factors.

In the present study, the highest number of patients with mucositis was observed in ALL, followed by AML. This finding aligns with the study by Dehabadi et al., in which most patients participating had ALL, and the majority of patients with oral mucositis belonged to this group (14).

In the first three months of treatment, a significant number of patients with ALL, more than one-third of neuroblastoma patients, and over one-fifth of rhabdomyosarcoma and osteosarcoma patients developed oral mucositis. This incidence increased significantly in the second three months, during which all patients with rhabdomyosarcoma, neuroblastoma, and osteosarcoma, as well as most patients with ALL, experienced oral mucositis.

While some studies argue that mucositis is not directly related to a specific malignancy, others suggest that certain types of cancer may exacerbate the severity of oral mucositis. For instance, the study by Guimaraes et al. demonstrated that patients with hematological malignancies are at a higher risk of developing severe oral mucositis compared to those with solid tumors (15).

### 5.1. Conclusions

The findings of the present study showed that the highest number of mucositis patients (78%) occurred in ALL and AML. The highest number of patients with mucositis was observed in grade II disease, while the lowest number of patients with mucositis caused by chemotherapy was observed in grade IV disease.

There was no significant relationship between the severity of mucositis and the gender or age of the patients. Additionally, no correlation was found between the severity of mucositis and the type of malignancy.

### Acknowledgements

The authors thank the patients and their parents for their cooperation.

### Footnotes

**Authors' Contribution:** G. M. A.: Study concept, study design, manuscript writing, and literature search; Z. S. G.: Literature search and manuscript editing; B. S.: Data acquisition, statistical analysis, and manuscript writing; Z. N. N.: Literature search and manuscript editing.

**Conflict of Interests Statement:** The authors declare there are no conflicts of interest regarding the publication of this article.

**Data Availability:** The dataset presented in the study is available on request from the corresponding author during submission or after publication.

**Ethical Approval:** The Zahedan University Ethics Committee with the code [IR.ZAUMS.REC.1397.044](#) approved this study.

**Funding/Support:** The authors declared that they have no funding or support.

## References

- Leite Cavalcanti A, Jose de Macedo D, Suely Barros Dantas F, Dos Santos Menezes K, Filipe Bezerra Silva D, Alves de Melo Junior W, et al. Evaluation of Oral Mucositis Occurrence in Oncologic Patients under Antineoplastic Therapy Submitted to the Low-Level Laser Coadjuvant Therapy. *J Clin Med*. 2018;7(5). [PubMed ID: 29695071]. [PubMed Central ID: PMC5977129]. <https://doi.org/10.3390/jcm7050090>.
- Patel P, Robinson PD, Baggott C, Gibson P, Ljungman G, Massey N, et al. Clinical practice guideline for the prevention of oral and oropharyngeal mucositis in pediatric cancer and hematopoietic stem cell transplant patients: 2021 update. *Eur J Cancer*. 2021;154:92-101. [PubMed ID: 34252760]. <https://doi.org/10.1016/j.ejca.2021.05.013>.
- Attina G, Romano A, Maurizi P, D'Amuri S, Mastrangelo S, Capozza MA, et al. Management of Oral Mucositis in Children With Malignant Solid Tumors. *J Front Oncol*. 2021;11:599243. [PubMed ID: 33859935]. [PubMed Central ID: PMC8042390]. <https://doi.org/10.3389/fonc.2021.599243>.
- Garcia-Gozalbo B, Cabanas-Alite L. A Narrative Review about Nutritional Management and Prevention of Oral Mucositis in Haematology and Oncology Cancer Patients Undergoing Antineoplastic Treatments. *Nutr J*. 2021;13(11). [PubMed ID: 34836330]. [PubMed Central ID: PMC8618139]. <https://doi.org/10.3390/nu13114075>.
- Hayes RB, Ahn J, Fan X, Peters BA, Ma Y, Yang L, et al. Association of Oral Microbiome With Risk for Incident Head and Neck Squamous Cell Cancer. *JAMA Oncol*. 2018;4(3):358-65. [PubMed ID: 29327043]. [PubMed Central ID: PMC5885828]. <https://doi.org/10.1001/jamaoncol.2017.4777>.
- Maagdenberg H, Oosterom N, Zanen J, Gemmati D, Windsor RE, Heil SG, et al. Genetic variants associated with methotrexate-induced mucositis in cancer treatment: A systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2021;161:103312. [PubMed ID: 33794308]. <https://doi.org/10.1016/j.critrevonc.2021.103312>.
- Ponce-Torres E, Ruiz-Rodriguez Mdel S, Alejo-Gonzalez F, Hernandez-Sierra JF, Pozos-Guillen Ade J. Oral manifestations in pediatric patients receiving chemotherapy for acute lymphoblastic leukemia. *J Clin Pediatr Dent*. 2010;34(3):275-9. [PubMed ID: 20578668]. <https://doi.org/10.17796/jcpd.34.3.y060151580h301t7>.
- Villa A, Vollemans M, De Moraes A, Sonis S. Concordance of the WHO, RTOG, and CTCAE v4.0 grading scales for the evaluation of oral mucositis associated with chemoradiation therapy for the treatment of oral and oropharyngeal cancers. *Supp Care Cancer J*. 2021;29(10):6061-8. [PubMed ID: 33788003]. <https://doi.org/10.1007/s00520-021-06177-x>.
- Allen G, Logan R, Revesz T, Keefe D, Gue S. The Prevalence and Investigation of Risk Factors of Oral Mucositis in a Pediatric Oncology Inpatient Population; a Prospective Study. *J Pediatr Hematol Oncol*. 2017;40(1):15-21. [PubMed ID: 29045267]. <https://doi.org/10.1097/MPH.0000000000000970>.
- Vitale MC, Modaffari C, Decembrino N, Zhou FX, Zecca M, Defabianis P. Preliminary study in a new protocol for the treatment of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) and chemotherapy (CT). *Lasers Med Sci*. 2017;32(6):1423-8. [PubMed ID: 28664389]. <https://doi.org/10.1007/s10103-017-2266-y>.
- Sonis S, Clark J. Prevention and management of oral mucositis induced by antineoplastic therapy. *Oncol J (Williston Park)*. 1991;5(12):11-8. discussion 18-22. [PubMed ID: 1840018].
- Cheng KK, Leung SF, Liang RH, Tai JW, Yeung RM, Thompson DR. Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life. *Supp Care Cancer J*. 2010;18(11):1477-85. [PubMed ID: 19916030]. <https://doi.org/10.1007/s00520-009-0771-7>.
- Gebri E, Kiss A, Toth F, Hortobagyi T. Female sex as an independent prognostic factor in the development of oral mucositis during autologous peripheral stem cell transplantation. *Sci Rep J*. 2020;10(1):15898. [PubMed ID: 32985512]. [PubMed Central ID: PMC7522228]. <https://doi.org/10.1038/s41598-020-72592-5>.
- Dehabadi F, Badiie Z, Parisay I. [The Prevalence of Oral Mucositis Caused by Chemotherapy and its Risk Factors in Children with Cancer who were Referred to Hematology and Oncology Wards of Doctor Sheikh Hospital in 2014]. *Med J Mashhad Univ Med Sci*. 2016;58(10):578-89. FA. <https://doi.org/10.22038/mjms.2016.6767>.
- Guimaraes JR, Carvalho LG, Damascena LC, Sampaio ME, Ribeiro IL, Sousa SA, et al. The incidence of severe oral mucositis and its occurrence sites in pediatric oncologic patients. *Med Oral Patol Oral Cir Bucal*. 2021;26(3):e299-303. [PubMed ID: 33247566]. [PubMed Central ID: PMC8141319]. <https://doi.org/10.4317/medoral.24185>.