

# The Study Progress and Analysis of Preventive Measures of Nursing Care for Chemotherapy-Induced Oral Mucositis in Pediatric Patients with Hematologic Malignancies: A Retrospective Study

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**Objective:** To analyze the preventive and therapeutic effects of comprehensive nursing interventions on chemotherapy-induced oral mucositis in pediatric patients with hematologic malignancies.

**Methods:** A retrospective analysis was conducted, and 80 pediatric patients with hematologic malignancies who underwent chemotherapy in our hospital from January 2020 to December 2023 were selected as the research subjects. According to different nursing intervention methods, the patients were divided into an experimental group (45 cases) and a control group (35 cases). The experimental group received comprehensive nursing interventions, including oral care, dietary guidance, and psychological support; the control group received routine care. The observation indicators included the incidence of oral mucositis, Oral Mucositis Daily Questionnaire (OMDQ) scores, pain index (Visual Analog Scale), and levels of inflammatory markers (IL-6 and CRP) in saliva.

**Results:** In the first, second, and fourth weeks of chemotherapy, the incidence of oral mucositis in the experimental group was significantly lower than in the control group ( $P < 0.05$ ), with a total incidence of 51.11% compared to 77.14% ( $P = 0.017$ ). Before chemotherapy, no significant difference was observed in OMDQ or VAS scores between the groups ( $p > 0.05$ ). However, in the first, second, and fourth weeks, OMDQ and VAS scores in the experimental group were significantly lower than those in the control group ( $P < 0.001$ ). Similarly, levels of IL-6 and CRP showed no baseline difference between groups but were significantly reduced in the experimental group during these weeks ( $P < 0.001$ ).

**Conclusion:** Comprehensive nursing interventions significantly reduce the incidence and severity of chemotherapy-induced oral mucositis in pediatric patients with hematologic malignancies, alleviate oral pain in pediatric patients, and effectively reduce the levels of inflammatory markers in saliva. The application of comprehensive nursing interventions in clinical nursing practice can improve the quality of care for pediatric patients with hematologic malignancies.

**Keywords:** pediatric oncology, hematologic malignancies, chemotherapy-induced oral mucositis, comprehensive nursing interventions, oral mucositis prevention, nursing outcomes, mucositis management, oral care, supportive care in pediatrics

## Introduction

Clinical data show that hematologic tumors are the most common type of malignancy in children under 15 years old, accounting for approximately 35% of cases and representing a leading cause of death among children in China. Chemotherapy is the primary treatment for hematologic tumors, but its cytotoxicity can lead to multiple complications. Oral mucositis, one of the most common and severe side effects of chemotherapy, affects 40% to 90% of patients, especially those with hematologic malignancies.<sup>1</sup> Oral mucositis can cause pain, bleeding, and infection, hinder normal eating, lead to

malnutrition, and, in severe cases, cause sepsis and treatment interruptions, significantly impacting the quality of life and treatment outcomes in pediatric patients.<sup>2,3</sup> The occurrence of oral mucositis is related to the direct cytotoxic effects of chemotherapy drugs on oral mucosal cells and immunosuppression. Given the weakened immune function in children with hematologic malignancies, the prevention and management of oral mucositis are particularly important.<sup>4</sup>

Currently, routine nursing measures include daily oral hygiene, saline mouth rinses, maintaining oral moisture, and avoiding spicy and irritating foods.<sup>5</sup> However, the effectiveness of these routine measures in preventing and treating oral mucositis is limited, with still relatively high incidence and severity rates. Recent studies<sup>6,7</sup> suggest that topical treatments like palifermin and tacrolimus may benefit early oral mucositis management in pediatric oncology. Palifermin, a keratinocyte growth factor, can reduce mucositis severity, while tacrolimus, an immunosuppressant, helps control inflammation and supports healing. Although not a central focus of this study, these interventions may complement nursing care strategies, offering additional therapeutic options to alleviate oral mucositis symptoms in children undergoing chemotherapy. Therefore, exploring more systematic and effective nursing interventions to reduce the incidence and severity of oral mucositis, improve the quality of life of pediatric patients with hematologic malignancies, holds significant clinical significance.<sup>8</sup>

In recent years, comprehensive nursing intervention, as a multi-level and multi-faceted nursing model, has gradually gained attention. Comprehensive nursing intervention not only includes routine oral care but also combines psychological care, dietary guidance, and local drug application, aiming to comprehensively improve the oral health status and overall treatment experience of pediatric patients.<sup>9</sup> Previous studies have shown that comprehensive nursing intervention has significant effects on reducing the incidence of oral mucositis, alleviating pain, and improving quality of life. However, these studies mostly focused on adult patients, with relatively fewer studies targeting pediatric patients with hematologic malignancies.<sup>10</sup>

This study systematically evaluates the impact of comprehensive nursing interventions on the prevention and management of chemotherapy-induced oral mucositis in pediatric patients with hematologic malignancies. By retrospectively comparing these interventions with routine care, this study aims to provide robust evidence for the effectiveness of comprehensive nursing approaches in clinical practice. Ultimately, this research will support the implementation of such interventions in pediatric oncology settings, with the goal of improving oral health and enhancing the overall treatment experience for children undergoing chemotherapy.

## Materials and Methods

### Ethics Approval and Consent to Participate

The protocol was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University. Informed consent was obtained from the parents / legal guardians of the patients, who signed the informed consent form; the patients received inpatient treatment at our hospital. All the methods were carried out in accordance with the Declaration of Helsinki.

### General Information

This study employed a retrospective analysis method, selecting 80 pediatric patients with hematologic malignancies who underwent chemotherapy in our hospital from January 2020 to December 2023 as the research subjects. There were no dropouts from the study during the research period. Among them, there were 42 males and 38 females, with ages ranging from 1 to 14 years old. Based on the nursing intervention received by the patients, they were divided into two groups, with 45 patients in the experimental group receiving comprehensive nursing interventions including oral care, dietary guidance, and psychological support, while 35 patients in the control group received routine care. General data of all patients were collected, including tumor types, course of disease, chemotherapy cycles, and family economic status.

## Inclusions and Exclusions Criteria

Inclusion criteria: (1) All research subjects were diagnosed with hematologic malignancies, including acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin's lymphoma, and non-Hodgkin's lymphoma; (2) the age of the research subjects ranged from 1 to 14 years old; (3) all patients received standardized chemotherapy regimens and experienced oral mucositis at least once during chemotherapy; (4) informed consent was obtained from the parents / legal guardians of the patients, who signed the informed consent form; (5) the patients received inpatient treatment at our hospital, with complete medical records and nursing records available for retrospective analysis.

Exclusion criteria: (1) Patients with other serious systemic diseases (such as severe heart disease, renal failure, etc.) or other types of tumors were excluded; (2) patients whose hospitalization was prolonged due to severe infectious diseases during the study period, affecting the assessment of oral mucositis; (3) patients with a clear history of allergy to any local drugs used in this study were excluded; patients with incomplete medical or nursing records that could not be comprehensively reviewed and analyzed; (4) patients who terminated chemotherapy early or transferred to another hospital for treatment due to personal reasons during the study period were also excluded.

## Methods

For the control group, pediatric patients received routine preventive nursing measures, including the following aspects:

Guidance on tooth brushing with a soft-bristled toothbrush after each of the three daily meals and before and after chemotherapy, ensuring moderate brushing force to avoid damaging the oral mucosa. After brushing, patients rinsed their mouths with saline solution, rinsing 3 to 5 times each time to clean the oral cavity. In addition, patients were instructed to maintain a clean diet, avoiding spicy, hard, and overheated foods to reduce the burden on the oral mucosa. Nurses also instructed patients to perform oral exercises at least 50 times daily to promote oral blood circulation. Furthermore, nurses provided regular health education guidance during the hospitalization period, including oral hygiene, prevention of oral infections, and chemotherapy-related precautions.

For the experimental group, comprehensive nursing interventions were added on the basis of routine care, with specific content as follows:

Establishment of a bundled care team. The team was led by the head nurse as the team leader, with a pediatrician serving as the consultant, and three nursing backbone members of the department as team members. All members had extensive clinical practice experience and received systematic training in bundled care. Based on clinical work experience and patient data, the main nursing problems related to chemotherapy-induced oral mucositis were analyzed, and key issues that needed to be addressed were determined, including oral care, dietary management, and psychological care, among others. Evidence retrieval and application were conducted. A literature search covering the period from 2016 to the present was conducted in databases such as Cochrane Library, Wiley, JBI Evidence-Based Practice Center, CNKI (China National Knowledge Infrastructure), and Wanfang Database. This search provided evidence-based support for formulating nursing intervention plans suitable for pediatric patients with chemotherapy-induced oral mucositis.

In terms of implementing intervention measures, concentrated health education was provided to patients and their parents, emphasizing the importance of maintaining good oral hygiene and methods for preventing oral infections. Meanwhile, the responsible nurse communicated with patients and their parents to understand and alleviate their tension, anxiety, and other negative emotions, thereby improving patient compliance with treatment. Patients were guided to brush their teeth with a soft-bristled toothbrush and rinse with saline solution every morning and evening, using gentle movements to avoid damaging the oral mucosa. Additionally, patients rinsed their mouths with honey water daily to prevent oral mucositis. In terms of dietary nursing, individualized scientific dietary plans were formulated to guide patients in choosing bland and easy-to-chew foods, while avoiding spicy and irritating foods. Oral hygiene was performed after each meal, with rinsing the mouth with honey water or brushing teeth. The Oral Mucositis Daily Questionnaire (OMDQ) and pain index assessment form were used regularly to evaluate the effectiveness of nursing interventions.

## Observation Indicators

The observation indicators in this study include the incidence of oral mucositis, Oral Mucositis Daily Questionnaire (OMDQ) scores, pain index, and inflammation-related biochemical markers. The diagnosis of oral mucositis is based on the World Health Organization (WHO) grading criteria for oral mucositis. Oral examinations were conducted weekly during chemotherapy to record the occurrence of oral mucositis in patients and calculate the incidence rate of oral mucositis in both groups. OMDQ scores were used to assess the severity of oral mucositis in patients on a daily basis. OMDQ includes self-assessment by patients of symptoms such as oral pain, bleeding, and ulceration, with scores ranging from 0 to 10, where 0 indicates no symptoms and 10 indicates the most severe symptoms. OMDQ scores of patients were recorded daily before chemotherapy and during chemotherapy, with weekly averages calculated at the end of each week. Pain index was assessed using a Visual Analog Scale (VAS). VAS is a 10-centimeter straight line, with “no pain” (0 points) and “worst pain” (10 points) marked at each end. Patients marked the intensity of their pain perception on the line before and after chemotherapy and at the end of each week. Nurses recorded these values and calculated the average pain index to evaluate the effect of nursing interventions on pain. To assess the physiological status of the oral mucosa, saliva samples were collected regularly from patients. Saliva samples were collected before chemotherapy and in the first, second, and fourth weeks after chemotherapy. Patients were required to fast for 1 hour before each sampling. After collection in sterile collection tubes, saliva samples were immediately stored at 4°C and subsequently sent to the laboratory for processing and analysis. Interleukin-6 (IL-6) and C-reactive protein (CRP) in saliva samples were detected as inflammation markers. Detection was performed using ELISA kits (IL-6: Thermo Fisher Scientific, USA; CRP: R&D Systems, USA). The specific detection steps included thawing and processing the samples according to the kit instructions. The processed samples were added to the wells of the ELISA plate and incubated, washed, and subjected to color reaction according to the kit instructions. Optical density values were read at a wavelength of 450 nm using an enzyme-linked immunosorbent assay reader (Model: Thermo Scientific Multiskan FC, USA). The concentrations of IL-6 and CRP in the samples were calculated using standard curves.

## Statistical Analysis

All data were analyzed using SPSS 26.0 statistical software. First, normality tests were conducted on the data. For normally distributed quantitative data, mean  $\pm$  standard deviation was used, and *t*-tests were used for intergroup comparisons. For non-normally distributed quantitative data, median (interquartile range) was used, and non-parametric tests (Mann–Whitney *U*-test) were used for comparisons. Count data were expressed as frequencies and percentages, and intergroup comparisons were performed using the chi-square test or Fisher’s exact test. The significance level was set at  $P < 0.05$ .

## Results

### General Information

There were no statistically significant differences between the experimental group and the control group in terms of gender, age, tumor type, course of disease, number of chemotherapy cycles, and family economic status ( $P > 0.05$ ), indicating comparability between the two groups. See [Table 1](#).

### Incidence Rate of Oral Mucositis

In the first, second, and fourth weeks of chemotherapy, the incidence rate of oral mucositis in the experimental group was significantly lower than that in the control group ( $P < 0.05$ ). Overall, the total incidence rate of oral mucositis in the experimental group (51.11%) was significantly lower than that in the control group (77.14%), with a statistically significant difference ( $P = 0.017$ ). See [Table 2](#).

### OMDQ Scores

Before chemotherapy, there was no statistically significant difference in OMDQ scores between the two groups ( $P = 0.678$ ). However, in the first, second, and fourth weeks of chemotherapy, the OMDQ scores in the experimental group were significantly lower than those in the control group ( $P < 0.001$ ). See [Figure 1](#).

**Table 1** Comparison of General Information of Patients

	Experimental Group (n=45)	Control Group (n=35)	$\chi^2/t$	P
Gender (Male/Female)	23/22	19/16	0.010	0.920
Age (years)	8.40±3.20	8.10±3.50	0.415	0.679
Tumor Type [n(%)]				
Acute lymphoblastic leukemia	22 (48.89%)	18 (51.43%)	0.060	0.806
Acute myeloid leukemia	13 (28.89%)	12 (34.29%)	0.273	0.601
Hodgkin's lymphoma	6 (13.33%)	4 (11.43%)	0.056	0.813
Non-Hodgkin's lymphoma	4 (8.89%)	1 (2.86%)	1.128	0.288
Course of Disease (months)	10.35±2.68	10.14±2.75	0.339	0.735
Number of Chemotherapy Cycles (weeks)	6.20±1.10	6.30±1.05	0.414	0.680
Family Economic Status (RMB/month) [n(%)]				
<5000	20 (44.44%)	16 (45.71%)	0.008	0.928
5000–10,000	15 (33.33%)	11 (31.43%)	0.036	0.849
>10,000	10 (22.22%)	8 (22.86%)	0.002	0.964

**Table 2** Comparison of Incidence Rate of Oral Mucositis Between the Two Groups of Patients

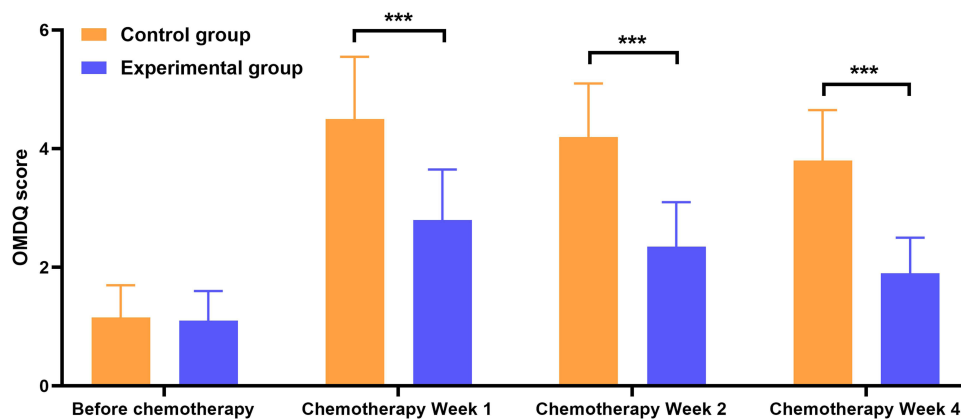
	Chemotherapy Week 1	Chemotherapy Week 2	Chemotherapy Week 4	Total Incidence Rate
Experimental group (n=45)	10 (22.22%)	8 (17.78%)	5 (11.11%)	23 (51.11%)
Control group (n=35)	15 (42.86%)	14 (40.00%)	13 (37.14%)	27 (77.14%)
$\chi^2$	4.079	5.345	7.996	5.739
P	0.043	0.021	0.005	0.017

### Pain Index (VAS Score)

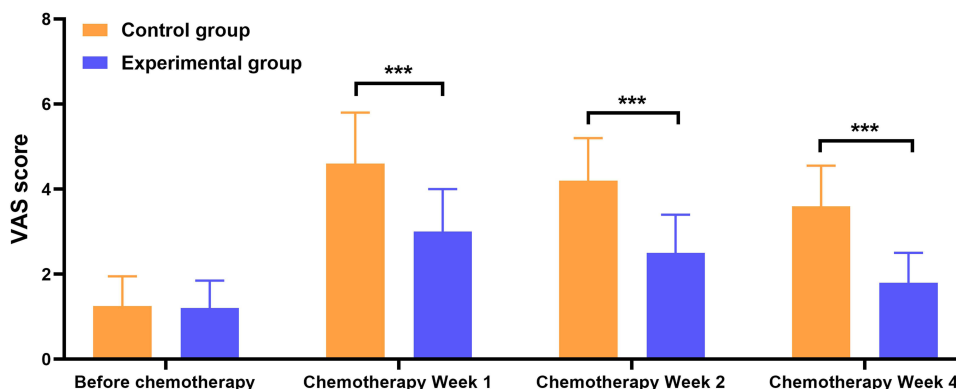
There was no statistically significant difference in VAS scores between the two groups before chemotherapy ( $P = 0.740$ ). However, in the first, second, and fourth weeks of chemotherapy, the VAS scores in the experimental group were significantly lower than those in the control group ( $P < 0.001$ ). See [Figure 2](#).

### Levels of Inflammatory Markers (IL-6 and CRP) in Saliva

Before chemotherapy, there was no statistically significant difference in the levels of IL-6 and CRP between the two groups of patients ( $P > 0.05$ ). However, in the first, second, and fourth weeks of chemotherapy, the levels of IL-6 and

**Figure 1** Comparison of OMDQ Scores.

**Note:** \*\*\* indicates  $p < 0.001$  between the two groups.



**Figure 2** Comparison of Pain Index (VAS Score) between the Two Groups of Patients.

**Note:** \*\*\* indicates  $p < 0.001$  between the two groups.

CRP in the experimental group were significantly lower than those in the control group ( $P < 0.001$ ), indicating that comprehensive nursing interventions effectively reduced the inflammation induced by chemotherapy. See [Table 3](#).

## Discussion

The results of this study show that comprehensive nursing interventions significantly reduce the incidence of oral mucositis, alleviate pain, and decrease inflammation in children undergoing chemotherapy for hematologic tumors. These findings highlight the effectiveness of integrated care strategies in improving both the physical symptoms and quality of life of pediatric cancer patients. In the following sections, we will explore the mechanisms and implications of these results in greater detail.

Oral mucositis is an inflammatory and ulcerative reaction that occurs in the epithelial tissue of the oral mucosa, often presenting as erythema and ulcers. The incidence of oral mucositis in patients receiving chemotherapy ranges from 15% to 40%.<sup>11</sup> The main pathogenesis involves direct damage to the DNA of oral mucosal epithelial cells by chemotherapy, leading to partial cell death and ulcer formation. Additionally, chemotherapy suppresses the hematopoietic and immune systems, resulting in the excessive proliferation of pathogenic microorganisms in the oral cavity, exacerbating epithelial damage. Oral mucositis is considered one of the most painful side effects experienced by cancer patients, not only affecting their quality of life but also potentially hindering the smooth progress of treatment and increasing the risk of systemic infection, which is a significant reason for patients to discontinue chemotherapy.<sup>12</sup> In recent years, scholars at home and abroad have conducted numerous exploratory studies on the prevention and treatment of oral mucositis, achieving significant progress.

Oral care can maintain oral hygiene, reduce the number of bacteria in the oral cavity, and prevent infection. Although the elements and methods of oral care lack unified standards, and related research lacks rigorously designed randomized

**Table 3** Comparison of Levels of Inflammatory Markers (IL-6 and CRP) in Saliva Between the Two Groups of Patients

	Time Point	Experimental Group (n=45)	Control Group (n=35)	t	P
IL-6 (pg/mL)	Before chemotherapy	7.50±1.20	7.45±1.25	0.175	0.861
	Chemotherapy Week 1	10.20±1.85	12.50±2.10	5.146	<0.001
	Chemotherapy Week 2	9.10±1.70	11.80±2.00	6.374	<0.001
	Chemotherapy Week 4	8.20±1.60	10.50±1.90	5.706	<0.001
CRP (mg/L)	Before chemotherapy	5.80±1.10	5.75±1.15	0.190	0.850
	Chemotherapy Week 1	8.30±1.50	10.20±1.80	5.162	<0.001
	Chemotherapy Week 2	7.60±1.45	9.70±1.75	5.869	<0.001
	Chemotherapy Week 4	6.70±1.25	8.90±1.60	7.064	<0.001

controlled trials, the role of oral care has been widely recognized in clinical practice. Studies have shown that maintaining an oral pH value between 6.5 and 7.5 can allow the normal functioning of oral defense mechanisms. However, patients often experience reduced salivary secretion and dry oral mucosa after chemotherapy, and the accumulation of viscous saliva lowers the pH value in the oral cavity.<sup>13</sup> When the pH value decreases, the accumulation of acidic substances can stimulate the mucosa, causing lesions and making it susceptible to fungal infections. Research has found that rinsing with a 2% sodium bicarbonate solution can effectively alleviate the oral mucositis reaction in patients receiving radiotherapy for nasopharyngeal cancer; routine use of 5% sodium bicarbonate and 1:5000 furacin alternate rinsing also yields good oral antimicrobial effects.<sup>14</sup> Other commonly used mouthwashes include compound chlorhexidine mouthwash, 0.05% acetic acid chlorhexidine solution, and povidone-iodine mouthwash, which can improve the oral environment, eliminate pathogenic bacteria, and are widely used in clinical practice. In addition, rinsing with saturated saline can reduce the incidence and severity of oral mucosal damage in patients undergoing hematopoietic stem cell transplantation, and chlorhexidine mouthwash is effective in reducing the severity of oral mucositis caused by radiotherapy.<sup>15</sup>

This study aimed to investigate the effect of comprehensive nursing interventions on the incidence of oral mucositis in children with hematologic tumors after chemotherapy and to evaluate its effectiveness in reducing the incidence of oral mucositis, alleviating pain, and reducing inflammatory reactions. The results showed that in the first, second, and fourth weeks of chemotherapy, the incidence of oral mucositis in the experimental group was significantly lower than that in the control group ( $P < 0.05$ ), indicating that comprehensive nursing interventions can effectively reduce the incidence of oral mucositis after chemotherapy. Comprehensive nursing interventions include strengthening oral hygiene education, psychological care, dietary guidance, and preventive treatment, among other measures. These measures work together to protect the oral mucosa of children, reducing the risk of oral infection. A study by Li et al showed that comprehensive nursing interventions, including health education, rinsing with cold water, measurement and adjustment of oral saliva pH value, and nursing based on the degree of ulceration, significantly reduced the incidence of chemotherapy-induced oral mucositis (incidence in the experimental group was 19.35%, compared to 54.84% in the control group), and improved the oral hygiene status of patients.<sup>16</sup> A multicenter randomized controlled trial by Kawashita et al found that a comprehensive oral management plan for oral cancer patients significantly reduced the incidence of severe oral mucositis in patients undergoing radiotherapy ( $P = 0.046$ ), but not in patients undergoing chemoradiotherapy ( $P = 0.815$ ).<sup>17</sup>

OMDQ scores and pain index are important indicators for assessing the severity of oral mucositis. The results of this study showed that the OMDQ scores and pain index in the experimental group were significantly lower than those in the control group in the first, second, and fourth weeks of chemotherapy ( $P < 0.001$ ). This indicates that comprehensive nursing interventions not only reduce the incidence of oral mucositis but also effectively alleviate the pain experienced by children and improve their quality of life. Lower OMDQ scores reflect a reduction in the symptoms of oral mucositis in children, which is closely related to the local application of medications and dietary guidance in comprehensive nursing interventions. Preventive treatments such as rinsing with honey water have good antibacterial and anti-inflammatory effects, helping to alleviate inflammation of the oral mucosa and reduce pain and discomfort. Additionally, psychological care interventions relieve children's anxiety and tension, improve their compliance with treatment, and indirectly promote the improvement of oral health. A study by Wong & Islahudin targeting hematopoietic stem cell transplant patients showed that patients' self-reported Oral Mucositis Daily Questionnaire (OMDQ) scores were significantly lower than those in the control group, indicating the effectiveness of comprehensive nursing interventions in pain control and symptom relief.<sup>18</sup> A systematic review by Goettems et al evaluated the impact of non-pharmacological interventions on children's behavior, anxiety, and pain perception during dental treatment, with results showing that most interventions effectively improved children's behavior and reduced anxiety and pain perception.<sup>19</sup>

The results of this study showed that the levels of IL-6 and CRP in the experimental group were significantly lower than those in the control group in the first, second, and fourth weeks of chemotherapy ( $P < 0.001$ ). This result indicates that comprehensive nursing interventions effectively reduce chemotherapy-induced inflammatory reactions, further confirming their anti-inflammatory effects. IL-6 and CRP are sensitive indicators of inflammation, and their levels are usually closely related to inflammation and infection. Chemotherapy can lead to a decrease in immune function in the

body, increasing the risk of infection and inflammation. The comprehensive nursing interventions in this study effectively controlled oral infections, alleviated inflammation, and thus reduced the levels of IL-6 and CRP by strengthening oral hygiene, dietary management, and preventive treatment. A study by Yu et al found that comprehensive nursing interventions effectively prevented and treated chemotherapy-induced oral mucositis, significantly improved the oral hygiene status and quality of life of pediatric patients, and significantly increased parental satisfaction after intervention.<sup>20,21</sup>

Despite significant achievements in this study, there are still some limitations. This study was a single-center retrospective study with a relatively small sample size, which may affect the generalizability and representativeness of the results. Future research could conduct multicenter, large-sample prospective studies to further validate the effectiveness and generalizability of comprehensive nursing interventions. Secondly, the observation period of this study was relatively short, and the long-term effects of nursing interventions and the long-term prognosis of children were not comprehensively evaluated. Future studies should extend the follow-up period to assess the long-term health and quality of life of children affected by comprehensive nursing interventions.

## Conclusion

In summary, this study demonstrates that comprehensive nursing interventions offer an effective approach to preventing and managing oral mucositis in children with hematologic tumors undergoing chemotherapy. Through interventions that address oral hygiene, psychological support, dietary guidance, and preventive treatments, the incidence of oral mucositis was significantly reduced, leading to alleviated pain, lowered inflammatory markers (such as IL-6 and CRP), and improved quality of life and treatment outcomes for children. These findings highlight the potential of comprehensive nursing interventions not only in reducing physical symptoms but also in supporting children's overall well-being and compliance with treatment.

This study provides an important foundation for future research and clinical practice, suggesting that the continued optimization and implementation of comprehensive nursing interventions could further improve the standard of care and health outcomes in pediatric hematologic oncology. Future studies could expand on these findings by investigating the long-term impact of these interventions and evaluating their applicability across diverse patient populations and treatment regimens.

## Disclosure

The authors report no conflicts of interest in this work.

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