CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

RISK FACTORS FOR CANCER TREATMENT - RELATED ORAL MUCOSITIS IN CHILDREN – AN UMBRELLA REVIEW

Dissertação apresentada à Universidade Católica Portuguesa para obtenção do grau de Mestre em Medicina Dentária

Por:
Tatiana dos Santos Henrique

Viseu, 2024

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DEDICATION

I dedicate this dissertation to my parents, more than anything. For allowing me to achieve my dreams and for giving me love, support and being my pillar at every moment of my life

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To begin with, I would like to thank my guidance team My deepest acknowledgment go to Professor Patrícia Correia for being tireless throughout this journey. Thank you for all your availability, encouragement, sympathy and dedication!

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RESUMO

Objetivo: O objetivo desta *umbrella review* é determinar os fatores de risco associados à mucosite oral relacionada com o cancro em pacientes pediátricos e estabelecer um sistema de classificação de cada fator individual baseado na evidência.

Materiais e Métodos: Esta *umbrella review* foi registada no PROSPERO (CRD42023477370). O estudo foi realizado de acordo com as diretrizes PRISMA. Foram utilizadas 4 bases de dados. A pesquisa bibliográfica foi efetuada em 26 de novembro de 2023. Os critérios de inclusão foram revisões sistemáticos com leitura integral em inglês, numa população pediátrica que apresente mucosite oral e que tenha estado exposta a tratamento oncológico. Os critérios de exclusão foram mucosite oral não derivada de tratamento oncológico, revisões sistemáticas que não incluíssem fatores de risco e cartas ao editor, revisões criticas e estudos primários de investigação. 101 artigos foram obtidos, sendo excluídos os duplicados (n=4). Foi feita a leitura de titulo e abstract desses 97 artigos, do qual 86 foram excluídos devido a não mencionarem a mucosite oral e crianças. 11 artigos foram sujeitos a leitura integral, sendo excluídos 6 devido a não mencionarem fatores de risco.

Resultados: 5 artigos foram avaliados neste estudo. Os fatores de risco mais relevantes para o desenvolvimento de mucosite oral foram o tipo de tumor e os agentes quimioterapêuticos. O baixo peso corporal, os parâmetros hematológicos, hepáticos, renais e a má higiene oral foram também fatores relevantes. Níveis elevados de creatina, ALT e AST, multivitaminas e níveis elevados de bilirrubina total e indireta foram fatores mencionados, embora num número menos significativo de artigos.

Conclusões: O tipo de tumor e o protocolo de quimioterapia são fatores de risco asspciados à MO, no entanto são necessários mais estudos neste domínio para estabelecer evidências sólidas.

Palavras-chave: Mucosite oral; fatores de risco; tratamento do cancro; pediatria; cancro

ABSTRACT

Aim: The aim of this umbrella review is to determine the risk factors associated with cancer-related oral mucositis in children and to establish a system for evidence-based grading of each individual factor.

Materials and Methods: This umbrella review was registered with PROSPERO (CRD42023477370). The study was conducted in accordance with the PRISMA guidelines. Four databases were used. The literature search was carried out on 26 November 2023. The inclusion criteria were systematic reviews read in full in English, in a paediatric population with oral mucositis and exposed to oncological treatment. The exclusion criteria were oral mucositis not derived from oncological treatment, systematic reviews that did not include risk factors and letters to the editor, critical reviews and primary research studies. 101 articles were retrieved, excluding duplicates (n=4). The title and abstract of these 97 articles were read, of which 86 were excluded because they did not mention oral mucositis and children. 11 articles were read in full and 6 were excluded because they did not mention risk factors.

Results: 5 articles were evaluated in this study. The most relevant risk factors for the development of oral mucositis were the type of tumour and the chemotherapeutic agent. Low body weight, haematological, hepatic, renal parameters and poor oral hygiene were also relevant factors. High levels of creatine, ALT and AST, multivitamins and high levels of total and indirect bilirubin were factors mentioned, although in a less significant number of articles.

Conclusion: The type of tumour and the chemotherapy modality are risk factors for OM, however, further studies are required in this field to establish robust evidence and guide the management of oral mucositis.

Keywords: Oral Mucositis; children; cancer treatment; risk factors; cancer

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Abbreviations list

ALL – Acute Lymphoblastic Leukemia

ALT – Alanine Aminotransferase

AST – Aspartate Aminotransferase

CNS – Central Nervous System

CT – Chemotherapy

CTCAE – Common Terminology Criteria for Adverse Events

DHPs – Dental Hygiene Protocols

EN – Enteral Nutrition

EMA – European Medical Agency

FDA – Food and Drug Administration

GI-M – Gastrointestinal Mucositis

HNC – Head and Neck Cancer

HSCT- Haematopoietic stem cell transplant

HSV – Herpes Simplex Virus

MASCC/ISOO - Mucositis Study Group of the Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology

MTX – Methotrexate

NCBI - National Centre for Biotechnology Information

NCI – National Cancer Institut

OM - Oral mucositis

OMAS – Oral Mucositis Assessment Scale

PN – Parental Nutrition

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO- International Prospective Register of Systematic Reviews

ROS – Reactive Oxygen Species

RT – Radiotherapy

WHO – World Health Organization

5-FU - 5- fluorouracil

1. INTRODUCTION

1.1 Childhood cancer

Childhood cancer is a condition that affects children worldwide and has a huge impact on their lives. According to the World Health Organisation, paediatric cancer is the cancer that occurs between birth and the age of 19 (1)

Childhood cancer accounts for 2-3% of all cancers. It is estimated that between 2015 and 2030 there will be 6.7 million cases of childhood cancer, with more than 450,000 cases annually. (2,3)

The most frequently occurring cancers in children are leukemia, brain and spinal cord tumours, neuroblastoma, Wilms tumour, lymphoma, rhabdomyosarcoma, retinoblastoma, and bone cancer (Figure 1). (4)

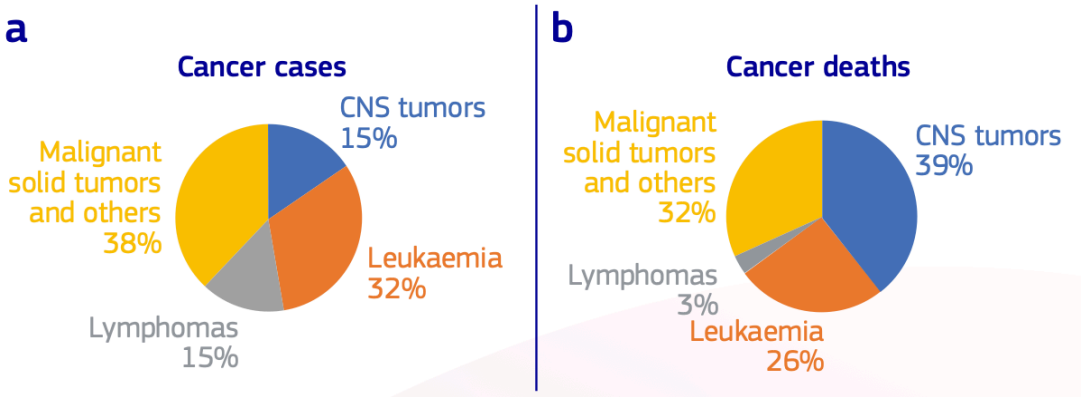

Figure 1 Projected breakdown of new cancer diagnoses and fatalities in 2022 for children aged 0 to 14 by cancer type in the EU-27, Norway, and Iceland. Source: European Commission. Inequalities in Childhood Cancer. 2023 Dec.(5)

Cancer is characterised by molecular alterations that result from a breakdown in the functional integrity of the cell cycle, leading to the production of abnormal cells with great invasive potential via the bloodstream and lymphatic tissue. (6,7) The growth of these malignant cells tends to be uncontrolled and aggressive, leading to the formation of tumours and metastases, which will affect the organs involved. (6,8)

This form of development is similar to all cancers, but differs from adult cancers in two important ways. The first difference is where the cancer occurs. Adult cancers usually start in mature tissues, meanwhile childhood cancers start in developing

organs and tissues. This makes the cancer grow faster and spread differently to adult cancers. This factor is ultimately very dangerous in diagnosing cancer in children, as the change can be sudden and the child goes from having subtle and few symptoms to very intense symptoms, often mimicking other childhood illnesses such as infections. (1) The second point is related to the first because, due to the location of these cancers, their biology, microscopic appearance and clinical behaviour will be very different from childhood cancers. This could result in a tumour with unique characteristics that could affect its growth and prognosis. (1)

Also, unlike cancer in adults, the etiology of childhood cancer is unknown in most cases. (1) It is known that in adults some risk factors take many years to influence the type of cancer. Some factors may be present in children, such as not doing enough exercise, having an unhealthy diet and being overweight. However others are not extrapolatable, such as smoking and drinking alcohol. In any case, these known factors are not thought to play a significant role in childhood cancers. (9)

Childhood cancer can be treated in a multimodal therapy. Examples of these methods are chemotherapy, radiotherapy, and surgery. These have a reasonably high survival rate. However, these methods can induce various adverse effects related to their mechanism against non-cancerous cells. (10,11)

It is important to have in mind that after the end of anti-cancer treatment, patients must undergo follow-up care (which can last several years). Although these treatments have a high success rate, sequelae can occur. It is therefore important for patients to have regular check-ups in order to maintain good health and be treated in the most effective way. (12)

Despite progress in improving survival rates for many types of childhood cancer, challenges remain, particularly in the context of limited resources, where it is still difficult to achieve timely diagnosis and optimal treatment. (13)

1.2 Mucositis related to cancer treatment in children

The National Cancer Institute defines mucositis as an important and frequent complication of some cancer therapies. It is characterised by inflammation of the mucous membranes of the digestive system and its clinical manifestation is very frequent, such as sores in the mouth. The definition given by the National Centre for Biotechnology Information (NCBI) in 2006 is very similar, with the addition of atrophy of the squamous epithelium and vascular lesions. (14)

Mucositis is subdivided into two types: oral mucositis and gastrointestinal mucositis. Patients with gastrointestinal mucositis may experience abdominal pain and nausea, diarrhoea or painful bowel movements, depending on the location of the inflammation. The first two symptoms mentioned occur when the inflammation is closer to the stomach and the other two, when the inflammation is located in the colon. (15)

Oral mucositis (OM) is frequently observed as a complication of chemotherapy, affecting a substantial majority of children undergoing cancer treatment, with estimates ranging from 52% to 80%. Children with mucositis often experience significant pain, chewing and/or swallowing discomfort, altered intestinal absorption, possible malnutrition (16–18), and the risk of local infection spreading. (19,20)

OM is diagnosed clinically based on clinical appearance, symptoms, history of stomatotoxic therapy, timing of onset lesions and location of lesions. (21)

The condition is marked by an inflammatory reaction that clinically manifests as erythema and/or ulceration with predilection for the oral mucosa, dorsal tongue, floor of the mouth, and soft palate (Figure 2). (22,23)

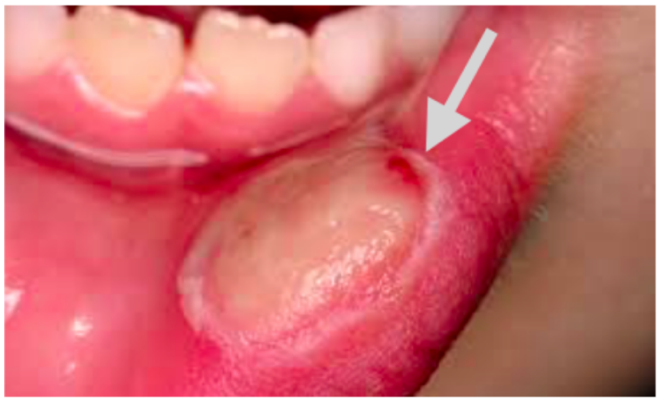

Figure 2- Ulcerative mucositis of the lip in a pediatric patient Source: Journal Dentistry [Internet]. 2019 Dec 1 [cited 2024 May]. (24)

OM frequently presents as ulcers. However, there are other conditions that can also cause this manifestation, such as aphthous stomatitis or dental trauma. (25,26) The main difference is that the edges of mucositis ulcers are challenging to delineate, and the usual peripheral ring of erythema, which results from inflammatory components is not observed. (25,26) Despite the fact that the location of the alterations are not typical, erythema and ulcers linked with mucositis can manifest in any area. If they are localised on the dorsal surface of the tongue, gums or hard palate (less common locations), it may be suspected that another factor is at play. (25,26)

The vast majority of patients undergoing radiotherapy are affected by oral mucositis and between 75 and 100% of patients undergoing hematopoietic stem cell transplantation (HSCT) are also affected by this condition. (27–30)

The evolution of oral mucositis varies based on the cancer treatment received. (26) In the case of patients treated with chemotherapy, they typically develops within 4–7 days after the start of treatment, reaching its peak within two weeks. (31)

In patients treated with radiotherapy, mucosity is less acute (26), since it has a more gradual progression, due to the way the dose is administered (over weeks, small fractions are given). (31) Tipically, by the end of the first week, patients will start to feel pain in their mucous membranes. The intensity of the mucositis will increase until ulcerations appear, in most cases by the end of the second week. By the end of the

third week, the ulcers will consolidate to form confluent ulcers on the mucosa. Once treatment begins, patients may experience ongoing ulcerative mucositis for up to two to four weeks following the final radiation dose. In most cases, the ulcers heal on their own without leaving scars. (26,32,33)

Both children and adolescents are more prone to developing oral mucositis than adults, with incidence rates ranging from 50 to 54 per cent in the later. (34–36) However, it is generally observed thtat children tend to recover from OM faster than adults. This may be linked to the fact that they have a very rapid rate of epithelial mytoticity. (34,37)

1.3 Pathogenesis of oral mucositis

The development of oral mucositis (OM) is associated with how oral mucosal cells interact with inflammatory cytokines and environmental factors within the oral cavity. (10,38)

The development of oral mucositis is complex and involves five stages: **initial stage**, when there is damage of oral mucosal by chemotherapy (CT) or RT, **primary damage response, damage amplification** (iv), mucosal **ulceration,** and **healing**. (27,39,40)

To initiate oral mucositis, DNA damage must occur. This can result from both chemotherapy (CT) and radiotherapy (RT). This damage leads to cell death of the basal and suprabasal epithelial layers. (41) Reactive oxygen species (ROS) are also formed during this phase. (25).

At this stage, transcription factors are activated, leading to an upregulation of pro-inflammatory cytokines, namely, TNF-α (tumour necrosis factor α), IL-6 (interleukin-6), and IL-1β (interleukin-1β), cytokine modulators, adhesion molecules, stress responders and matrix metalloproteinases. (25,41).

The epithelium becomes thinner, and destruction of the oral mucosa occurs as a result of tissue damage and cell death. (20,25) There is signal amplification and some

of the molecules present in the previous phases will amplify and increase the tissue damage. (25,42) The next phase is the most significant in oral mucositis, as it is symptomatic. This is when ulceration of the mucosa occurs. These ulcers are colonised by gram-positive and gram-negative bacteria, which are naturally found in the oral cavity. As a result of the products from bacterial metabolism, there may be exacerbated damage to the mucosa and a stimulus for the additional release of pro-inflammatory cytokines. (25,42)

Finally, the last and most anticipated phase. The healing of ulcerated lesions, which occurs spontaneously and requires a series of biological processes that take place in the submucosal layer. (25)

Understanding how the mechanism of action of oral mucositis works is extremely important, as it plays a key role in preventing it and can completely change a child's wellbeing by minimising its impact on them.

1.4 Scales for measuring oral mucositis

The frequency and intensity of OM can be affected by various factors, including the type, dosage, and schedule of systemic cytotoxic drugs, the targeted area, as well as the simultaneous administration of chemotherapy and radiation therapy. (10,31)

In terms of scales for measuring OM, the WHO (World Health Organization) Mucositis Scale is most commonly used in clinical and research contexts (25), while the NCI (National Cancer Institute) CTCAE (Common Terminology Criteria for Adverse Events) is often used as a measure of overall toxicity. (41)

The World Health Organization scale includes 5 grades (grades 0-4), with the corresponding symptoms. The Common Terminology Criteria for Adverse Events is divided into two fields: clinical and functional/symptomatic examination and includes 5 grades (grades 1-5).

Although the two most common OM scales are those mentioned above, there are other scales that are also very valid. As such, below is a table containing other scales, that are commonly used (Table 1).

Table 1- Other scales of OM. Table from Kumar PS, 2009. Radiation Induced Oral Mucositis. (42)

Source	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO	No change	Soreness/erythema	Erythema, ulcers, can eat solids	Ulcers; requires liquid diet only	Alimentation not possible
RTOG	No change over baseline	May experience mild pain not requiring analgesic	Patchy mucositis may have a serosanguinous discharge. May experience pain requiring analgesics. <1.5 cm, noncontiguous	Confluent fibrinous mucositis/may include severe pain requiring narcotics, > 1.5 cm, contiguous	Necrosis or deep ulceration, ± bleeding
NCI CTC	None	Painless ulcers, erythema or mild soreness	Painful erythema, oedema or ulcers, but can eat	Painful erythema, edema or ulcers cannot eat	Requires parenteral or enteral support
van Der Schueren *et al.*	None	Slight erythema	Pronounced erythema	Spotted mucositis	Confluent mucositis patches >0.5 cm
Byfield *et al.*	-	Minimal dysphasia, thinning but no overt break in mucosal integrity	Significant dysphasia, semi soft foods only, focal mucosal vesicles or denuded patches	Fluids only tolerated, obviously large confluent patches of mucosal denudation	Parenteral fluids only, severe confluent mucosal denudation with bleeding
Seto *et al.*	-	Localized erythema with no pain	Generalized erythema without pain or localized erythema or ulcers with mild pain	Multiple ulcers or generalized erythema with moderate pain	Generalized erwythema or ulcers with moderate to severe pain
Eilers *et al.*	-	Pink and moist	Reddened or white film without ulcerations	Ulceration with or without bleeding	-
NCIC	None	Painless ulcers, erythema, or mild soreness	Painful erythema, oedema, or ulcers, but can eat	Painful erythema, oedema, or ulcers, but cannot eat	Mucosal necrosis and/or requires parenteral or enteral support, dehydration
Spijkervet *et al.*	None	White discoloration	Erythema	Pseudomembrane	Ulceration
Maceijewski	None	Type: Mild erythematous area: <25%	Type: Severe erythematous area: 25-50%	Type: Spotted mucositis area >50%	Type: Confluent mucosistis
Hickey *et al.*	No sto-matitis	Whitish gingival or slight burning sensation or discomfort	Moderate erythema and ulcerations or white patches. Pain, but can eat, drink and swallow	Severe erythema and ulcerations or white patches. Severe pain and cannot eat, drink or swallow	-

1.5 Risk Factors of oral mucositis

The occurrence of mucositis is influenced by various factors including the specific anticancer treatment regimen, dosage, treatment cycles, and individual patient characteristics. Female patients, particularly those treated with 5-Fluorouracil (5-FU) and those with a deficiency in dihydropyrimidine dehydrogenase (an enzyme crucial for 5-FU breakdown), are at a higher risk of developing severe mucositis. (41,43,44) Conversely, patients with aberrant epithelial proliferation, such as psoriasis, exhibit a reduction in the incidence of mucositis. In general, advanced age, female gender, high body weight, decreased drug clearance, and genetic susceptibility are risk factors for mucositis. (41)

When assessing the risk factors linked to the onset of OM, it is crucial to take into account chemotherapeutic agents (such as Methotrexate (MTX)), genetic variants associated with the development of OM, and the diversity of the oral microbiota. (22)

Further research is required in paediatric oncology to establish standardized risk factor assessment and scales for OM evaluation. (22)

1.6 Complications of oral mucositis

The severity of mucositis can impact a patient's capacity to consume food and liquids, disabling nutrient absorption and raising vulnerability to infections. Moreover, mucositis may contribute to malnutrition and a diminished quality of life. (10,45)

In the mild form of oral mucositis, the disease can be managed adequately with existing supportive care. (46)

When it reaches a more severe form, it can lead to a series of complications that can be potentially lethal, such as infections, kidney failure and graft-versus-host disease. As such, it will require intensive inpatient supportive care. (46–49)

Severe cases require treatment interruption or reduction, which negatively affects therapeutic efficacy and prognosis. (16,29,50)

1.7 Management of oral mucositis

The MASCC/ISOO (Mucositis Study Group of the Multinational Association for Supportive Care in Cancer/International Society of Oral Oncology). 2014 clinical practice guide recommends several treatment methods, categorized into seven categories: basic oral care; growth factors and cytokines; anti-inflammatory agents; anti-microbials, coating agents, anesthetics and analgesics; laser and other light therapy; cryotherapy; and natural and miscellaneous agents. (51,52)

Additionally, not all these interventions are suitable for the pediatric population. Low Level Laser Therapy either alone or combined with photochemotherapy leads to better healing of the oral cavity, along with a reduction in infections. The use of glutamine, olive oil and honey is also indicated and chlorhexidine plays a very positive role in controlling oral mucositis in children. (53)

1.8 Prevention of oral mucositis

Although there are various methods of treating oral mucositis, there are few therapeutic options for preventing it in patients undergoing high doses CT plus total body RT prior to HSCT (haematopoietic stem cell transplant). (41,54)

The only drug approved for this purpose by both the FDA (Food and Drug Administration) and the European Medical Agency (EMA) is palifermin. Palifermin is a recombinant human keratinocyte growth factor 1. It promotes the proliferation and differentiation of epithelial cells, which will lead to faster tissue regeneration after damage induced by chemotherapy and/or radiotherapy. It has various antioxidant, anti-inflammatory and anti-apoptotic properties. (41) However, this drug has some cons, such as its high cost and concerns that it may support the growth of cancer cells. This second point makes it considered unsuitable for the management of OM in patients with HNC (head and neck cancer). (41)

2. AIMS

The aim of this study is to provide scientific evidence on the risk factors associated with cancer-related oral mucositis and to establish evidence-based grading of each factor.

3. MATERIALS AND METHODS

This study consists of an umbrella review, which is defined as “systematic reviews of previous ones, provide an overall assessment of the information available on a specific topic“. (55) (56) During this process it was necessary to outline a methodical and rigorous search strategy with a great deal of sensitivity in order to obtain relevant articles.

3.1 Registration protocol

This work was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for the development of the study methodology and was registered in PROSPERO (International Prospective Register of Systematic Reviews) and accepted, under the code CRD42023477370 (Appendix 1).

3.2 Research question

A research question was defined according to the PICO strategy, where the acronym is defined as, P- Population, I- Intervention, C- Comparison, O- Outcome. (29) Therefore, this systematic review aims to define What are the risk factors (I) associated (C) with cancer-related oral mucositis (O) in children (P)?

3.3 Search strategy

The bibliographic search was carried out using PubMed®, Web of Science®, Scopus and Cochrane Database of Systematic Reviews, on the 26th of November , 2023. When searching the PubMed® database, controlled vocabularies (MeSH) were used to find information with greater precision. For all databases, free-text vocabularies and Boolean terms "AND" and "OR" were used in order to combine the search terms. This search was limited to human studies, published in English, in full text with no time limit.

Table 2- Search terms used in Pubmed

	PUBMED
#1	"Child, Preschool"[MeSH] OR "Preschool child" OR "Paediatric population" OR "Paediatric patient*" OR "Child"[MeSH] OR "Child*" OR "Adolescent"[MeSH] OR "Adolescen*" OR "Pre-schooler*" OR “Youth” OR "Teenager*" OR "Teen*" OR "Preteen*" OR "Pre teen*" OR “Pediatrics” [Mesh] OR “Paediatric*” OR “Pediatric*”
#2	“Risk factors” [Mesh] OR “Risk factors“
#3	“Stomatitis” [Mesh] OR “Stomatitis” OR “Oral mucositis” OR “Mucositis” [Mesh] OR “Mucositis”
#4	“Radiotherapy”[Mesh] OR “Radiotherapy” OR “Chemoradiotherapy” OR “Chemoradiotherapy”[Mesh] OR “Chemotherapy protocols” OR “Radiation” OR “Chemotherapy” OR “Cancer treatment” OR "Cancer therap*” OR "Chemotherapy, adjuvant"[Mesh] OR “Anticancer therapies” OR "Oncological therapy" OR "Chemoirradiation" OR "Chemoradiation"
#5	“Systematic Review*”
#6	#1 AND #2 AND #3 AND #4 AND #5

Table 3- Search terms used in Web of Science

	WEB OF SCIENCE
#1	“Preschool child" OR "Paediatric population" OR "Paediatric patient" OR "Paediatric patients" OR "Children" OR "Child" OR "Adolescen" OR "Adolescent" OR OR "Pre-schooler" OR “Youth” OR "Teenager" OR "Teen" OR "Preteen" OR "Pre teen" OR "Pediatrics" OR “Paediatric" OR “Pediatric”
#2	“Risk factors” OR “Risk factor“
#3	”Stomatitis” OR “Oral mucositis” OR ”Mucositis”
#4	“Chemotherapy” OR “Radiotherapy” OR “Chemoradiotherapy” OR “Radiation” OR "Oncological therapy" OR “Anticancer therapies” OR "Anticancer therapy" "Cancer therapy" OR "Cancer therapies" OR "Chemoradiation" OR "Chemoirradiation" OR ”Chemotherapy protocols”
#5	“Systematic Review”
#6	#1 AND #2 AND #3 AND #4 AND #5

Table 4- Search terms used in Scopus

	SCOPUS
#1	TITLE-ABS-KEY ("children" OR "adolescent" OR "Pre-schooler" OR "Youth" OR "Teenager" OR "Preteen" OR "pediatric" OR "Paediatric patient" OR "Paediatric population")
#2	TITLE-ABS-KEY (“Risk factor”)
#3	TITLE-ABS-KEY (”Stomatitis” OR “Oral mucositis” OR ”Mucositis”)
#4	TITLE-ABS-KEY ("chemotherapy" OR "radiotherapy" OR "chemoradiotherapy" OR "Radiation" OR "oncological therapy" OR "anticancer therapy" OR "cancer therapy" OR "Chemoradiation" OR "Chemoirradiation")
#5	TITLE -ABS-KEY (“Systematic review”)
#6	#1 AND #2 AND #3 AND #4 AND #5

Table 5- Search terms used in Cochrane Database of Systematic Reviews

	COCHRANE DATABSE OF SYSTEMATIC REVIEWS
#1	(Child*) OR (Adolescen*) OR "Pre-schooler" OR “Youth” OR "Teenager" OR "Preteen" OR (Pediatric*) OR (Paediatric patient*) OR "Paediatric population"
#2	(Risk factor*)
#3	“Oral mucositis” OR "Mucositis" OR "Stomatitis"
#4	(Chemotherap*) OR (Radiotherap*) OR (Chemoradiotherap*) OR “Radiation” OR (Oncological therap*) OR (Anticancer therap*) OR (Cancer therap*) OR "Chemoradiation" OR "Chemoirradiation"
#5	(Systematic review*)
#6	#1 AND #2 AND #3 AND #4 AND #5

In order to obtain an adequate bibliographic list for the study and answer the research question in a rigorous way, inclusion and exclusion criteria were established.

3.4 Inclusion Criteria

This umbrella review was based on all systematic reviews, available as full text, with no publication date limit, in the paediatric population with oral mucositis that has been or is being exposed to cancer treatment.

3.5 Exclusion criteria

All critical/narrative articles, letters to the editor, primary research studies, non-cancer derived oral mucositis and systematic reviews without risk factors were excluded.

3.6 Screening process

The search and screening were carried out independently by two reviewers (TH and PC) with the aid of Rayyan software. (57) Analysing the titles and abstracts was the first stage of the process. The systematic reviews to be included were then read in full and analysed according to the inclusion and exclusion criteria for subsequent data extraction. Cohen's kappa coefficient was used to assess agreement between the reviewers.

Any disagreement between the reviewers was addressed by consensus and whenever necessary a third reviewer (RS) would be involved.

3.7 Data Extraction

Findings are presented in tabular format with supporting text. Extracted data include: author, year and country; characteristics of the included studies (tables 6-8) and conclusions (table 9).

3.8 Qualitative Analysis, Risk of Bias Assessment and Level of Evidence

It is important to carefully assess the quality of the articles, so the following questionnaires were used (AMSTAR-2 tool (58) for methodological quality and ROBIS tool (59) for assessing the risk of bias) in order to ensure that the reviews were conducted to the highest standard of scientific rigour, screening out any errors that could affect the analysis of the results and the conclusions drawn, and ensuring that clinical decisions are made using the best scientific evidence.

The level of evidence of each risk factor was assessed using the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation).

4. RESULTS

After combining the search terms and applying the filters, 101 articles were obtained, including three articles in PubMed, three articles in Web of Science, four articles in Scopus and 91 articles in the Cochrane Database of Systematic Reviews.

The first stage of the process consisted of identifying duplicate articles. At this stage, four articles were excluded. This was followed by the selection of articles by title and abstract. 97 articles were collected, of which 86 were excluded. Finally, eleven studies were selected for full-text analysis. After applying the eligibility criteria, five articles were selected for this systematic review. The results are presented schematically in the form of a PRISMA flowchart (Figure 1).

At the first stage of the selection process, a k value of 1 was obtained. For the selection of studies based on the title and abstract, the k-value was 0.95, indicating almost perfect agreement. For full text selection of articles, the k value was 0.81, indicating good agreement.

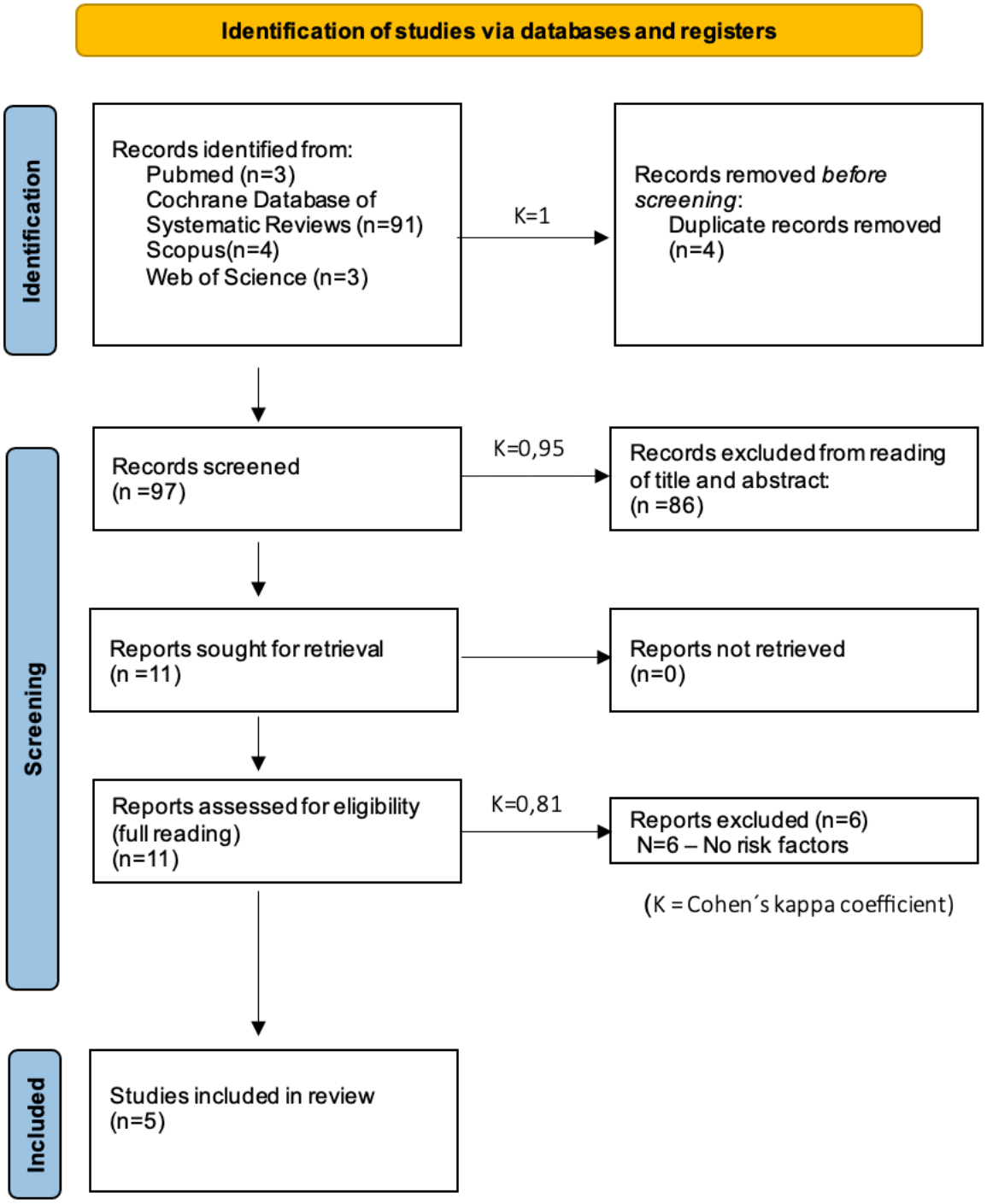

Figure 3- PRISMA flowchart of the articles selection process

Tables 6, 7 and 8 describe the characteristics of the studies included in this umbrella review . Conclusions are presented in Table 9.

Table 6- Characteristics of the studies included in the umbrella review

AUTHOR YEAR COUNTRY	PICO	REGISTRATION PROTOCOL	ARTICLES INCLUDED	META-ANALYSIS	DATABASES	STRATEGIC SEARCH
Docimo, R *et al.* *2022* Italy	Yes	Yes	17	No	PubMed, Scopus, Cochrane Library, Web of Science, EBSCO (N=5)	Yes
Wardill HR et al. *2020* International (MASCC/ISOO)*	No	Yes	113	No	PubMed, Web of Science (N=2)	Yes
De Farias, GA *et al.* 2021 Brazil	Yes	Yes	19	Yes	MEDLINE/ PubMed, EMBASE, Web of Science, Scopus (N=4)	Yes
Martins, JO. et al. 2023 Brazil	Yes	Yes	39	Yes	PubMed, Scopus, Web of Science, LILACS, EBSCOhost, LIVIVO and EMBASE (N=6)	Yes
Ward, EJ et al. 2015 United Kingdom	No	Yes	14	Yes	MEDLINE, EMBASE (via Ovid), The Cochrane Central Register of Controlled Trials, CINAHL (via Ebsco). (N=4)	Yes

Table 7-Characteristics of the studies included in the umbrella review (continued)

AUTHOR	SEARCH DATE	LANGUAGES INCLUDED	NUMBER OF REVIEWERS	INCLUSION CRITERIA	EXCLUSION CRITERIA
Docimo, R *et al.*	Up to 8/11/2020.	English	2	• Human studies; • Study population aging ≤ 21 years; • Patients that received chemotherapy for malignant or non-malignant tumours; • Sample size of 21 or more participants; • Medications approved by the FDA; • Studies explicity deailing oral mucositis; • Studies that used standardized indices to define OM; • Study design: retrospective or prospective longitudinal studies, case-control studies, cohort studies, and randomized control trials.	• Phase I and Phase II studies; • Research combining chemotherapy and radiotherapy ; • Study design: case report, case series, review, and meta-analysis.
Wardill HR *et al.*	01/2000 to 07/2019	No restrictions	2 (+1)	• Clinical investigations to identify predictors of oral mucositis/gastrointestinal mucositis or associations between baseline characteristics and mucositis outcomes.	• Reviews; • Preclinical research; • Clinical trials exclusively • Case studies.
De Farias, GA et al.	No restrictions	English	3 (+1)	• Research involving individuals aged 0 to 19 years undergoing various antineoplastic therapy protocols for treating different baseline diseases.	• Review papers; • Letters to the editor; • Thesis; • Conference papers; • Book chapters; • Unpublished data; • Animal studies;
Martins, JO et al.	No restrictions	No restrictions	2(+1)	• Controlled clinical trials were incorporated to assess the efficacy of any oral and/or dental hygiene protocol compared to a placebo	• Literature reviews; • Letters to the editor; • Author´s personal viewpoints; • Book chapters; • Meeting abstracts; • Cross-sectional studies; • Laboratory experiments.
Ward, EJ et al.	1950 to 2013 (MEDLINE) 1974 to 2013 (EMBASE) 1982 to 2013 (CINAHL)	English	2 (+1)	• All randomised trials or quasi-randomised trials; • Children and young people ≤ 21 years with any type of malignant disease requiring chemotherapy; • Comparison of one type of nutritional support with another or with no nutritional support.	• Controlled studies that are non randomised or quasi-randomised; • Studies in adults; • No chemotherapy; • Vitamin supplementation and micronutrient supplementation.

Table 8- Characteristics of the studies included in the umbrella review (continued)

AUTHOR	STUDIED GROUPS	OUTCOME EVALUATED	QUALITY ANALYSIS	RISK OF BIAS TOOL
Docimo, R *et al.*	• 2,434 children submitted to cancer chemotherapy ; • Average age of 7.52; • 61,7% male and 38,3% female; • Three of the 17 included studies did not provide details regarding the age and gender of their study participants.	• Incidence of OM; • Severity of OM; • Risk Factors for chemotherapy-induced oral mucositis in the pediatric, and adolescent populations.	Yes	Newcastle-Ottawa Scale (NOS)
Wardill HR *et al.*	• Most studies were conducted in adult patient. Only ten in children.	• Evidence for each mucositis risk predictor	No	None
De Farias, GA et al. .	• Population sample size ranged from 28 to 970 patients; • Mean age0 months to 18 years; • Majority of boys; Different hematological neoplasms or solid tumours. Acute lymphoblastic leukemia (ALL) was the only disease included in 5 studies.	• Risk factors linked to the onset of OM without assessing its severity.	Yes	JBI Critical Appraisal
Martins, JO et al.	• RCTs: 2109 patients 1045 were women, 843 were man and 221 patients were unspecified sex; Age ranged from 7.0 to 68.3 years. • N-RCTs: 754 patients were evaluated in the RCTs. 754 were women, 356 were men and 93 were unspecified sex. Age ranged from 7.0 to 76 years.	• Whether oral and dental hygiene protocols (DHPs) decrease the occurrence and severity of oral mucositis (OM) during antineoplastic treatment.	Yes	ROB-2
Ward, EJ et al.	• 595 patients under the age of 21 diagnosed with leukemia or solid tumors undergoing chemotherapy.	Primary outcome: • Alteration in nutritional indicators; • Adverse events; • Calorie and nutritional intake. Secondary outcome: • Mortality rate at the conclusion of the study; • Duration f hospitalization; • Patient tolerance of or adherence to nutritional intervention; • Participant perceived health status, where possible using validated tools for measuring performance and/or quality of life.	Yes	The Cochrane Handbook for Systematic Reviews of Interventions

Table 9- Conclusions of the studies

AUTHOR	CONCLUSIONS
Docimo, R et al.	• Half the children develop OM after chemotherapy; • Most of the articles have been carried out on the adult population; • Most articles describe methods to prevent OM and reduce its symptoms.
Wardill HR et al.	• Very few articles on the paediatric population; • Many factors in adults can not be extrapolated to children, and children's microbial communities are also different from those of adults
De Farias, GA et al.	Risk factors for developing OM: • The chemotherapeutic agents (Methotrexate (MTX) and associations); • Gene variants and biomarkers; • Herpes simplex vírus andoral candida ssp;
Martins, J.O. et al.	• In patients undergoing antineoplastic treatment, oral health care strongly reduces the severity of OM and moderately reduces the incidence of OM • Combining oral hygiene education and chlorhexidine mouthwash is the most promising intervention to reduce OM.
Ward, EJ et al.	• Evidence is inconclusive regarding the effect of glutamine supplementation and the development of OM and the incidence and severity of mucositis.

4.1 Risk Factors

Docimo R, *et al*. 2022 reported that the average incidence of OM was 53.6% and ranging from 16.7% to 91.5%, while severe oral mucositis ranged from 15.8% to 35.2. (10) Regarding risk factors, the type of tumor and chemotherapy regimen were found to be the most associated with OM. In the articles included in the study by Docimo, R *et al*, other factors contributing to an an increase risk of OM after chemotherapy were also identified. Some authors suggested that low pre chemotherapy body weight, neutropenia, hepatic and renal dysfunction during chemotherapy could significantly contribute to OM development in children. (10) Furthermore, other researchers have stated that there may be a relationship between increased body weight loss and a higher incidence of OM. In another study, the risk of OM could be increased by a factor of 2,46 if oral hygiene was not practiced. (10)

In the study by Wardill HR, *et al*. 2020 ,various investigations explored the impact of medication. One study reported that the use of multivitamins prior to therapy was related to lower OM scores. (46) Another study mentioned that antibiotic therapy for more than 10 days, one month before treatment, was a predictor of GI-M (Gastrointestinal mucositis) in children with ALL (Acute Lymphoblastic leuukemia). (46) The type of tumour in children was also mentioned, with germline tumours (versus non-germline tumours) and haematological malignancies (versus central nervous system tumours), specifically Hodgkin's lymphoma, having a higher risk of HSCT-induced OM. (46)

De Farias GA, *et al*. 2021 stated that 42% of the studies included in their review suggested chemotherapeutic agents as potential risk factors for the development of OM. More specifically, high doses of MTX alone, and the level of MTX66h ≥ 0.2 mmol/l in plasma. MTX used in clinicals trials conducted by Children's Oncology Group (COG) AHOD0031 (focused on paediatric patients with intermediate-risk Hodgkin's lymphoma) and AHOD0832 (focused on paediatric patients with high risk Hodgkin's lymphoma) for the treatment of Hodgkin’s lymphoma, leukaemias, Burkitt’s lymphoma, ALL and Ewing’s sarcoma were also considered factors in another three studies. Other

agents were also identified as as potential risk factors. (22) Four studies highlighted the underlying disease (i.e. the type of tumour) as a risk factor for OM: hematological neoplasms were referenced in two studies; acute leukemia, solid tumors, and lymphoma were noted in one study; furthermore, solid tumors, including germ cell tumors and undifferentiated nasopharyngeal carcinoma, were identified as risk factors. (22) De Farias, GA *et al* 2021, considered the type of cancer as a risk factor, and the protocols were also indicated as risk factors in the same articles.

Low body weight, nausea/vomiting, anxiety prior to OM and specific therapeutic regimens were identified as risk factors in five studies. Hematological, hepatic, and renal parameters, including neutropenia, white blood cell count <9,500/mm³, low lymphocyte count in patients with solid tumors, high and low platelet levels, were reported in eight studies. (22) One study associated elevated creatinine, ALT (Alanine aminotransferase) AST (Aspartate aminotransferase) levels with OM. High levels of total and indirect bilirubin were also indicated in one study. (22)

Genetic variants and inflammatory biomarkers were identified as predictors of OM in four studies. (22) For the c.3435C>T variant (rs1045642) of the *MDR1* gene (also known as *ABCB1*), the CT genotype has been identified as a risk factor for OM. (22) For the c.75-23516T>C variant (rs7317112) of the *ABCC4* gene, the AA genotype was also identified as a factor in the increased incidence of OM. (22)

The Arg194Trp, c.580C>T variant (rs1799782) and Arg399GIn, c.1196G>A variant (rs25487) of the *XRCC1* gene increase the risk of severe OM and the 194Trp allele has been shown to be protective against OM. (22)

Pro-inflammatory cytokines (IL-6, IL-8 and IFN-c) in higher concentrations together with low levels of the antimicrobial protein pro-LL-37 in patients presenting with acute leukaemia, are related to higher levels of OM. (22)

Finally, oral microflora (positive herpes simplex, in three studies and oral *candida spp.* in one study) was also mentioned as a potential risk factor in four studies. (22)

According to Martins JO, *et al* 2023, dental hygiene protocols (DHPs) are associated with a significant reduction in severity and a moderate reduction in frequency of OM. (60)

With regards to the article by Ward EJ, *et al*. 2015, the authors found that the advantages of glutamine supplementation in reducing not only the occurrence and severity of mucositis, but also infection rates and length of stay in hospital, did not reach statistical significance, and more research is needed in this field. (61)

4.2 Methodological quality assessment (AMSTAR-2)

Tables 10 and 11 show the criteria adopted for methodological quality analysis of the studies using the AMSTAR-2 tool (Appendix 2) and the respective responses. All the included articles had a favorable score for the following criteria: data extraction and selection of duplicate studies, conducting a comprehensive literature search, the list of excluded articles and their justification, the characteristics of the included studies, the explanation of any observed heterogeneity and the declared conflict of interest.

The criterion relating to the explanation of the designs of the included studies and the criterion on the sources of funding of the included studies received a negative response for all the included articles.

Ward EJ, *et al* 2015 and Wardill HR, *et al* 2020 presented a research question, but it was not according to the PICO criteria. Therefore, both were evaluated with a “no” in this parameter. (46,61)

Regarding the parameters of an “a priori” design and a satisfactory RoB technique, along with its inclusion in the interpretation and discussion of results, Wardill HR, *et al* 2020 received a negative response, since no risk of bias was provided. (46)

De Farias GA, *et al*. 2021, Martins JO, *et al*. 2023 and Ward EJ, *et al*. 2015, were the only articles that carried out a meta-analysis, responding positively to the appropriate methods of combining the results and the potential impact of RoB on the individual studies. (22,60,61) Also with regards to the articles that had meta-analysis, only one had a negative response regarding the likelihood of publication bias (De Farias GA, *et al*. 2021). (22)

Table 10- Criteria for analysis of the methodological quality of the studies on their respective responses (AMSTAR-2)

Criteria / Author	Were the components of PICO included?	Was an 'a priori' design provided?	Was an explanation about the included study designs?	Was a comprehensive literature search performed?	Was there duplicate study selection and data extraction?	Was a list of excluded studies (and justification) provided?	Were the characteristics of the included studies provided?	Was a satisfactory technique for assessing the RoB provided?
Docimo R, *et al*.	YES	YES	NO	YES	YES	YES	YES	YES
Wardill HR, *et al*.	NO	NO	NO	YES	YES	YES	YES	NO
De Farias GA, *et al*.	YES	YES	NO	YES	YES	YES	YES	YES
Martins JO, *et al*.	YES	YES	NO	YES	YES	YES	YES	YES
Ward EJ, *et al*.	NO	YES	NO	YES	YES	YES	YES	YES

Table 11- Criteria for analysis of the methodological quality of the studies on their respective responses (AMSTAR-2) (continued)

Criteria / Author	Were sources of funding for the included studies provided?	Was an appropriate method for statistical combination of results provided? (if meta-analysis was performed)	Was assessed the potential impact of RoB in individual studies? (if meta-analysis was performed)	Was RoB included in interpretation /discussion of the results?	Was a satisfactory explanation of any heterogeneity observed?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Docimo R, *et al*.	NO	NO META-ANALYSIS	NO META-ANALYSIS	YES	YES	NO META-ANALYSIS	YES
Wardill HR, *et al*.	NO	NO META-ANALYSIS	NO META-ANALYSIS	NO	YES	NO META-ANALYSIS	YES
De Farias GA ,*et al*.	NO	YES	YES	YES	YES	NO	YES
Martins, JO, *et al*.	NO	YES	YES	YES	YES	YES	YES
Ward EJ, *et al*.	NO	YES	YES	YES	YES	YES	YES

4.3 Risk of bias (ROBIS) assessment in individual studies

Analysis of the risk of bias of the included studies was evaluated using the ROBIS tool (Appendix 3). The criteria considered, as well as the result of this analysis, are described in Table 12.

All the articles, except for one article (Wardill HR, *et al*. 2020), received a positive response in all the evaluated criteria. (46)

Table 12- Criteria adopted for bias risk assessment of included studies and their respective classifications (ROBIS)

Criteria / Author	1.Study eligibility criteria	2.Identification and selection of studies	3.Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Docimo R, *et al*					
Wardill HR, *et al*					
De Farias GA, *et al*					
Martins JO, *et al*					
Ward EJ, *et al*					

 = Low risk  = High Risk  = Unclear risk

4.3 Level of evidence assessment in individual studies (GRADE tool)

Table 13 shows the level of evidence that was acquired by applying the GRADE tool.

Regarding the level of recommendation of the risk factors: type of tumour chemotherapy regimen, low body weight before the therapy, neutropenia, hepatic and renal dysfunction, oral hygiene, genetic variants and inflammatory biomarkers and oral microbiota have a high level of evidence with a good degree of recommendation. The remaining parameters do not have such a satisfactory level of evidence, requiring more studies in the area to arrive at more conclusive, safe and reliable results.

Table 13- Level of evidence using the GRADE tool

Risk factors	Degree of recommendations	Level of evidence
Type of tumour	I	A
Chemotherapy regimen	I	A
Low body weight before the therapy	IIa	A
Neutropenia	I	A
Hepatic and renal dysfunction	I	A
Oral hygiene	IIa	A
Use of multivitamins prior to the therapy	IIb	B
Elevated creatinine, ALT and AST	IIb	B
High levels of total and indirect bilirubin	IIb	B
Genetic variants and inflammatory biomarkers	I	A
Oral microbiota	IIa	A

5. DISCUSSION

This study aims to understand the risk factors for oral mucositis secondary to anti-cancer treatment in children, to determine the role of each factor and subsequently provide a precise and effective prevention and management strategy of OM. .

Since oral mucositis is a common condition secondary to cancer treatment, it is important to understand the determinants of OM. It is surprising that children under the same circumstances present different outcomes for OM. Unfortunately, this dilemma remains unsolved.

All the selected studies were of high quality and presented relevant data that provide scientific evidence about specific factors in the development of OM.

The tools used to assess the risk of bias in the articles included in this study are well established in the literature. Newcastle-Ottawa Scale (WHO) was used in the article of Docimo R, *et al* 2022 (10), JBI Critical Appraisal in the article of De Farias GA, *et al* 2021 (22), ROB-2 in Martins JO, *et al* 2023 (60) and The Cochrane Handbook for Sytemtic Reviews of Interventions in Ward EJ, *et al* 2015 (61).

All but Wardill HR, *et al* 2020 did not mention the Risk of Bias tool. (46) This study presented a research question, but it was not according to the PICO criteria. Despite some technical flaws in the revision design, the authors are field experts and part of the MASCC group.

5.1 Study population

About the population of interest in this study (paediatric population), Wardill HR *et al*. 2020 and Martins JO, *et al* 2023 presented a larger number of articles included in their study. (46,60) This could possibly be explained by the fact that they included not only children, but also adults who had been or were currently being exposed to cancer treatment. Although one of our inclusion criteria was paediatric population, we decided to include these articles and extract the results from the children´s section, so as not to lose relevant information for our research.

Another topic to be addressed is the age of children in the included studies. . In most countries the paediatric age limit is 18 years. However, in some countries , the

age limit was 21 years. (10,61) Ward EJ, *et al* 2015 justified that many paediatric oncology units in the UK and elsewhere, include patients up to 21 years old. (61) Docimo R, *et al* 2022 also considered the age limit of 21 years , based on the definition of late adolescence of the American Academy of Pediatrics. (10) Overall, we also considered this age range and included these articles in our review.

5.2 Risk factors

Regarding risk factors, the most prominent risk factor with the greatest impact in the development of OM was the type of tumour and chemotherapeutic agents. Low body weight, haematological, hepatic, renal parameters (10,22) and poor oral hygiene (10,60) were also highlighted in several articles. Other factors, such as: high levels of creatine, ALT and AST, multivitamins and high levels of total and indirect bilirubin were mentioned in a small number of articles. (22) More primary research studies are required to determine its importance in the development of oral mucositis.

5.2.1 Chemotherapeutic agents

The chemotherapeutic agent MTX is mentioned in more than one article. (10,22,46)

As well as being used alone, it can also be used in combination with other chemotherapeutic agents. De Farias GA, *et al* 2021 (22), mentions the COPADM and Vid protocols, which include various agents such as doxorubicin, cisplatin, cyclophosphamide, vincristine, ifosfamide and etoposide in addition to MTX. In the case of the ALL-BFM-95 protocol, it also uses other compounds in association with MTX, such as vincristine, daunorubicin, ara-c, 6-mercaptopurine, ifosfamide, etoposide, doxorubicin, cyclophosphamide and 6-thioguanine.

De Farias GA, *et al* 2021 said that the chemotherapeutic agents for childhood neoplasms are used in large doses, leading to high levels of toxicity and that MTX on

its own has a high toxic potential, which leads to greater toxicity when used concomitantly with other agents. (22)

In addition to the association of MTX with other chemotherapeutic agents, De Farias GA, *et al* 2021 also mentioned another link to this chemotherapeutic agent. Serum concentrations of creatinine lead to MTX delay. (22) This is a very negative action, because as mentioned above, MTX has great toxic potential. As it is eliminated more slowly, it may accumulate, which will lead to more toxicity and a higher incidence of OM in these patients.

5.2.2 Type of cancer

The most prevalent factor in the articles was the type of cancer. The most frequently mentioned were haematological malignancies, which were mentioned in 3 of the articles selected in this review. (10,22,46)

Wardill HR, *et al* 2020 said that germ cell tumours (when compared to non-germ cell tumours) and haematological malignancies versus CNS tumours (specifically Hodgkin's lymphoma) were mentioned as increasing the risk of OM. (46)

In the articles by De Farias GA, *et al* 2021 and Docimo R, *et al*. 2022 , studies indicated haematological malignancies (such as leukaemia and Hodgkin's lymphoma) versus solid tumours, with a greater association with OM. (22)

Additionally, Docimo R *et al* 2022, said that the severity of OM in patients with haematological malignancies is greater compared to other types of malignant neoplasms. (10)

Another combination of factors to take into account is also the type of cancer, along with the type of chemotherapy protocol applied. In the paper by De Farias GA, *et al* 2021, of the four studies that presented cancer as a risk factor, three also indicated

the protocols as risk factors. (22) This relationship may be related to the fact that there is a direct link between the two topics, since there are different treatments and doses for different types of cancers.

5.2.3 Oral hygiene

Martins JO, *et al* 2023 and Docimo R, *et al* 2022 emphasise the importance of oral health. Poor oral hygiene appears to be also significant, particularly as it is a preventable risk factor that can be improved , opposing to factors such as health status and therapeutic regimen. There is information in the literature to the effect that dental problems such as untreated caries, poor dental hygiene and infectious periapical lesions can trigger an inflammatory response from the host. Oral mucositis (OM) can be exacerbated by these conditions. (20,62–64)

5.2.4 Neutropenia

Neutropenia was also selected as a relevant factor in the development of OM in various articles. (10,22,46,60)

Neutrophils act in the line of defence against pathogens by generating an inflammatory response. (65) According to one study cited in De Farias GA, *et al*. 2021, a decrease in neutrophil count may hinder the ability to mount an effective inflammatory response against chemotherapy-induced damage to the oral mucosa. (22)

Furthermore, a small amount of toxicity can cause ulceration of the soft tissues in the oral cavity. (66,67) Due to the compromised inflammatory response, patients with neutropenia are susceptible to oral infections by opportunistic and acquired oral pathogenic microorganisms, leading to severe oral mucositis. (66,68)

Neutropenia and other risk factors involving haematological, hepatic and renal toxicities can develop concurrently with oral mucositis. (22) Hence, monitoring these parameters is crucial, not only for early detection of oral mucositis but also for understanding the systemic condition of patients..

5.2.5 Oral microbiota

Infections by herpes simplex and oral *Candida* spp., were also referred in some of the studies. (22,46)

Wardill, HR *et al* 2020 mentions that the herpes simplex virus showed a relationship with the risk of OM, with infected patients having a risk of up to 6.8 times more severe OM (grade III-IV) after chemoradiotherapy. (46) In addition to the paediatric population, this article also includes the adult population and although it is not mentioned whether this would be a risk factor common to both adults and children or exclusive to one of the populations, it is mentioned in another article exclusively for children, which reinforces this point.

As such, De Farias GA, *et al* 2021 said that herpes simplex virus (the virus manifests itself when the immune system weakens) often manifests itself in children. (22) Two of the studies in the article by De Farias GA ,*et al* 2021 say that one of the reasons for this may be that children with cancer have a very immunosuppressed immune system, which increases the occurrence of herpes. (22) A positive manifestation of herpes simplex is related to a worsening of OM, because can affect the immune response. (22)

In the study by De Farias GA, *et al* 2021, oral *Candida* spp. was also identified as a potential risk factor for OM in 1 article. (22)(17) This study says that since oral mucositis (OM) typically leads to the formation of clinical ulcers, alterations in the oral microbiota could be linked to secondary infections. Consequently, the oral microbiota might contribute to the development of OM. (22)

There is information in literature that this infection occurs as a secondary factor to xerostomia, which is caused by radiation damage to the salivary glands. (21) This may imply that, although it is a concomitant component, it is not an etiological factor in OM secondary to anti-cancer treatment. (26) However, the study mentioned in the

article by De Farias, GA *et al* 2021 (De Mendonça *et al* 2015) is more recent than the one by Sonic ST 2012, which could mean a new perspective and scientific evidence.

Wardill HR, *et al*. (2020) emphasize the significance of the microbiota, indicating that evidence suggests the microbial composition before treatment influences the mucositis induced by chemotherapy and radiotherapy. (46) Early microbial changes can predict the development of OM. They also highlight that this area is gaining interest due to the microbiota's modifiable nature and its substantial impact on both local mucosa and immune function. (46) Considering this, it is an area that needs further study but which has great potential for predicting risk.

5.2.6 Genetic variants

De Farias, GA *et al* 2021, said that the variant rs1045642 of the MDR1 gene has been recognized as a risk factor for OM. The link lies in the fact that this gene encodes a protein that is responsible for the movement of various chemotherapeutic agents in malignant neoplasms. (22) Recent evidence also supports a role of this polymorphism in the development of OM (33)

The variant rs7317112 of the *ABCC4* gene was also identified as a factor in the increased incidence of OM.The ABCC4 gene encodes a protein that is linked to drug resistance and also plays a role in the elimination of chemotherapeutic agents (22), which may increase their toxicity.

The variants rs1799782 and rs25487 of the XRCC1 gene increase the risk of severe OM, although the 194Trp allele has been shown to have a protective effect against OM. This correlation is attributed to the gene's role in DNA damage repair mechanisms induced by active oxygen, ionising agents and alkylating agents. (22)

5.3 Limitations of the study

Umbrella reviews have many advantages and certain limitations, including the fact that the accuracy of the general review results is contingent upon the quality of the included systematic reviews and meta-analyses. Additionally, the review does not cover interventions or epidemiological associations not addressed in these systematic reviews and meta-analyses. Potential quality issues and biases may also exist in both the primary studies and the overarching review process. (69)

In our study, the main objective was to identify and assemble the risk factors associated with OM. On the other hand, the limitations derive from the quality of the eligible studies, including both primary studies and systematic reviews, as well as the lack of detailed data.

Another limitation is related to the fact that there were fewer systematic reviews compared to articles presenting clinical cases, which meant that we obtained a smaller number of articles, making it difficult to relate data between the various articles.

All the selected articles mentioned that more research is needed in this field. There are many reasons for that. Performing research in children raises ethical and technical issues , which justify the lack of studies. Many studies have low patient number or heterogeneous populations of patients, including different types of cancer and therapeutic regimens. Hence, many studies rely on an adult population, which affects knowledge transfer. Considering that adult cancers have certain risk factors and that children do not, we cannot directly correlate certain data to the paediatric population. (46)

6. CONCLUSION

Oral mucositis is a multifactorial disorder with a high prevalence in children. It has specific manifestations in children, which makes it difficult to determine risk factors.

The exact mechanism of oral mucositis is not completely understood, but there are several explanations to consider.

The most important factor relating to OM was the chemotherapy protocol and the type of tumour. There were other relevant factors such as low body weight, haematological, hepatic, renal parameters, and poor oral hygiene. Less significant factors werehigh levels of creatine, ALT and AST, multivitamins and high levels of total and indirect bilirubin. These factors need further investigation to determine if they can be considered reliable and valid risk factors.

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8. Appendices

8.1 Appendix 1 – PROSPERO

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Risk factors for oral mucositis secondary to oncological treatment in children - an umbrella review

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided here.

Citation

Tatiana Henrique, Patrícia Correia, Anna Moura, Raquel Silva. Risk factors for oral mucositis secondary to oncological treatment in children - an umbrella review. PROSPERO 2023 CRD42023477370 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023477370

Review question

What are the risk factors (I) associated (C) with cancer-related oral mucositis (O) in children (P)?

Searches

PRISMA methodology will be used to perform this systematic review.

The following bibliographic databases will be used: PubMed, Scopus, Web of Science and Cochrane Database of Systematic Reviews.

Types of study to be included

Systematic review, systematic review and meta-analysis

Condition or domain being studied

Oral mucositis is one of the most common complications of chemotherapy. It greatly affects quality of life, leading to significant pain, discomfort when chewing and/or swallowing, altered intestinal absorption, possible malnutrition and potentially widespread local infection. It is therefore necessary to understand the risk factors for oral mucositis in order to minimise the effects and try to act preventively.

There are many systematic reviews on the risk factors for oral mucositis secondary to oncological treatment in children. However, there are no umbrella reviews on this subject. This study will provide new scientific evidence on the risk factors associated with this specific group and will also attempt to establish new relationships and the weight of each one.

Participants/population

Inclusion criteria: Systematic reviews about oral mucositis; in oncology children.

Exclusion criteria: Critical/narrative reviews, letters to the editor

Intervention(s), exposure(s)

Risk factors

Comparator(s)/control

Associated

Main outcome(s)

Cancer-related oral mucositis

Measures of effect

Risk Factors

Additional outcome(s)

None

Data extraction (selection and coding)

Two reviewers will extract independently quantitative and qualitative data from each selected study, according to the risk factors. Findings will be presented in tabular format with supporting text. Quantitative tabulation of results will include: first author name and year of publication; country where the study took place; characteristics of the study population; number of RCTs included in the systematic reviews; findings related to the degree of oral mucositis.

Risk of bias (quality) assessment

The methodological quality of this umbrella review will be assessed using the AMSTAR-2 tool, while the risk of bias will be assessed using ROBIS. Two reviewers will independently carry out the quality and risk of bias analyses.

Strategy for data synthesis

A qualitative description of the included studies will be given. When quantitative data is presented, the number of studies reporting the outcome, the number of participants (from the included studies) and the heterogeneity of the results of the included reviews will be reported. The results of qualitative systematic reviews included in the general review will be presented in a table format in which the final conclusions or general syntheses of the included reviews will appear, with enough relevant contextual information next to each synthesised conclusion to ensure that each one is interpretable for the reader.

Analysis of subgroups or subsets

None

Contact details for further information

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Organisational affiliation of the review

Universidade Católica Portuguesa - Faculty of Dental Medicine

https://www.ucp.pt/pt-pt/viseu

Review team members and their organisational affiliations

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Professor Anna Moura. Universidade Católica Portuguesa - Faculty of Dental Medicine
Professor Raquel Silva. Universidade Católica Portuguesa - Faculty of Dental Medicine

Type and method of review

Systematic review

Anticipated or actual start date

06 November 2023

Anticipated completion date

01 February 2024

Funding sources/sponsors

Centre for Interdisciplinary Research in Health (CIIS)

Grant number(s)

State the funder, grant or award number and the date of award

Grant: UIDB/04279/2020

Conflicts of interest

None known

Language

English

Country

Portugal

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

30 November 2023

Date of first submission

19 November 2023

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

30 November 2023

30 November 2023

8.2 Appendix 2 – Amstar- 2 tool

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)

- ☐ Timeframe for follow up

- ☐ Yes
- ☐ No

---

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:

- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:

- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ a plan for investigating causes of heterogeneity

- ☐ Yes
- ☐ Partial Yes
- ☐ No

---

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☐ OR Explanation for including both RCTs and NRSI

- ☐ Yes
- ☐ No

---

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☐ No

---

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- ☐ Yes
- ☐ No

---

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

- ☐ Yes
- ☐ Partial Yes
- ☐ No

---

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
☐ described populations	☐ described population in detail	☐ Yes ☐ Partial Yes ☐ No
☐ described interventions	☐ described intervention in detail (including doses where relevant)	
☐ described comparators	☐ described comparator in detail (including doses where relevant)	
☐ described outcomes	☐ described study's setting	
☐ described research designs	☐ timeframe for follow-up	

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
☐ unconcealed allocation, and	☐ allocation sequence that was not truly random, and	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, and	☐ methods used to ascertain exposures and outcomes, and	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs
☐ from selection bias	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☐ No meta-analysis conducted

For NRSI

For Yes:

☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

- ☐ There was no significant heterogeneity in the results
- ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

☐ Yes
☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

- ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

☐ Yes
☐ No
☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☐ Yes
☐ No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

8.3 Appendix 3 – ROBIS tool

ROBIS: Tool to assess risk of bias in systematic reviews

Phase 1: Assessing relevance (Optional)

ROBIS is designed to assess the risk of bias in reviews with questions relating to interventions, aetiology, diagnosis and prognosis. State your overview/guideline question (target question) and the question being addressed in the review being assessed:

Intervention reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Intervention(s):		
Comparator(s):		
Outcome(s):		

For aetiology reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients/Population(s):		
Exposure(s) and comparator(s):		
Outcome(s):		

For DTA reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients):		
Index test(s):		
Reference standard:		
Target condition:		

For prognostic reviews:

Category	Target question (e.g. overview or guideline)	Review being assessed
Patients:		
Outcome to be predicted:		
Intended use of model:		
Intended moment in time:		

Does the question addressed by the review match the target question?	YES/NO/UNCLEAR

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings	LOW/HIGH/UNCLEAR
Rationale for concern:	

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding methods used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review	RISK: LOW/HIGH/UNCLEAR
Rationale for risk:	

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

8.4 Appendix 4 – Poster presented at the IPO Porto Summit. Received 2nd place award

IPO PORTO SUMMIT 9 a 11 MAIO 2024

Risk factors for cancer treatment-related oral mucositis in children

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Introduction: Oral mucositis (OM), one of the most common complications of chemotherapy and radiotherapy, affects approximately 52% to 80% of children treated for cancer. In pediatric oncology, identifying risk factors for OM is of great value for patient care. It helps determine the optimal preventive measures and ensures the patient receives the appropriate therapeutic regimen.

Objectives: To determine the risk factors associated with cancer treatment-related oral mucositis.

Materials and Methods: This systematic review was registered with PROSPERO (CRD42023477370) and conducted in accordance with PRISMA guidelines. The search was conducted using PubMed, Web of Science, Scopus, and the Cochrane Database of Systematic Reviews. Two independent reviewers performed the search and screening using Rayyan software. Cohen's kappa coefficient was used to assess agreement between the reviewers. The methodological quality was assessed using the AMSTAR-2 tool, while the risk of bias was evaluated using ROBIS.

Results and Discussion: From 101 articles obtained at the initial search stage, 5 articles were evaluated in this study (Fig. 1). The risk factors found to have the greatest impact on the development of oral mucositis were the type of tumour and chemotherapeutic agents, Tables 1 and 2. Additionally, low body weight, haematological, hepatic, and renal parameters, as well as poor oral hygiene, were identified as contributing factors. Certain gene variants and biomarkers were also associated with OM, Tables 1 and 2. Overall, the quality of the studies was deemed good, and the risk of bias was low.

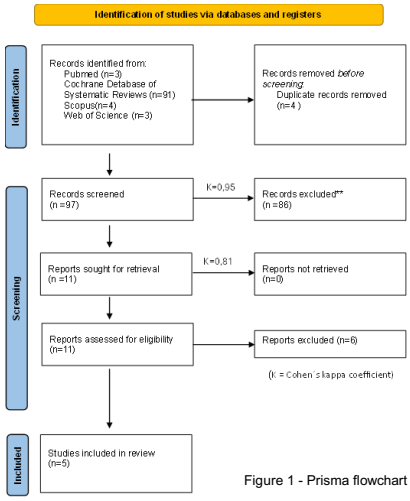

Figure 1 - Prisma flowchart

Tables 1 and 2 - Summary of results

AUTHOR	CONCLUSIONS
Docimo, R et al.	Approximately half the children develop OM after chemotherapy. The exact risk factors associated with the development of OM have not yet been described, despite the large number of articles published in the literature. Most of the articles have been carried out on the adult population and have focused on describing methods to prevent OM and reduce its symptoms.
Wardill HR et al.	Only 10 of the 113 articles included in the analysis related to children (greater difficulty in reaching a conclusion about OM risk prediction). Such prediction in children is difficult because many factors known to influence the development of mucositis in adults are poorly extrapolated to children (e.g. comorbidities, smoking, medication). Microbial communities differ between adults and children, which complicates efforts to predict paediatric mucositis based on microbial enterotypes identified in adults. A growing body of evidence also suggests that mucosal barrier damage and microbial injury are catalysts for other late-onset conditions (seen in both adults and children), including cardiac toxicity, graft-versus-host disease, fatigue and neurocognitive impairment.
Gabriel, AD et al.	Important risk factors for developing OM: ○ Chemotherapeutic agents (methotrexate and associations); ○ Variants related to the course of OM (gene variants and biomarkers); ○ Diverse oral microbiota (positive herpes simplex vírus, oral candida ssp...); However, more studies are necessary in pediatric oncologic patients to standardize the assessment of risk factors and OM scales.
Martins, JO et al.	In patients undergoing antineoplastic treatment, oral health care strongly reduces the severity of OM and moderately reduces the incidence of OM. Based on the meta-analysis results, Martins, JO et al. suggest that combining oral hygiene education and chlorhexidine mouthwash is the most promising intervention to reduce OM. To optimise the approach on individualised oral health care, future clinical trials based on specific cancer subpopulations are needed.
Ward, EJ et al.	In well-nourished children and young people with cancer undergoing chemotherapy, there is limited evidence that NP is more effective than NS. The evidence for other methods of nutritional support is unclear. There is no evidence for a reduction in the incidence and severity of mucositis, infection rates and length of hospital stay with glutamine supplementation. More research is needed.

Conclusion: The most relevant risk factors for the development of oral mucositis were the type of tumour and the chemotherapeutic agent. However, it is important to note that most studies have been conducted in adults, and their findings cannot be generalized to children. Further studies are required in this field to establish robust evidence and guide oral mucositis management.

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8.5 Appendix 5 – Diploma for best Poster. Presented at the IPO Porto Summit. Received 2nd place award