Research

Oral Mucositis in Patients Undergoing Haematopoietic Stem Cell Transplantation: A Retrospective Analysis

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Abstract

Introduction. Oral mucositis (OM) is a prevalent and debilitating complication in patients undergoing haematopoietic stem cell transplantation (HSCT), particularly following high-dose chemotherapy and total body irradiation. Despite its clinical significance, observational data on OM incidence, severity, and associated factors in HSCT recipients remain limited. This study aimed to evaluate the clinical presentation of OM, its severity, and related outcomes during hospitalisation.

Methods. A retrospective observational study was conducted at La Maddalena Cancer Center, Palermo, Italy, including 211 patients who underwent HSCT between January 2018 and December 2020. OM severity was assessed using the World Health Organization Oral Toxicity Scale. Data on demographic and clinical characteristics, total par-enteral nutrition (TPN), hospital stay, and oral care protocols were systematically extracted. Associations between OM severity and relevant variables were analysed using non-parametric tests and Spearman's correlation.

Results. Post-transplantation, nearly all patients developed OM, with a median severity grade of 2.0 (IQR: 2.0–3.0). Male patients experienced significantly more severe OM than females ($p = 0.01$). Mucositis severity correlated modestly with hospital stay duration ($\rho = 0.15$, $p = 0.03$), and strongly

with the number of TPN days ($\rho = 0.50$, $p < 0.001$). A significant association was also observed between OM and nausea severity ($\rho = 0.20$, $p = 0.003$). No significant correlations were found with age or educational level.
Discussion. OM remains a high-impact complication in HSCT, associated with nutritional impairment and pro-longed hospitalisation. These findings highlight the importance of comprehensive oral care protocols and underscore the need for targeted, sex-sensitive interventions and prospective multicentre research.

Keyword: Oral Mucositis, Haematopoietic Stem Cell Transplantation, Supportive Care, Retrospective Study

Introduction

Oral mucositis (OM) is a frequent and clinically significant complication observed in patients undergoing cancer treatment, particularly among those receiving high-dose chemotherapy as part of haematopoietic stem cell transplantation (HSCT) protocols (Biala, 2022; Nakagaki et al., 2022). OM is characterised by acute inflammation and ulceration of the oral mucosa, with clinical manifestations ranging from erythema and oedema to the formation of pseudomembranes and deep ulcerations exposing the submucosal tissue (Fitzpatrick et al., 2019). The pathogenesis of OM involves epithelial injury triggered by cytotoxic agents, followed by inflammatory amplification and mucosal breakdown (Sonis et al., 2004).

Histopathologically, OM extends beyond superficial epithelial damage, compromising mucosal integrity and increasing susceptibility to infection, particularly in immunocompromised patients. This disruption of the mucosal barrier renders the oral cavity susceptible to colonisation by pathogenic microflora and microbial translocation, heightening the risk of systemic infections such as bacteraemia and sepsis, especially in immunocompromised individuals (Cheong et al., 2017; Ellonen et al., 2023).

The prevalence of OM varies according to treatment intensity and patient-related factors. OM affects approximately 40%–80% of oncology patients receiving conventional chemotherapy, whereas in HSCT recipients, particularly those undergoing myeloablative conditioning (MAC) regimens, the prevalence may reach 75%–100% (Nakagaki et al., 2022). European multicentre data have reported similarly high incidence rates among HSCT recipients, confirming the consistency of OM prevalence across transplant centres (Vagliano et al., 2011). Although national Italian registry data specifically focusing on OM are limited, reports from tertiary oncology settings suggest comparable clinical patterns in Italian HSCT populations.

Agents such as cyclophosphamide, melphalan, and busulfan, especially when combined with total body irradiation (TBI), are strongly associated with OM onset. Methotrexate, commonly used for graft-versus-host disease (GVHD) prophylaxis, is also recognised as a mucotoxic agent (Deeg et al., 1991; Kennedy et al., 2025).

Clinically, oral mucositis (OM) imposes a substantial burden by impairing oral intake and communication and by jeopardising adherence to anticancer treatment. When severe, OM may necessitate opioid analgesia, intravenous hydration and/or nutritional support (including parenteral nutrition), with consequent prolongation of hospital stay and increased healthcare costs (Elad et al., 2022; McCann et al., 2009). OM may also become dose-limiting, leading to treatment delays or dose reductions that can compromise therapeutic effectiveness and adversely influence survival (Chaudhry et al., 2016; Nakagaki et al., 2022).

In Italy, a large nurse-led study conducted across 19 GITMO centres (n = 1841) reported OM in 71% of HSCT recipients and severe OM in 21.6% (WHO scale), underscoring the magnitude of this complication in routine transplant practice (Vagliano et al., 2011). Comparable burdens have been documented in other European cohorts, such as a retrospective analysis of 496 HSCT recipients reported OM in 63.3% overall,

with marked differences by transplant and conditioning intensity (Radochová et al., 2021).

Among HSCT recipients, OM is a particularly prevalent and distressing adverse effect. Both autologous and allogeneic transplant recipients are affected, although the incidence and severity tend to be higher in allogeneic cases due to more aggressive conditioning and immunosuppressive regimens (Kara et al., 2024). The clinical picture is dominated by severe pain—often described as burning or stabbing—with substantial impairment in swallowing and speech and deterioration in quality of life. Sleep disturbance, anxiety and depressive symptoms are also reported and may be exacerbated by inadequate pain control and the adverse effects of opioid therapy (Hodgson et al., 2012; Schiavone et al., 2012).

Despite the prevalence and clinical impact of OM, observational studies that longitudinally characterise its clinical course and associated pain burden in HSCT patients are sparse (Sanz et al., 2024). Much of the existing literature is focused on preventive strategies or interventional approaches, leaving a gap in our understanding of the natural history of OM during the post-transplant period. This study aims to describe the incidence, severity and clinical presentation of OM and mucositis-related events in hospitalized patients undergoing HSCT.

Methods and Materials

This retrospective observational study was conducted at La Maddalena Cancer Center, a tertiary oncology hospital located in Palermo, Italy. This retrospective observational study was conducted at La Maddalena Cancer Centre, a tertiary oncology hospital in Palermo, Italy. The Centre includes a dedicated unit for haematopoietic stem cell transplantation (HSCT) and manages a high annual volume of haematological oncology admissions. A total of 212 medical records were reviewed, corresponding to all HSCT procedures performed at the Centre between January 2018 and December 2020.

The years 2021 and 2022 were deliberately excluded from the analysis, as the organisation and delivery of care during the COVID-19 pandemic, particularly in its acute phases, were substantially altered due to emergency protocols and constraints, making them not directly comparable to pre-pandemic conditions. Eligible patients were aged 18 years or older and had been admitted for transplantation due to haematological malignancies. All data were anonymised prior to analysis in accordance with ethical and data protection standards.

Clinically, OM manifests as erythema, edema, ulceration, and pseudomembrane formation, typically appearing 5-7 days post-conditioning and resolving within 2-3 weeks (Elad et al., 2022; Sonis et al., 2004).

Data collection Procedures

Data were retrospectively collected from both digital records and archived paper-based files by a trained re-searcher between March and December 2023. Clinical information was retrieved through systematic screening of the hospital's information systems and physical documentation. Data collected included sociodemographic characteristics, clinical diagnosis, smoking status, and detailed OM classification. OM severity was assessed at two time points: baseline (pre-transplant) and the phase of maximum mucositis post-transplant. Nursing records and treatment protocols were also reviewed to capture oral care practices and supportive therapies applied during hospitalization.

The clinical pathway of HSCT patients and oral mucositis monitoring is illustrated in Figure 1.

Instruments and Measures

The WHO Oral Toxicity Scale was utilised to assess the severity of OM. This internationally validated scale classifies OM into five grades from Grade 0 (no symptoms) to Grade 4 (severe ulceration and inability to eat or drink). Grade 1 includes erythema and mild discomfort; Grade 2 al-lows solid food intake; Grade 3 restricts intake to liquids only; and Grade 4 denotes complete functional impairment due to oral lesions (Hong et al., 2019; Peterson et al., 2011; Vagliano et al., 2011; Yamagata et al., 2012). Moreover, a form, developed by the research team, was used to gather data related to patient demographics, medical history, comorbidities, and therapeutic regimens.

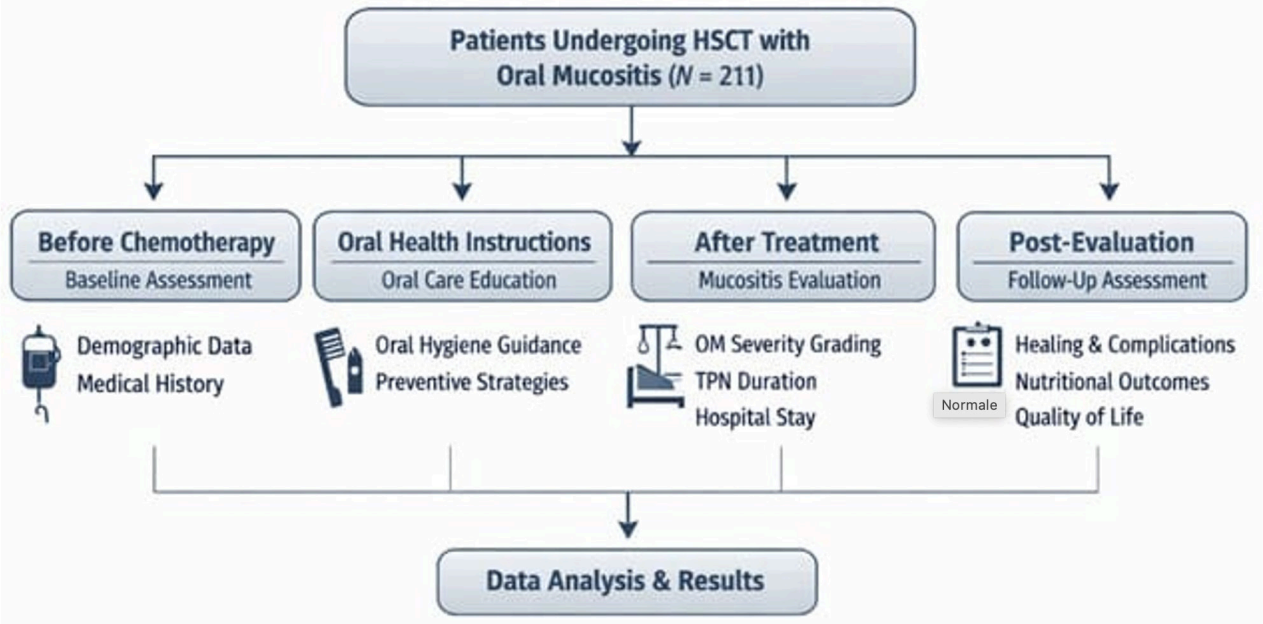

Figure 1. Clinical pathway for oral mucositis monitoring and management in patients undergoing HSCT.

Oral Mucositis Management Protocol

In accordance with the institutional guidelines of the La Maddalena Oncology Center and current evidence-based recommendations from the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO), a comprehensive OM prevention and management protocol was implemented for all patients undergoing HSCT (Elad et al., 2020, 2022; Miranda-Silva et al., 2021).

Prior to admission, patients received structured education on oral hygiene, including both verbal and written instructions on the prevention, early recognition, and self-monitoring of oral complications. Dietary counselling was also provided, with tailored recommendations to preserve mucosal integrity. Patients were strongly encouraged to promptly report any oral changes to enable early and appropriate clinical intervention.

A multidisciplinary team consisting of haematologists, oncology nurses, dentists, and clinical nutrition specialists was responsible for the application and dynamic adjustment of the oral care plan throughout the transplant period. Before HSCT, each patient underwent a comprehensive dental and mucosal evaluation to address any pre-existing conditions. Upon admission, a baseline assessment of oral mucosal status, including erythema, ulceration, denture-related trauma, and hygiene, was performed. A standardised oral care protocol was then initiated and subsequently adapted based on the severity of mucositis and the patient's clinical status. Regular reassessments al-lowed for continuous refinement of the care plan according to OM grading.

Interdental cleaning was promoted in patients without bleeding risk, and removable dentures were to be cleaned with soap and water at least twice daily and ideally removed at night to prevent mucosal trauma. Special attention was given to patients receiving oxygen therapy or xerogenic medications (e.g., opioids, corticosteroids, anti-histamines), with intensified monitoring to prevent xerostomia-related complications.

Core elements of the oral hygiene regimen included adequate hydration, which supported both oral cleansing and symptomatic relief; the use of non-alcoholic, pH-neutral chlorhexidine mouthwashes as prophylactic antiseptics to reduce microbial colonization and mitigate infection risk during neutropenia; and a protective oral solution containing hyaluronic acid and verbascoside, aimed at minimizing mucosal irritation and exerting anti-inflammatory effects (Al-Maweri et al., 2021; Tavakoli Ardakani et al., 2016). Although the MASCC/ISOO guidelines do not specifically recommend chlorhexidine for the prevention of oral mucositis, they acknowledge its value in infection control and maintaining oral hygiene in patients undergoing treatment for hematologic malignancies (Hong et al.,

2019). MASCC/ISOO guidelines were followed regarding structured patient education, base-line mucosal assessment, and standardized mucositis grading. The additional use of chlorhexidine and hyaluronic acid-verbascoside rinses reflected institutional protocols and served as supportive adjuncts beyond the formal recommendations provided by MASCC/ISOO (Colella et al., 2010; Elad et al., 2020; Nigro et al., 2020; Sorensen et al., 2008; Xia et al., 2025).

The protocol followed a graded, patient-centred approach to OM management. This integrative and severity-adapted management protocol aimed to reduce the incidence and progression of severe oral mucositis, mitigate the risk of secondary infections, support treatment continuity, and ultimately enhance the quality of life of patients undergoing haematopoietic stem cell transplantation.

Statistically Analyses

All statistical analyses were performed using R Studio (v4.3.3) and standard libraries for scientific computing. Descriptive statistics were calculated for all variables. Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the distribution.

The severity of OM was treated as an ordinal outcome variable. The association between mucositis severity and various clinical and demographic variables were examined. Correlations between mucositis grade and continuous clinical variables (e.g., age, length of hospital stay, number of days on total parenteral nutrition, nausea score) were assessed using Spearman's rank correlation coefficient (ρ). The associations between mucositis grade and categorical predictors (e.g., sex, smoking status, diagnosis, educational level) were tested using the Mann–Whitney U test for two-group comparisons and the Kruskal–Wallis test for comparisons across more than two groups. Post hoc pairwise comparisons were performed using Mann–Whitney U tests with Bonferroni correction. Statistical significance was set at $p < .05$ (two-tailed). Bonferroni-adjusted significance levels were applied for multiple comparisons where appropriate.

Ethical Considerations

Data were collected and managed in accordance with national regulations and institutional policies concerning retrospective observational studies. As the research involved the analysis of anonymised data from medical records without direct patient contact, the requirement for individual informed consent was waived. All procedures conformed to the principles outlined in the Declaration of Helsinki.

Results

Sociodemographic Characteristics

The sample included 211 patients who underwent hematopoietic stem cell transplantation (HSCT) and had complete documentation regarding OM grading. The mean age was 59.4 years (SD = 6.4), and the gender distribution was relatively balanced, with 52.6% male and 47.4% female participants. Additional sociodemographic data are presented in Table 1.

Table 1. Sociodemographic characteristics of the sample (N = 211 patients).

Variable	N (%)
Sex	
Male	111 (52.6%)
Female	100 (47.4%)
Educational Level	
Bachelor	17 (8.1%)
High School	55 (26.1%)
Middle School	87 (41.2%)
Primary School	48 (22.7%)
Illiterate	4 (1.9%)
Diagnosis	
Multiple Myeloma	111 (52.6%)
Lymphoma	61 (28.9%)
Leukemia	39 (18.5%)
Smoker	
No	146 (69.2%)
Yes	65 (30.8%)

Clinical Characteristics

Before transplantation, nearly all patients (99.1%) had no clinical evidence of oral mucositis. Post-transplantation assessments revealed a median mucositis grade of 2.0 (IQR:

2.0–3.0), while the median grade for nausea was 2.0 (IQR: 1.0–3.0), as detailed in Table 2. The average duration of total parenteral nutrition (TPN) was 5.7 days (SD = 9.0), and the mean length of hospitalization was 24.7 days (SD = 8.1). Nausea was frequently reported, with an average severity score of 2.5 (SD = 0.7) assessed using the WHO Oral Toxicity Scale.

Table 2. Clinical characteristics related to oral mucositis and supportive care (N = 211 patients undergoing HSCT).

Variable	
Mucositis (WHO) Me (IQR)	2.0 (2.0-3.0)
Nausea Me (IQR)	2.0 (1.0-3.0)
Pre-HSCT mucositis-free patients, n (%)	209 (99.1%)
Post-HSCT mucositis-free patients, n (%)	2 (0.9%)

Legend. WHO=World Health Organization; Me (IQR)= Median Interquartil Range; HSCT= Hematopoietic Stem Cell Transplantation.

The most frequently affected sites included the buccal mucosa, lateral tongue, floor of the mouth, and soft palate, consistent with established HSCT literature (See Table 3 and Figure 2).

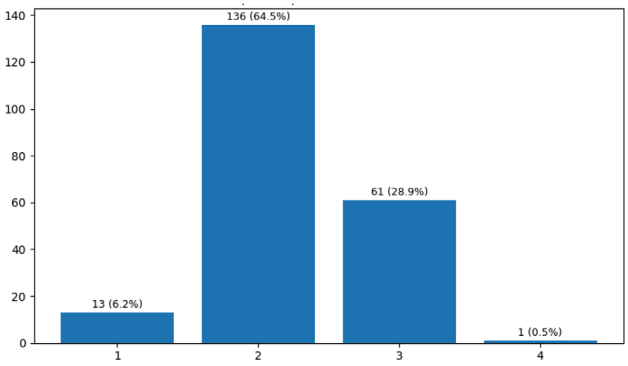

Figure 2. Frequency distribution of OM grades among patients undergoing HSCT (N = 211 events with recorded mucositis grade).

Table 3. Oral mucositis grade and frequency of the sample (N = 211 patients undergoing HSCT).

Mucositis grade	Frequency	% of total
1	13	6.2%
2	136	64.5%
3	61	28.9%
4	1	0.5%

Association Between Mucositis Severity and Clinical or Demographic Variables

No significant correlation was observed between mucositis grade and age (r_s = 0.07; p = 0.33), educational level ($\chi^2(5)$ = 8.07, p = 0.15), or smoking status. However, a significant association was found with sex, as male patients exhibited higher mucositis scores than female patients (U = 6503.50, p = 0.01). The median mucositis grade was 3.0 (IQR = 2.0–3.0) in male patients, compared to 2.0 (IQR = 2.0–3.0) in female patients. These findings are consistent with recent evidence indicating sex-related differences in mucositis severity among adult HSCT recipients (Dahrouge et al., 2014). Several clinical variables showed significant associations with mucositis severity. A weak but statistically significant correlation was found between length of hospital stay and mucositis grade (r_s = 0.15, p = 9.03). The number of days on TPN was strongly correlated with mucositis severity (r_s = 0.50, p < 0.001). Moreover, nausea se-verity was significantly associated with mucositis grade (r_s = 0.20, p = 0.003).

Discussion

This retrospective study provides a comprehensive evaluation of OM in patients undergoing HSCT, focusing on its incidence, severity, and associations with key clinical and demographic variables. Despite the adoption of a robust oral hygiene protocol, our findings confirm that OM remains a highly prevalent and clinically burdensome complication within the HSCT setting.

Consistent with previous literature, the overall incidence of OM in our sample was remarkably high, with nearly all patients developing some degree of mucosal in-jury following transplantation (Chaudhry et al., 2016; Elad et al., 2020; Miranda-Silva et al., 2021; Pereira et al., 2025). While this reflects the well-documented mucotoxic effects of conditioning regimens, the predominance of moderate-grade mucositis (Grade 2) suggests that early detection and supportive care measures may have effectively mitigated progression to more severe stages (Bell & Kasi, 2025; Gem et al., 2024). These findings align with those reported by Kara et al. (2024) who observed a reduction in severe OM rates in centres implementing structured oral care protocols (Kara et al., 2024; Lorini et al., 2019).

While some studies have failed to identify sex-based differences (Ferreira et al., 2020),

our results are in agreement with those in the literature who hypothesised that hormonal, anatomical, or behavioural factors, including potential differences in oral hygiene adherence, may influence susceptibility (Owlia et al., 2012).

A modest yet statistically significant correlation was observed between mucositis severity and length of hospital stay ($r_s = 0.15$, $p = 0.03$). This underscores the clinical and organisational impact of OM, as patients with more severe mucosal lesions often require prolonged hospitalisation for symptom management, nutritional support, and prevention of secondary complications. Previous research has demonstrated that OM is associated with increased healthcare resource utilisation and extended recovery times, reinforcing its role as a key contributor to the therapeutic burden in oncology(Al-Maweri et al., 2021; Lima et al., 2021; Piredda et al., 2017).

The association between OM severity and the number of days of TPN was particularly pronounced ($r_s = 0.50$, $p < 0.001$), highlighting the functional implications of oral mucosal damage. Severe OM frequently precludes adequate oral intake, necessitating parenteral nutritional support (Senesse et al., 2015; Strączek et al., 2023). This correlation is strongly supported by studies showing that OM contributes to significant alterations in nutritional status, with re-percussions for immune function, wound healing, and overall treatment tolerance (Hong et al., 2019; Staudenmaier et al., 2018).

Furthermore, a statistically significant association was found between the severity of nausea and OM grade ($r_s = 0.20$, $p = 0.003$). This relationship may reflect overlapping pathophysiological pathways triggered by high-dose chemotherapy conditioning regimens. Cytotoxic agents induce widespread epithelial injury and activate pro-inflammatory cascades mediated by reactive oxygen species (ROS), nuclear factor kappa B (NF-κB), and cytokines such as TNF-α and IL-6, which contribute not only to oral mucosal breakdown but also to gastrointestinal mucosal toxicity. The disruption of mucosal barrier integrity along the gastrointestinal tract may enhance vagal afferent stimulation and central emetic pathway activation, thereby increasing nausea severity.

Moreover, severe oral mucositis itself may exacerbate nausea through indirect mechanisms, including pain-induced sympathetic activation, reduced oral intake, altered salivary composition, and heightened sensory sensitivity within the oral cavity. The coexistence of mucosal inflammation and gastrointestinal dysregulation likely amplifies the overall symptom burden in HSCT recipients, reinforcing the need for integrated supportive care strategies targeting both oral toxicity and chemotherapy-induced nausea and vomiting (CINV). These findings highlight the importance of considering OM not only as a localized oral complication but as part of a broader mucosal toxicity syndrome affecting multiple epithelial surfaces.

The co-occurrence of moderate OM and nausea further illustrates the complex symptom burden experienced by HSCT recipients and highlights the need for integrated symptom management strategies (Peterson et al., 2011).

Notably, no significant associations were found between OM severity and patient age or educational level. However, the observed trend towards higher mucositis scores among patients with lower educational attainment may suggest a potential role for health literacy in influencing adherence to oral hygiene practices and early symptom reporting. In this context, patients' preferences and beliefs, including the use of complementary and alternative medicines, may also modulate self-care behaviours and engagement with conventional supportive care strategies, as reported in palliative cancer populations (Cerqueira et al., 2025; Mercadante et al., 2022). Previous literature has identified health literacy as a determinant of self-management capacity and clinical outcomes in oncology indicating that this variable warrants further exploration in future prospective designs. Moreover, the increasing role of patient empowerment in decision-making highlights the importance of shared management strategies that respect individual autonomy, symptom control, and continuity of care.

Limitations, Strengths and Future Prospects

This study has several limitations that should be considered when interpreting the results. First, its monocentric design restricts generalizability. Conducted in a single tertiary cancer center, the findings reflect institutional-specific protocols, staff expertise, and organizational practices, particularly in oral hygiene management, which

may not be representative of other settings, especially those operating within different healthcare systems or with varying resource availability. Second, the retrospective design introduces potential selection and information bias. Although data extraction was performed systematically, the accuracy and completeness of clinical records—especially regarding nursing interventions, symptom documentation, and adherence to oral care protocols—could not be fully verified. Protocol adherence itself was not systematically assessed, limiting the ability to evaluate its impact on mucositis outcomes.

A further limitation related to the retrospective nature and reliance on medical documentation was the absence of patient-reported outcome measures (PROMs), such as pain severity, functional impairment, and quality of life. PROMs are essential for capturing the patient perspective and should be included in future prospective studies (Staudenmaier et al., 2018). Additionally, the study did not examine biological, microbiological, or genetic factors that may influence mucositis severity, such as oral microbiota composition, cytokine profiles, or nutritional and inflammatory biomarkers (Gem et al., 2024; Mittal et al., 2014). While basic demo-graphic and clinical variables (e.g., sex, education level, length of hospitalization) were included, key confounders—such as these comorbidities, genetic predispositions, and the use of supportive pharmacological therapies—were not comprehensively assessed. Moreover, although transplant type and chemotherapy conditioning regimens were identified as relevant methodological factors, stratified analyses based on conditioning intensity or specific agents were not feasible due to insufficient data. As conditioning regimens are well-established determinants of oral mucositis risk and severity, this limitation constrains interpretative depth and highlights a critical direction for future research. Additionally, although conditioning regimen type and intensity are recognised predictors of oral mucositis risk (Chaudhry et al., 2016; Nakagaki et al., 2022), stratified analyses by specific agents or conditioning intensity were not feasible in this study due to incomplete documentation in the available medical records. This limitation reduced the capacity to explore regimen-specific effects and underscores the need for future prospective multicentre studies with standardised collection of conditioning regimen details.

These gaps underscore the need for multicenter, prospective studies integrating biomolecular and longitudinal data (Berger et al., 2018). Finally, photobiomodulation therapy (low-level laser therapy), recommended by recent MASCC/ISOO guidelines as an effective preventive and therapeutic measure for oral mucositis in adult HSCT patients, was not available at our center during the study period (Biala, 2022).

Despite these limitations, the study offers several strengths. To our knowledge, it is among the few recent investigations to systematically evaluate the incidence, severity, and clinical implications of OM in a large cohort of Italian HSCT recipients. The sample size was substantial, and data collection was conducted with methodological rigor, using validated instruments such as the WHO Oral Toxicity Scale. The study also integrated both clinical and demographic variables and explored multiple associations with relevant outcomes, including parenteral nutrition and hospital stay, thereby providing a multifaceted understanding of OM in real-world settings.

Looking forward, future research should aim to address these limitations by adopting multicentre, prospective designs that enhance heterogeneity and external validity. Incoporating PROMs, biomolecular analyses, and longitudinal follow-up would enable a more comprehensive characterisation of the natural history and patient experience of OM. It would also be valuable to investigate the effectiveness of individual components of oral care protocols and their relationship with health literacy, particularly in vulnerable subgroups. Finally, the development of predictive models integrating clinical, biological, and behavioural variables could improve risk stratification and support the personalization of preventive strategies for patients undergoing HSCT.

Conclusion

This study reinforces OM as a multifactorial and clinically impactful complication of haematopoietic stem cell transplantation, shaped by both clinical and demographic determinants. The findings support the implementation of comprehensive, protocol-driven oral hygiene interventions and highlight the relevance of addressing sex-related differences in mucositis

severity. Although limited by its retrospective and single-centre design, this study provides clinically meaningful insights that may inform future prospective, multicenter investigations aimed at optimising mucositis prevention and management in HSCT populations.

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