ASSESSMENT OF ORO-DENTAL HEALTH PARAMETERS, FUNGAL INFECTION AND THE SEVERITY OF CHEMOTHERAPY INDUCED -ORAL MUCOSITIS: FINDINGS FROM A SOUTHWESTERN NIGERIAN TERTIARY CARE CENTRE

I.K. Mogaji[1], F.J. Owotade [2], R.A. Bolarinwa[3], E.O. Oyetola[4], O.M. Adesina[4]

1. Department of Preventive Dentistry, Federal Medical Centre, Idi-Aba, Abeokuta, Ogun State, Nigeria.
2. Department of Oral Medicine and Oral Pathology, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria.
3. Department of Haematology and Blood Transfusion, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria.
4. Department of Oral Medicine and Oral Pathology, Obafemi Awolowo University Teaching Hospitals, Ile-Ife, Osun State, Nigeria.

Correspondence:
Dr. I.K. Mogaji
Department of Preventive Dentistry,
Federal Medical Centre,
Idi-Aba, Abeokuta.
Email: ibrahimtasnan@gmail.com

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ABSTRACT

Objectives: **The objective of this study was to determine the relationship of Oro-dental health parameters and fungal infection with the severity of oral mucositis (OM) in cancer patients receiving chemotherapy.**

Study design: **This cross-sectional study was carried out among cancer patients receiving chemotherapy at a tertiary institution in south western Nigeria. Oral pain, oral hygiene status, periodontitis, gingivitis and fungal infection and their relationship with OM were investigated.**

Results: **Among 82 patients that were assessed, OM was present in 44 (53.66%) participants. Oral pain was present in 47 (57.32%) participants and 42 (95.45%) of those with OM (p <0.001). Periodontitis was present in 9(20.25%; p=0.947), severe gingivitis in 3 (6.82%; p=0.067) and poor oral hygiene in 6(13.64%; p=0.214) participants with OM. Severe OM (Grades 3 and 4) was present in 5 (6.09%) participants. All participants with severe OM had severe pain (p d" 0.001). In patients with severe mucositis, periodontitis was present in 2 (p=0.750), while severe gingivitis was observed in 1 (p=0.359) participant. Four out of the five participants with severe mucositis had poor oral hygiene (p=0.004). Fungal infection was present in 45(54.88%) participants and 31 (70.45%) of those with OM (p=0.002). Ordered logistic regression also showed that fungal infection was associated with a fourfold risk of increased severity of OM (OR 3.9, CI 1.57, 9.87, p= 0.004).**

Conclusion: **Our study showed that increased severity of OM was associated with a higher grade of pain and poor oral hygiene. Fungal infection was associated with increased prevalence and a fourfold risk of increased severity of OM.**

INTRODUCTION

Cytotoxic chemotherapy has been associated with a high risk of toxicity on the oral tissues. Due to their high rate of turnover, mucosal cells in the oral cavity are highly susceptible to the toxic effects of cancer treatment.[1] Mucositis is a common dose-limiting complication in patients receiving systemic anticancer chemotherapy, bone marrow transplantation, and local irradiation for tumors in the head and neck area.[2] Mucositis is a diffuse ulcerative condition usually in the non-keratinized oral mucosa, involving mostly the soft palate, the buccal mucosa, the lateral and ventral surface of the tongue, the lips and the floor of the mouth.[3,4] The prevalence of oral mucositis ranges from 20% to 40% who receive standard dose chemotherapy and 75-85% of those who undergo high dose regimen for bone marrow transplantation.[5] The development of mucositis depends on both therapy and patient related factors. The therapy related risk factors include the modality of treatment (chemotherapy alone or combined chemoradiotherapy), type of agent used, dosage, intensity and schedule of administration. The risk increases with the intensity and cycle of chemotherapy as the cumulative effect of chemotherapy is well established.[6] High doses of methotrexate, etoposide, and melphalan, are implicated in the most severe forms of mucositis.[7] Drugs that affect DNA syntheses such as antimetabolites, increase the incidence of OM up to 60%.[8] The secretion of such drugs (methotrexate, 5-flourouracil and etoposide) in saliva also favours oral toxicity.[9]

Older age, female gender, body weight, poor renal and hepatic function are some of the major patient related risk factor for mucositis.[10]

There has been increased interest in Oro-dental health parameters, such as periodontitis, gingivitis and oral hygiene status as risk factors for increased severity of mucositis in patients on chemotherapy.[11,12] These studies are however scarce in sub-Saharan Africa and the role of these factors in OM are not clearly elucidated.[13,14] Many cancer centers recommend comprehensive oral examinations and treatments before antineoplastic therapy, a concept known as 'dental clearance'. This pre-chemotherapy protocols aim to eradicate of foci of infection including dental-periodontal foci before chemotherapy.[15] Studies have confirmed that dental evaluation prior to antineoplastic chemotherapy prevent and minimize the occurrence of opportunistic infections and the potential systemic spread of a local infection.[16]

Pain and discomfort associated with oral mucositis impacts negatively on the quality of life of patients undergoing chemotherapy.[17] OM is an important risk factor for systemic infection and patients with mucositis have a four-fold risk of sepsis than those without mucositis.[18]

The last two decades have seen increased research interest and better understanding of the pathogenesis of oral mucositis, however, despite these considerable efforts, management still relies majorly on symptoms relief and prevention of complications.[19,20] It has been postulated that patients who have improved oral health parameters will positively modify the incidence and severity of mucositis.[21] The above reasons have motivated this study to create baseline data in this environment on the relationship between oro-dental health parameters and the severity of chemotherapy induced- OM. The objective of this study was to determine the relationship between Oro dental health parameters (periodontitis, gingivitis, oral hygiene index and fungal infection) on occurrence and severity of OM.

MATERIALS AND METHODS

Study design

The study is an analytical cross-sectional study carried out at the department of Oral Medicine and Oral Pathology at the Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria. The sample was made up of 82 cancer patients undergoing standard dose chemotherapy at the paediatrics, haematologic and surgical wards of Obafemi Awolowo University Teaching Hospital Complex. Informed consent or assent from legal guardian was given prior to inclusion in the study. The inclusion criteria were those aged 6 years and above who were receiving cancer chemotherapy. Patients diagnosed with primary head and neck cancers, oral cancer, patients with debilitating systemic health, and low cognitive awareness were excluded. Consenting participants on both in-patient and out-patient cancer care were assessed. Those who were on out-patient care had dental examination done at the Oral medicine clinic, while those on hospital admission were examined in their respective units

Oral Examination Protocol

The oral mucosa examination was conducted according to the World Health Organization (WHO) "Oral Health Surveys: Basic Methods 2013" guidelines. As a senior registrar in oral medicine with specialized training in oral mucosa examination, I, the lead investigator, performed the examinations under the supervision of the second author. Given my expertise and experience, I was the sole examiner in this study, ensuring consistency in the assessment and diagnosis of oral mucosal lesions. The WHO guidelines provided a standardized framework for the examination, which helped to minimize variability and ensure reliability in the findings.

This standardized protocol ensured a thorough and systematic evaluation of the oral mucosa, including visual examination and assessment of the lips, tongue, floor of the mouth, buccal mucosa, gingiva, and palate.

Data analysis was done using STATA 15 statistical software (STATACORP COLLEGE STATION TEXAS USA). Descriptive statistics was used to characterize socio-economic variables while means and standard deviations were used for continuous variables. Frequencies and proportions were used for categorical variables. Determination of the relationship between Oro dental parameters and fungal infection with oral mucositis was analysed with likelihood ratio chi-square. Multivariate analysis was used to control for confounders. Statistical significance was set at $p < 0.05$. Ethical clearance was obtained from the Ethics and Research Committee (ERC), Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Osun State, Nigeria with number ERC/2019/01/01

The Oro dental health parameters assessed included:
Gingival status - Assessed using Gingival Index (GI) of Loe and Silness (1963).[22] This was assessed thus:
Score 0: Absence of visual signs of inflammation.
Score 1: Slight change in colour and texture.
Score 2: Visual inflammation and bleeding tendency from the gingival margin when the probe is run along the gingival margin.

Score 3: Overt inflammation with tendency for spontaneous bleeding.

Oral hygiene – Assessed using Greene and Vermilion simplified oral hygiene index (OHI-S).[23] The OHI-S has two components, the debris index-simplified and the calculus index-simplified, both of which are calculated separately and are added to get the OHI-S for an individual. The corresponding deciduous teeth were examined for paediatric participants without the permanent index teeth. The scores are interpreted as follows:
0.0 – 1.2 = good
1.3 – 3.0 = fair
3.1 – 6.0 = poor

Periodontal status – Periodontal status was assessed with the presence or absence of periodontal pocket. An established pocket of more than 3mm depth was taken as a positive sign of periodontal pathology.[22] A Williams' periodontal probe was used for diagnosis and it was marked present or absent.

Scoring of chemotherapy induced mucositis: This was done according to the World Health Organization (WHO) classification [24]
Grade 0: No change;
Grade 1 : Soreness/ erythema
Grade II: Erythema and Ulcers, patient can eat solids
Grade III : Ulcers, the patient requires liquid diet only
Grade IV : Food intake is not possible

Mouth and throat soreness (MTS): Grading was adapted from a patient reported validated scale, Oral Mucositis Daily Questionnaire (OMDQ)[25]
Grade 0 : No Soreness
Grade 1/ Mild : Soreness in one location
Grade 2/ Moderate : Soreness in two locations
Grade 3/ Severe : Soreness in three locations
Grade 4/ Extreme : Soreness in more than 3 locations

Fungal infection – Presumptive clinical diagnosis based on clinical findings (e.g presence of whitish coating/erythematous or atrophic areas etc) followed by exfoliative cytology via tongue scrapings with sterile tongue swab and viewing under light microscopy after staining with haematoxylin and eosin (H&E) stain and PAS (Periodic Acid Schiff) stain. *Candida* hyphae invasion of the epithelium was taken as positive diagnosis of fungal infection.

Oral pain: This was assessed using the visual analogue scale for adults.[26] A 10 cm line with 0 as no pain and 10 as worst possible pain. The point on the line marked by the participant was measured to determine the severity of pain.
- 0 is no pain,
- 1- 3 is mild pain
- 4- 7 is moderate pain
- 8- 10 is severe pain.

Cooperative children 6 years and above were assessed using the Wong Baker Facial Rating Scale.[27] This is a horizontal scale of 6 hand-drawn faces, scored from 0 to 10, that range from a smiling "no hurt" face on the left to a crying "hurts worst" face on the right. The participants were asked to pick the facial expression that most represents the pain.

Chemotherapeutic agents used by the participants in the study were classified into 6 groups based on mucotoxicity for the purpose of this study:
1. 5 fluoro-uracil based regimen either singly or in combination with other chemotherapy agents
2. Methotrexate based regimen either singly or in combination
3. Cytarabine based regimen either singly or in combination
4. Regimen containing more than one of the markedly mucotoxic agents, (5 Flourouracil (5 FU), Methotrexate and Cytarabine
5. Regimen without any of the markedly mucotoxic agents
6. Glivec® (Imatinib besylate, a targeted therapy)

RESULTS

A total of 82 patients with 34 (41.46%) males and 48 (58.54%) females participated in the study. The mean age of participants was 41.33 (±20.49) years with age range from 6 years to 80 years. Participants in the fifth decade of life were the most frequent (18, 21.95%). Breast cancer was the most prevalent solid tumour while chronic myeloid leukaemia (CML) was the most prevalent lymphoproliferative tumour with 15 (18.29%) (Table 1)

OM was present in 44(53.66%) participants while oral pain was reported by 42(95.45%) of those with OM and 5(13.16%) of those without OM *p*d" 0.001 (Table 2). However, oral pain was present in 47(57.32%) of all participants with majority 20 (24.39%) reporting that they first felt oral pain on the fourth day after the start of chemotherapy. (Fig. 1) Evaluation with the visual analogue scale revealed that more participants, 10 (12.20%) scored their pain as 5 and grade of pain was generally higher in participants with OM. (Fig. 2). The grade of pain was significantly related to the grade of mucositis $p \leq 0.000$ (Table 3). The range of pain was 9, with mean score being 4.22 (SD ±10.23) for those without OM and 4.88 (SD ± 2.93) for those with OM.

Table 1: Demographic and clinical characteristics of participants

Characteristics	n = 82 (%)
Gender	
Male	34 (41.45)
Female	48 (58.54)
Age (years old)	
1 – 10	9 (10.98)
11 – 20	10 (12.20)
21 – 30	4 (4.88)
31 = 40	9 (10.98)
41 – 50	18 (21.95)
51 – 60	15 (18.25)
61 – 70	11 (13.41)
71 – 80	6 (7.32)
Range 6 – 80 years	
Mean Age (±SD)	41.33 (±20.49)
Cancer Type	
Breast	23 (28.05)
Pancreas	5 (6.10)
Gestational Trophoblastic DX	5 (6.10)
Other Solid	15 (18.29)
CML	15 (18.29)
NHL	9 (10.98)
ALL	5 (6.10)
Other Lymphoproliferative	5 (6.10)
Fungal Infection	
Present	17 (20.73)
Absent	65 (79.27)
Fungal Infection Site	
Cheek, Tongue	5 (6.10)
Cheek	1 (1.22)
Tongue	11 (13.41)
No	65 (79.27)
Fungal Type	
Pseudomembranous	13 (15.85)
Erythematous	4 (4.88)

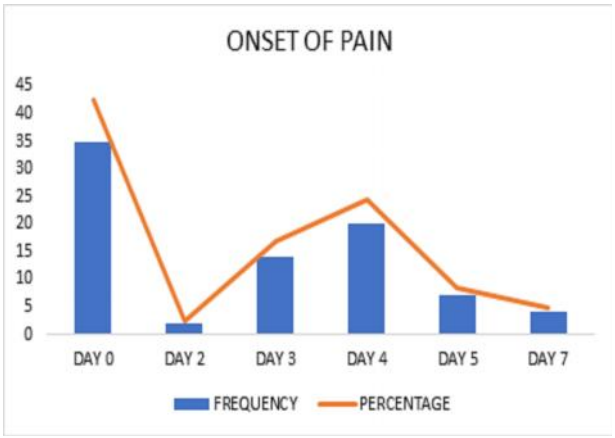

Figure 1: Day of pain onset

In terms of severity of mucositis, 39 (47.56%) of participants had grade 1 or 2 mucositis. Severe mucositis (Grade 3 and 4) was rare, as it was only present in five participants (6.09%). Patients reported mouth and throat soreness (MTS) was present in 38 (46.34%) participants while clinically confirmed presence of mucositis was in 44 (53.66%). Mild MTS was in 19 (23.17%), moderate in 15 (18.29%) and severe in 4 (4.88%). (Fig. 3) The ventral tongue was the most reported location for MTS either singly 12 (14.53), or in combination with other oral mucosae 31 (37.80). (Fig. 4) The grade of MTS was significantly related to both the grade of mucositis ($p \leq 0.000$) and the grade of pain ($p \leq .0.000$).(Tables 5 and 6 respectively)

Periodontal pocket was present in nine (20.25%) participants with mucositis and in eight participants (21.05%) without mucositis (p=0.947). Severe gingivitis was present in three (6.82%) participants with mucositis and one participant (2.36%) without mucositis

Table 2: Relationship of oral health parameters with oral mucositis

Oral Changes	Mucositis (N=82)			
	Present (%)	Absent (%)	Total (%)	*p* -Value
Periodontal Pocket				
Present	9 (20.45)	8 (21.05)	17 (20.73)	
Absent	35 (79.35)	30 (78.95)	65 (79.27)	0.947
Oral Hygiene Index				
Poor	6 (13.64)	10 (26.32)	16 (19.51)	
Fair	21 (47.73)	12 (31.58)	33 (40.24)	
Good	17 (38.63)	16 (42.10)	33 (40.24)	0.214
Fungal Infection				
Positive	31 (70.45)	14 (36.84)	45 (54.88)	
Negative	13 (29.55)	24 (63.16)	37 (45.12)	0.002*
Gingival Index				
Mild	0 (0)	3 (7.89)	3 (3.66)	
Moderate	41 (93.18)	34 (89.47)	75 (91.46)	
Severe	3 (6.82)	1 (2.63)	4 (4.88)	0.067
Oral Pain				
Yes	42 (95.45)	5 (13.16)	47 (57.32)	
No	2 (4.55)	33 (86.84)	35 (42.68)	≤ 0.001*

**Likelihood Ratio Chi- Square* *P-value < 0.05*

(p=0.067). Poor oral hygiene was present in six participants (37.5%) with mucositis and ten participants (62.5%) without mucositis (p=0.214) (Table 2).

Periodontal pocket was present in two participants with severe OM and only one participant with severe gingivitis also had severe OM. However, four of the five participants that had severe OM, had poor oral hygiene (p= 0.004) (Table 3).

Clinical diagnosis of fungal infection was made in 17 participants (20.73%) comprising 13 (15.85%) cases of pseudomembranous candidiasis and four (4.88%) cases erythematous candidiasis (Table 1). However, cytological confirmation of candidiasis was positive in 45 (54.88%) participants including 31 (70.45%) of those with OM and 14(36.84%) of those without OM (p=0.002) (Table 2). Multivariate analysis further confirmed that aside from the use of mucotoxic group

Table 3: Relationship of oral health parameters with severity of oral mucositis

Oral Changes	Mucositis Status (N=82)						
	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)	*P*-Value
Periodontal Pocket							
Present	8 (47.06)	3 (17.65)	4 (23.53)	1 (1.54)	1 (5.88)	17 (20.73)	
Absent	30 (46.15)	19 (29.23)	13 (20)	1 (1.54)	2 (3.08)	65 (79.27)	0.750
Oral Hygiene Index							
Poor	10 (26.32)	2 (9.09)	0 (00)	2 (100)	2 (66.67)	16 (19.51)	
Fair	12 (31.58)	12 (54.55)	9 (52.94)	0 (0)	0 (0)	33 (40.24)	
Good	16 (42.11)	8 (36.36)	8 (47.06)	0 (0)	1 (33.33)	33 (40.24)	0.004*
Fungal Infection	14 (36.84)	14 (63.64)	13 (76.47)	1 (50.00)	3 (100)	45 (54.88)	
Positive	24 (63.16)	8 (36.36)	4 (23.53)	1 (50.00)	0 (00)	37 (45.12)	0.013*
Negative							
Gingival Index	3 (7.89)	0 (00)	0 (0)	0 (00)	0 (00)	3 (3.66)	
Mild	34 (89.47)	21 (95.45)	16 (94.12)	1 (50)	3 (100)	75 (91.46)	
Moderate	1 (2.63)	1 (4.55)	1 (5.88)	1 (50)	0 (00)	4 (4.88)	0.359
Severe							
Oral Pain							
Mild	38 (100)	8 (36.36)	0 (0)	0 (0)	0 (0)	46 (56.10)	
Moderate	0 (0)	14 (63.64)	13 (76.47)	0 (0)	0 (0)	27 (32.93)	
Severe	0 (0)	0 (0)	4 (23.53)	2 (100)	3 (100)	9 (10.98)	<0.001*

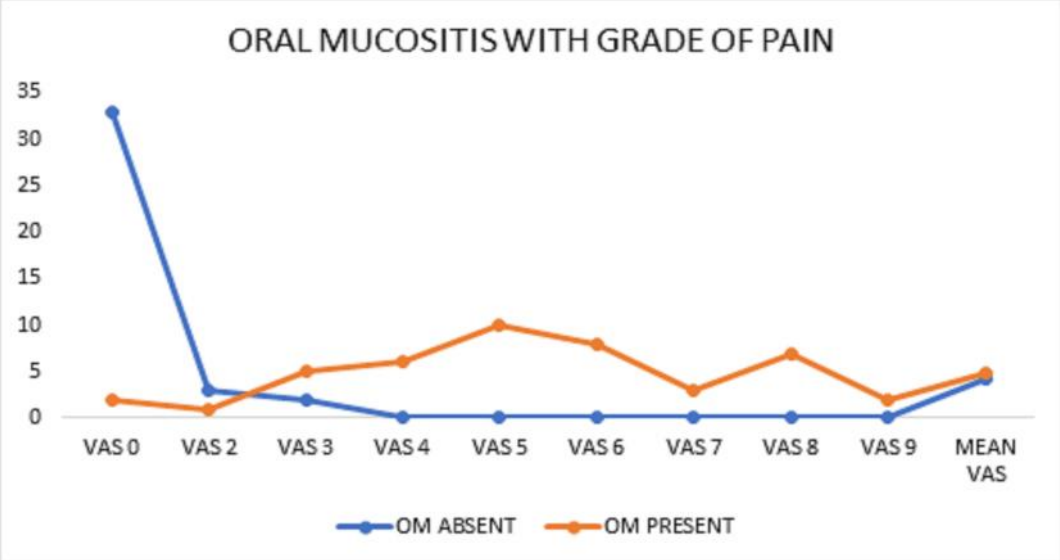

Fig. 2: Oral mucositis with grade of pain

VAS= Visual Analogue scale ; Mean VAS = OM Absent 4.22 (SD ± 10.3) ; OM Present 4.89 (SD ± 2.92)

Table 4: Risk factors for higher grade of mucositis (ordered logistis regression)

Predictors Mucositis Grade	Odd Ratio	95% Confidence Interval	*P*-Value
Mucotoxic Drug	4.0	1.58, 10.16	0.003*
Ref. (less Mucotoxic)			
OH1	0.8	0.23, 2.72	0.720
Fungal infection	3.9	1.57, 9.87	0.004*
Solid tumour	2.1	0.85, 5.21	0.104
Ref (lymphoproliferative)			

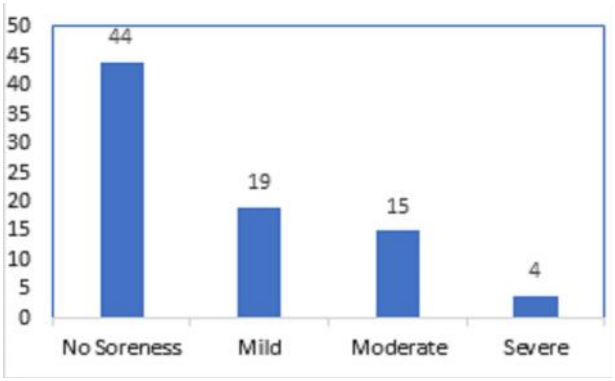

Fig. 3: Grade of mouth and throat soreness (mts)

Table 5: Relationship between grade of mucositis and Mts grade

MTS GRADE	Mucositis Status (N=82)						
	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)	*P*-Value
No Soreness	34 (89.47)	8 (36.36)	2 (11.76)	0 (00)	0 (00)	44 (53.66)	0.0000*
Mild	4 (10.53)	9 (40.91)	5 (29.41)	1 (50.0)	0 (00)	19 (23.17)	
Moderate	0 (00)	4 (18.18)	7 (41.18)	1 (50.0)	3 (100.0)	15 (18.29)	
Severe	0 (00)	1 (4.55)	3 (17.65)	0 (00)	0 (00)	4 (4.88)	

**Likelihood Ratio Chi- Square P-value < 0.05*

Table 6: Relationship between grade of pain and Mts grade

MTS GRADE	Grade of pain (N=82)				
	Mild (%)	Moderate (%)	Severe (%)	Total (%)	*P*-Value
No Soreness	38 (82.61)	5 (18.52)	1 (11.11)	44 (53.66)	0.0000*
Mild	7 (15.22)	11 (40.74)	1 (11.11)	19 (23.17)	
Moderate	1 (2.17)	8 (29.63)	6 (66.67)	15 (18.29)	
Severe	0 (0.00)	3 (11.11)	1 (11.11)	1 (11.11)	

**Likelihood Ratio Chi- Square P-value < 0.05*

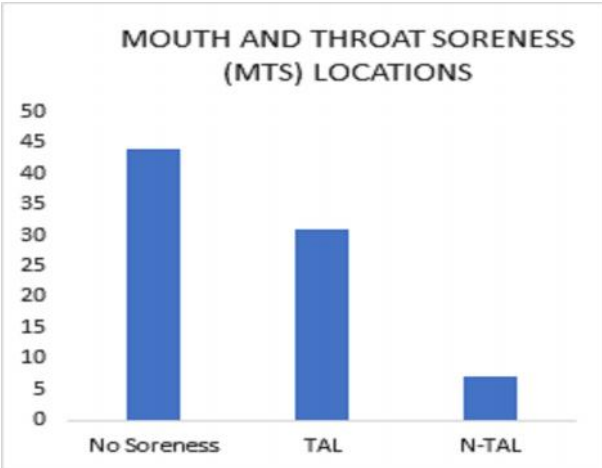

Fig. 4: Mouth and throat soreness (Mts) location

TAL= Tongue Associated Locations (Lower labial Mucosa and Ventral Tongue (4); Buccal Mucosa and Ventral Tongue (10); Ventral Tongue (12); Lower labial Mucosa, Buccal Mucosa and Ventral Tongue (4); Soft palate and Ventral Tongue (1)

N-TAL= Non- Tongue Associated Locations (Alveola Mucosa (1) ; Buccal Mucosa (4); Lower Labial Mucosa (2).

of chemotherapy agents, fungal infection confers a fourfold risk of having a higher grade of mucositis (OR 3.9, CI 1.57- 9.87, *P*=0.004) (Table 4) adjusting for type of chemotherapy agent, type of cancer and oral hygiene index.

DISCUSSION

This study has added to the existing literature that OM is a common occurrence in patient receiving chemotherapy. Our prevalence of 53.66% is similar to 51% reported by Elting *et al.*[28] and Jankovic *et al.*[29] (55%) but higher than 32% reported by Goldberg *et al.*[30] and 42.9% reported by Atwiine *et al.*[31]

This study demonstrated that oral pain is almost always associated with mucositis. Almost all (95.45%) of participants with OM had oral pain. Feller et al (2010)[32] and Elting *et al.* (2003)[28] have both supported this finding. However, two participants with OM did not have pain. There were also participants that had pain but did not have OM. Elting *et al.* also reported in their study that some patients developed oral pain but did not have OM.[33] The cause of oral pain in patients

taking chemotherapy is multifactorial and can be nociceptive and neuropathic in origin.[34] The differential diagnosis of such pain should therefore not just be OM but should also include, pulpal pain, periodontal pain and 'cytotoxic chemotherapy induced odontalgia'.[35] Cytotoxic agents like vincristine, vinblastine and platinum derivatives are often associated with orofacial pain and neuropathies.[34]

This study also highlights that patient reported presence of MTS during chemotherapy should not be taken to be synonymous to presence of OM. Indeed, our study found statistical significant relationship between the grade of MTS with both the grade of mucositis and oral pain. This is similar to studies that have found MTS scores by patients are comparable to clinicians' assessment of OM. However, significant gaps exist between clinicians' assessment and patients' experience of severity.[36,37] In this study, the subjective patient reported MTS scores lagged behind the objective diagnosis of OM by the clinician.

The accurate clinical diagnosis of OM is crucial, as improper assessment can lead to misdiagnosis or overlooked cases. This concern is echoed by Farrel *et al* (2005)[38] who highlighted that up to 80% of concerns expressed by cancer patients undergoing chemotherapy may go unaddressed by clinicians, underscoring the need for precise assessment tools to ensure comprehensive care.

Periodontal pocket was present in about one-fifth of our study participants with slightly over half having moderate to severe gingivitis. Interestingly, none of these two orodental health parameters were associated with either occurrence or severity of mucositis. This is similar to a study that also found that gingival index was not related to the occurrence of mucositis.[11] A 2021 study also found that OM prevalence and severity was also not affected by periodontal disease.[39] However, an earlier study on patients undergoing high dose chemotherapy regimen for haemopoietic stem cell transfer, showed that dental plaque and periodontal status were predictive of oral mucositis incidence and severity.[40] A study also found that prevalence of mucosal injury increases as periodontal risk increases.[41]

It has been postulated that the periodontopathogen will exacerbate the severity of OM due to the common inflammatory pathway. Chemotherapy in patients with chronic periodontal diseases may lead to acute exacerbation of the chronic state in pre-existing disease sites.[42] The role of periodontal diseases (gingivitis and periodontitis) in some systemic diseases have been established.[43] A number of studies have established a link between periodontal diseases and diabetes, cardiovascular diseases, refractory craniofacial pain and neurovascular conditions.[44-47] The patho-mechanism involved in this link have been related to dysregulation of inflammatory response and bacteremia.[48] There is also a well-established role of systemic inflammation and bacteremia in the pathogenesis of oral mucositis.[49] Thus both oral mucositis and periodontal diseases share similar patho-mechnanisms and it is interesting to note that the cytokines involved in the pathogenesis of oral mucositis are also involved in the pathogenesis of periodontal diseases. The increased levels of pro inflammatory cytokines (such as IL 1, IL-6, and TNF-á), metalloproteinases, PGE2, COX-2 are common to both pathologies. It is also worthy of note that as chemotherapy or radiotherapy can activate NF-êB with the consequent upregulation of inflammatory cytokines. Infectious agents and inflammatory cytokines from periodontal diseases can also activate NF-êB giving the same results.[8]

The 'two hit' model hypotheses which has previously been used to explain the association between periodontitis and systemic diseases[50] like rheumatoid arthritis has recently been used to justify the association between periodontitis and radiation induced mucositis. This model suggests that inflammation at the periodontium level which is periodontitis (first "hit") followed by radiation (second "hit") can lead to an exacerbated response in the form of oral mucositis. The converse may also hold true in that radiation-induced oral mucositis (first 'hit') exacerbates the inflammatory response of developing periodontitis (second 'hit').[51] This model therefore suggest a bi-directional relationship. While this was initially postulated for radiation induced mucositis, it will also hold true for chemotherapy induced mucositis (or any other inflammatory stimulus on the body)[6] as the patho-mechanism for the development of mucositis in both are the same. If this hypothesis is established, it means that pre-existing periodontal diseases in patients receiving chemotherapy can predispose to the occurrence and increased severity of mucositis in cancer patients. It also gives the hope that specific intervention to treat periodontal diseases, with the aim of reducing periodontopathogens, can be expected to have positive impact on incidence and severity of mucositis.[51]

Despite the relatively high volume of researches on OM, the management remains a challenge. Management has been anchored majorly on symptoms relief with prevention and treatment of complications. Anti-inflammatory agents have not been consistent in its efficacy to prevent or treat OM. Aside for benzydamine hydrochloride, whose use was restricted to patients on radiotherapy-induced mucositis, the MASSC/ISSO mucositis guideline could not

recommend any other anti-inflammatory for the prevention and treatment of OM due to conflicting results from clinical trials.[52] The role of micro-organisms in the development of mucositis is unclear. It is known that bacteria increase in numbers during the ulcerative phase of mucositis and the return to normal proportions lead to the ulcer resolution, yet clinical trials have shown that antimicrobial strategies have been ineffective as OM interventions.[17,53] The perception that the application of topical antimicrobials may have better benefit in OM have also not proven to be true.[53] However, mechanical disruption of dental biofilm may need to be further explored because the magnitude of its effects has not been consistent across studies neither has the sustainability over time been convincingly established.[17,51] Further well designed studies will therefore, be required to establish the link between periodontal diseases and OM.

In our study, fungal infection was confirmed via cytology in 45 (54.88%) of participants. It has been reported that *Candida* spp. especially *Candida albicans* are the most implicated fungal infection in patients on chemotherapy.[54] Changes in the oral or systemic environment due to myelosuppression, hyposalivation and local tissue damage in cancer patients receiving chemotherapy, shift this delicate balance and favour the growth of opportunistic *Candida* organisms. Chemotherapy patients are colonized more by *Candida albicans* species. Other species of importance are *C. glabrata, C. tropicalis, C.krusei.*[55] This is important because non-albicans *Candida* species, like *C. glabrata* and *C.tropicalis*, have greater complications, mortality rates, intrinsic resistance and are more likely to spread into the systemic circulation.[56] The common forms of intraoral candidiasis reported in oncology patients are pseudomembranous, erythematous candidiasis and angular cheilitis[57], while hyperplastic candidiasis is rarely reported.[58] The pseudomembranous form is the most common.[9] It clinically presents as plaques which can be scraped away leaving areas of erythema. These presentations could be symptomatic or not. The major presenting symptoms are burning pain, altered taste sensation, oral malodour, fiery red appearance which bleeds on mild trauma and difficulty in mouth opening is common in angular cheilitis.

In this study, clinical diagnosis of candidiasis was made in 17 (20.73%) of participants and lagged behind cytopathological diagnosis of 45 (54.88%) of participants. The cytopathological diagnosis of candidiasis is based on hyphae growing into the epithelium. Our finding is similar to a 2021 study which proved cytopathological diagnosis to be a useful tool in confirming clinical diagnosis of candidiasis and identifying subclinical cases.[59] This brings to fore the importance of cytological confirmation of suspected cases of candidiasis. While candidiasis is often a clinical diagnosis, this is easier for pseudomembranous variant which shows obvious plaques or flecks. This position is also supported by Meira HC *et al.* who observed that while (*Candida*) lesions are easier to diagnose clinically and as such most reported by clinicians but erythematous lesions often need the use cytopathology to confirm diagnosis.[60] Erythematous candidiasis can be confused clinically with denture stomatitis unrelated to candidiasis, mucosa atrophy due to anaemia, inflammatory reaction in the oral cavity, erythroplasia and so on[59] Positive culture as well, in the absence of other signs and symptoms may need to be interpreted with caution. The diagnosis of any form of oral candidiasis is essentially clinical,[61] however, both clinical and cytological diagnosis have limitations in the diagnosis of candidiasis and as such clinicians should see them as complementary especially in cases of doubt.[61]

This study also found pseudomembranous candidiasis as the most frequent clinical variant as a number of studies have reported.[9] However, Meira HC *et al.* reported that erythematous lesions are generally more prevalent though all forms of candidiasis that appear red were included in their classification.[48] Single site lesions were most commonly found on the dorsal surface of the tongue in our study and followed by the buccal mucosa and the tongue for multiple site lesions, perhaps because pseudomembranous was our most prevalent variant. Gonzalez-Gravina H *et al.* also found the lesions more on the tongue and followed by inside of the cheeks.[62] Those who document erythematous lesions as most prevalent have found the most affected sites being palate and then the tongue.[48]

The current study showed that fungal infection was significantly associated with the incidence (p=0.002) and severity of mucositis (p=0.013). This is similar to a study on paediatric patients that found an association between *Candida* spp. and severity of mucositis.[63] Hong *et al.*[64] and Epstein *et al* did not find a significant difference between *Candida* colonization and the presence or severity of mucositis.[65] We can conclude from our findings that the more severe the mucositis, the greater the predisposition to fungal infection. This is not surprising, immune suppression from the underlying malignancy, use of chemotherapy and local tissue damage from mucositis are major predisposition for opportunistic fungal infection. Multivariate analysis showed that when compared to those without fungal infection, those with fungal infection have almost a fourfold risk of having higher grades of mucositis

(OR 3.9, CI 1.57- 9.87, *P*=0.004) adjusting for the type of chemotherapy agent, cancer diagnosis and oral hygiene index

In this study, oral hygiene index of participants while not predictive of rate of occurrence of mucositis, was predictive for worse severity gradings. This emphasises the importance of oral hygiene protocols for patients taking chemotherapy. This result however, should be interpreted with caution because the severe mucositis may have been responsible for the difficulty in keeping good oral hygiene, although one of the participants in this study with grade 4 mucositis, had good oral hygiene index. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASSC/ISSO) guidelines also recommend the use of oral hygiene protocols to prevent worse severity of OM.[21] However, studies have also stated its efficacy in both prevention and reduction of severity.[11,40]

CONCLUSIONS

The oro-dental health parameters evaluated in this study had varying relationships with OM. The study showed that oral pain is commonly associated with mucositis and the severity of pain is related to the severity of OM. Periodontitis and gingivitis were not associated with OM. Participants with poor oral hygiene had severe form of mucositis. This emphasizes the importance of good oral hygiene among patients taking chemotherapy. Fungal infection does not only predispose patients on chemotherapy to increased occurrence of mucositis but also to a fourfold increased risk of OM severity.

STRENGTHS AND LIMITATIONS OF THE STUDY

Our study adds to the scarce but growing body of knowledge on the prevalence and complex associations between orodental health parameters and chemotherapy-induced oral changes in sub-Saharan Africa, providing a foundation for future studies and informing clinical practice in this environment. The study provides insight into the role of fungal infections, highlighting the significant association between fungal infections and increased severity of oral mucositis. Notably, the study underscores the importance of cytopathological diagnosis as a complement to clinical diagnosis in identifying fungal infections, particularly in cases where clinical presentation is ambiguous or non-classical, or in subclinical cases. Furthermore, the study demonstrates that patient-reported symptoms, such as oral pain and soreness, are not reliable indicators of oral mucositis post-chemotherapy, emphasizing the need for thorough clinical examination and objective diagnostic methods to accurately diagnose oral mucositis.

However, the study has some limitations. The hospital-based design and single-center nature of the study may limit the generalizability of the results to other populations and settings, highlighting the need for further research in diverse contexts. Additionally, while multivariate analysis was done to control for some confounders, the study did not control for certain variables, such as analgesic use and chemotherapy cycle, which may have influenced the observed relationships between orodental health parameters and oral mucositis.

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