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José Alcides Almeida de Arruda

MUCOSITE ORAL QUIMIOINDUZIDA: *ASPECTOS CLÍNICOS, LABORATORIAIS, QUALIDADE DE VIDA, ANSIEDADE E DEPRESSÃO*

Belo Horizonte
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José Alcides Almeida de Arruda

MUCOSITE ORAL QUIMIOINDUZIDA: *ASPECTOS CLÍNICOS, LABORATORIAIS, QUALIDADE DE VIDA, ANSIEDADE E DEPRESSÃO*

Tese apresentada ao Colegiado do Programa de Pós-Graduação em Odontologia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Doutor em Odontologia – área de concentração em Patologia Bucal.

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“Os enigmas do universo só lentamente se revelam à nossa investigação. Existem questões às quais o homem, atualmente, não pode nos dar respostas, mas, o trabalho científico constitui o único caminho que pode nos levar a um verdadeiro conhecimento da realidade externa a nós.”

Sigmund Freud

RESUMO

O presente estudo é fundamentado em três objetivos: 1. sintetizar informações sobre ansiedade/depressão de indivíduos em regimes antineoplásicos que desenvolveram mucosite oral por meio de uma revisão sistemática da literatura; 2. avaliar o perfil de citocinas inflamatórias e a formação de redes extracelulares de neutrófilos em amostras de saliva de pacientes em quimioterapia e suas associações com mucosite oral; e 3. investigar ansiedade/depressão e qualidade de vida e associações com mucosite oral quimioinduzida. No primeiro estudo, buscas eletrônicas foram realizadas em cinco bases de dados, complementadas por escrutínio manual e pesquisas na literatura cinzenta. Oito estudos observacionais foram incluídos e a amostra analisada foi de 954 indivíduos. Sete instrumentos diferentes foram aplicados para mensurar ansiedade e/ou depressão. Associações de ansiedade e/ou depressão com a gravidade da mucosite oral foram observadas em 75,0% dos estudos. Os outros dois estudos foram análises longitudinais prospectivas com indivíduos adultos com diagnóstico de doenças hematolinfóides e em tratamento quimioterápico e/ou condicionamento para transplante de células-tronco hematopoiéticas no Hospital das Clínicas da Universidade Federal de Minas Gerais. Os níveis de citocinas inflamatórias (IL-1, IL-6, IL-8, TNF-α e TGF-β1) e a formação de redes extracelulares de neutrófilos foram analisados por ELISA e identificação do complexo mieloperoxidase-DNA, respectivamente. As coletas de saliva foram realizadas em quatro momentos: dias D0, D3, D10 e D15. Dos 60 pacientes avaliados, 26 (43,3%) desenvolveram algum grau de mucosite oral. Os níveis de concentração de citocinas revelaram diferenças entre indivíduos com e sem mucosite oral. Concentrações significativamente maiores de IL-6 e TNF-α e menores concentrações de TGF-β1 foram identificadas naqueles que desenvolveram mucosite oral. Houve uma diminuição na formação das redes extracelulares de neutrófilos entre aqueles que tiveram mucosite oral. Entretanto, não foram identificadas diferenças estatísticas entre as concentrações de citocinas e a formação de redes extracelulares de neutrófilos com variáveis clínicas e gravidade da mucosite oral. No terceiro estudo, os instrumentos *Hospital Anxiety and Depression Scale*, *World Health Organization Quality of Life-BREF* e *Oral Health Impact Profile* (versão abreviada – OHIP-14) foram aplicados a 37 pacientes nos dias D0 e D15. Aproximadamente 38% (*n*=14) dos indivíduos desenvolveram mucosite oral e obtiveram escores mais altos de ansiedade/depressão no início da análise. A mucosite oral teve um impacto negativo na qualidade de vida relacionada à saúde bucal, particularmente nas dimensões limitação funcional, dor física e incapacidade física. Em conjunto, os dados deste estudo contribuem para medidas preventivas e redução de comorbidades em pacientes com mucosite oral induzida por esquemas quimioterápicos. As citocinas inflamatórias participam do desenvolvimento da mucosite oral e podem ser úteis como biomarcadores na predição e monitoramento. Ademais, sintomas de ansiedade e depressão estão associados à mucosite oral que, por sua vez, afetam a saúde geral e a qualidade de vida relacionada à saúde bucal.

Palavras-chave: adulto; ansiedade; antineoplásicos; câncer; depressão; estomatite; neoplasias; qualidade de vida.

ABSTRACT

Chemotherapy-induced oral mucositis: clinical and laboratory aspects, quality of life, anxiety, and depression

The present study is based on three purposes: 1. to synthesize by means of a systematic literature review information about anxiety/depression in individuals undergoing antineoplastic therapy who developed oral mucositis; 2. to evaluate the profile of inflammatory cytokines and neutrophil extracellular trap formation in salivary samples from patients undergoing chemotherapy and its associations with oral mucositis; and 3. to investigate anxiety/depression and quality of life and their associations with chemotherapy-induced oral mucositis. In the first study, electronic searches were conducted on five databases, complemented by manual scrutiny and grey literature searches in three other databases. Eight observational studies conducted on 954 individuals were included. Seven different instruments were applied to measure anxiety and/or depression. Associations of anxiety and/or depression with the severity of oral mucositis were observed in 75.0% of the studies. The other two studies were prospective longitudinal analyses of adult individuals diagnosed with hematolymphoid diseases and undergoing chemotherapy treatment and/or conditioning for hematopoietic stem-cell transplantation at the Hospital das Clínicas of Universidade Federal de Minas Gerais. The levels of inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, and TGF-β1) and neutrophil extracellular trap formation were analyzed by ELISA and by the identification of the myeloperoxidase-DNA complex, respectively. Saliva sampling was performed at four time-points, i.e. days D0, D3, D10, and D15. Of the 60 patients evaluated, 26 (43.3%) developed some degree of oral mucositis. Cytokine concentration levels revealed differences between individuals with and without oral mucositis. Significantly higher concentrations of IL-6 and TNF-α and lower concentrations of TGF-β1 were identified in those who developed oral mucositis. There was a decrease in neutrophil extracellular trap formation among those who experienced oral mucositis. However, no statistical differences were identified between cytokine concentrations or neutrophil extracellular trap formation and clinical variables or severity of oral mucositis. In the third study, the Hospital Anxiety and Depression Scale, World Health Organization Quality of Life-BREF and Oral Health Impact Profile (short-form – OHIP-14) were the instruments applied to 37 patients on days D0 and D15. Nearly 38% (*n*=14) of individuals developed oral mucositis and had higher anxiety/depression scores at baseline. Oral mucositis had a negative impact on quality of life related to oral health, particularly functional limitation, physical pain, and physical disability. Taken together, the data from this study contribute to the application of preventive measures and the reduction of comorbidities in patients with chemotherapy-induced oral mucositis. Inflammatory cytokines participate in the development of oral mucositis and may be useful as biomarkers in prediction and monitoring. Moreover, anxiety and depressive symptoms are associated with oral mucositis, affecting, in turn, overall health and oral health-related quality of life.

Keywords: adult; antineoplastic agents; anxiety; cancer; depression; neoplasms; quality of life; stomatitis.

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LISTA DE ABREVIATURAS E SIGLAS

5-FU	5-Fluorouracil
CI	Confidence Interval
CXCL4	C-X-C Motif Chemokine Ligand 4
CXCL9	C-X-C Motif Chemokine Ligand 9
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay/Ensaio de Imunoabsorção Enzimática
HADS	Hospital Anxiety and Depression Scale
HC-UFMG	Hospital das Clínicas da Universidade Federal de Minas Gerais
IARC	International Agency for Research on Cancer
IL-1β	Interleucina 1 Beta
IL-6	Interleucina 6
IL-8	Interleucina 8
INCA	Instituto Nacional de Câncer
MTX	Metotrexato
NET	Redes Extracelulares de Neutrófilos
NF-κB	Fator Nuclear Kappa B
nm	Nanômetro
OD	Odds Ratio
OHIP	Oral Health Impact Profile
OHRQoL	Oral Health-Related Quality of Life
OMS	Organização Mundial de Saúde
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-

	analyses
PROMS	Patient Reported Outcome Measures
PROSPERO	National Institute for Health Research International Prospective Register of Systematic Reviews
ROS	Espécies Reativas de Oxigênio
Smad7	SMAD Family Member 7
STAI	State-Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational studies
TCLE	Termo de Consentimento Livre e Esclarecido
TCTH	Transplante de Células-Tronco Hematopoiéticas
TFBM	Terapia de Fotobiomodulação
TGF-β1	Fator de Crescimento Transformador Beta 1
TNF-α	Fator de Necrose Tumoral Alfa
WHOQOL	World Health Organization Quality of Life

LISTA DE SÍMBOLOS

®	Marca Registrada
%	Porcentagem
α	Alfa
β	Beta
°	Graus
≥	Maior ou Igual

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1 CONSIDERAÇÕES INICIAIS

A mucosite oral é um dos efeitos colaterais mais frequentes associados à quimioterapia, radioterapia e quimiorradioterapia (ELAD *et al*., 2022). Estimativas indicam uma incidência de mucosite oral entre pacientes submetidos a quimioterapia e/ou transplante de células-tronco hematopoiéticas (TCTH) entre 14% e 84% (BERGER *et al*., 2018). A patogênese da mucosite oral engloba uma sequência de eventos biológicos moldados por inflamação, interações microbioma oral-hospedeiro e sinalização neuroimune (BOWEN *et al*., 2019).

Clinicamente, a mucosite oral é caracterizada por lesões eritematosas e/ou ulcerativas (ELAD *et al*., 2020). A dor provocada pela mucosite oral é frequentemente descrita como excruciante (CHRISTOFOROU *et al*., 2019) e afeta a ingestão alimentar e a higiene bucal, além de aumentar o risco de infeção local/sistêmica (CINAUSERO *et al*., 2019). A progressão da mucosite oral pode interromper a terapia antineoplásica, impactando os desfechos dos pacientes (CINAUSERO *et al*., 2019; PACHECO *et al*., 2021).

A influência da mucosite oral na qualidade de vida parece se estender além das complicações bucais e envolve aspectos físicos, funcionais, emocionais e psicológicos, mas os resultados ainda são conflitantes se de fato os sintomas relacionados influenciam (ou são influenciados pela) gravidade da mucosite oral (AL-RUDAYNI *et al*., 2020). Enquanto isso, a mucosite oral pode causar sofrimento psicológico, entre outros efeitos que podem estar por trás do desenvolvimento de ansiedade e depressão (CHAITANYA *et al*., 2016; DODD *et al*., 2001). No entanto, os mecanismos fisiopatológicos da relação entre ansiedade/depressão e mucosite oral ainda não foram totalmente elucidados.

A literatura recente identificou as citocinas salivares como biomarcadores para prever o risco de ocorrência de mucosite oral e avaliar sua gravidade em indivíduos submetidos à radioterapia ou quimiorradioterapia (NORMANDO *et al*., 2017). Entretanto, em relação a mucosite oral quimioinduzida ainda não há conclusões definitivas. Em parte, isso se deve à heterogeneidade dos agentes quimioterápicos disponíveis e ao número limitado de participantes inseridos nos estudos (DIESCH *et al*., 2021; NORMANDO *et al*., 2017).

O presente estudo buscou avaliar aspectos clínicos, laboratoriais, qualidade de vida, ansiedade e depressão em pacientes em regime quimioterápico e possíveis associações com a mucosite oral.

2 REVISÃO DE LITERATURA

2.1 Epidemiologia das neoplasias malignas

Em 2023, espera-se que 1.958.310 novos casos de câncer e 609.820 mortes ocorram nos Estados Unidos, incluindo aproximadamente 350 mortes por dia por câncer de pulmão, a principal causa de morte por malignidade (SIEGEL *et al*., 2022; SIEGEL *et al*., 2023). Em 2020, a Agência Internacional de Pesquisa sobre o Câncer (IARC) informou que o câncer foi a segunda principal causa de morte prematura em uma proporção significativa ao redor do mundo (IARC, 2020). No Brasil, excluindo-se os tumores de pele não melanoma, o câncer de mama é o mais frequente em mulheres entre todas as localizações anatômicas, com maiores taxas nas regiões Sul e Sudeste. Para o triênio de 2023 a 2025, foram estimados 704 mil novos casos, representando uma taxa de incidência ajustada de 17% maior em homens (INCA, 2022).

A leucemia e o linfoma são doenças malignas que acometem o sistema hematolinfóide, resultando na proliferação de células neoplásicas. Existem mais de 12 tipos de leucemia, sendo as principais: leucemia mielóide aguda, leucemia mielóide crônica, leucemia linfocítica aguda e leucemia linfocítica crônica (CORTES; PAVLOVSKY; SAUßELE, 2021; DINARDO *et al*., 2023; MALARD; MOHTY, 2020). Tradicionalmente, os linfomas são classificados como linfoma não Hodgkin e linfoma de Hodgkin. O primeiro revela uma miríade de entidades que são subcategorizadas em neoplasias maduras de células B, T e NK. No linfoma de Hodgkin, dois tipos principais são reconhecidos, i.e., linfoma de Hodgkin predominantemente linfocitário nodular e linfoma de Hodgkin clássico (SWERDLOW *et al*., 2017). O número estimado de casos novos de leucemia, linfoma não Hodgkin e linfoma de Hodgkin para o Brasil, para cada ano do triênio de 2023 a 2025, é respectivamente de 11.540, 12.040, 3.080 casos (INCA, 2022).

2.2 Manejo dos indivíduos com neoplasias malignas

Existem três formas principais de tratamento do câncer: cirurgia, radioterapia e quimioterapia. As terapias podem ser utilizadas em conjunto, variando apenas quanto à suscetibilidade das neoplasias a cada uma das modalidades terapêuticas e a melhor

sequência de administração. Atualmente, poucas neoplasias malignas são tratadas com apenas uma modalidade terapêutica. Os protocolos terapêuticos variam de acordo com o tipo de doença e estadiamento (PARMAR *et al*., 2021). No câncer de cabeça e pescoço, por exemplo, além da cirurgia, a radioterapia em combinação com a quimioterapia é a forma mais comum de tratamento (IOCCA *et al*., 2018).

Nas últimas quatro décadas, avanços significativos foram feitos no tratamento do câncer na população adulta. Atualmente, cerca de 80% dos indivíduos podem ser curados quando diagnosticados precocemente e tratados em centros especializados, e a maioria apresenta boa qualidade de vida após o tratamento (KEEGAN *et al*., 2017; MORENO *et al*., 2017). No entanto, a maioria dos indivíduos em tratamento com esquemas antineoplásicos, particularmente 5-fluorouracil, busulfan, cisplatina, doxorrubicina, etoposídeo, melfalan, metotrexato, taxanos e vimblastina, desenvolvem complicações bucais (ALLEN *et al*., 2018; CURRA *et al*., 2018; GARROCHO-RANGEL *et al*., 2018; MAZHARI; SHIRAZI; SHABZENDEHDAR, 2019; QUTOB *et al*., 2013; SHETTY *et al*., 2022).

2.3 Mucosite oral e orofaríngea decorrentes de esquemas antineoplásicos

Sonis (2021) documentou que dos 1,8 milhão de indivíduos diagnosticados com neoplasias malignas no ano de 2021 nos Estados Unidos, quase metade poderia ter algum grau de mucosite oral. Barkokebas *et al*. (2015) relataram que quase todos os pacientes que receberam quimiorradioterapia para câncer de cabeça e pescoço desenvolveram múltiplas reações agudas, incluindo mucosite oral, durante o curso do regime antineoplásico. Pulito *et al*. (2020) afirmam que cerca de 40% dos pacientes tratados com quimioterapia desenvolvem mucosite oral. A incidência global dessa condição naqueles em tratamento para câncer de cabeça e pescoço é de quase 90% (PACHECO *et al*., 2021), enquanto para o transplante alogênico de células-tronco hematopoéticas, a ocorrência varia de 70% a 90% (CHAUDHRY *et al*., 2016). No entanto, a incidência de mucosite oral varia de acordo com o regime de condicionamento utilizado para o TCTH. Assim, quanto maior a intensidade e a duração da mielossupressão, maior a probabilidade de o paciente apresentar mucosite oral severa (CHAUDHRY *et al*., 2016).

A mucosite oral pode se manifestar como atrofia, eritema, erosão e ulceração, ou como uma combinação dessas manifestações (FIGURA 1). Ademais, pode ser exacerbada por dentes afiados/fraturados, bruxismo e microrganismos (RABER-DURLACHER; ELAD; BARASCH, 2010; SHETTY *et al*., 2022; SONIS, 2021). As manifestações clínicas da mucosite oral são comumente observadas em tecidos não queratinizados, iniciando-se com eritema doloroso e inflamação da mucosa acometida. Assim, as ulcerações subsequentes tornam-se uma porta de entrada livre para microrganismos. Além disso, a disfagia causada pela mucosite oral e orofaríngea pode agravar ainda mais a gravidade das lesões bucais e exacerbar os sinais e sintomas sistêmicos, como fadiga e anorexia, além dos aspectos psicológicos (AL-RUDAYNI *et al*., 2020; SHETTY *et al*., 2022).

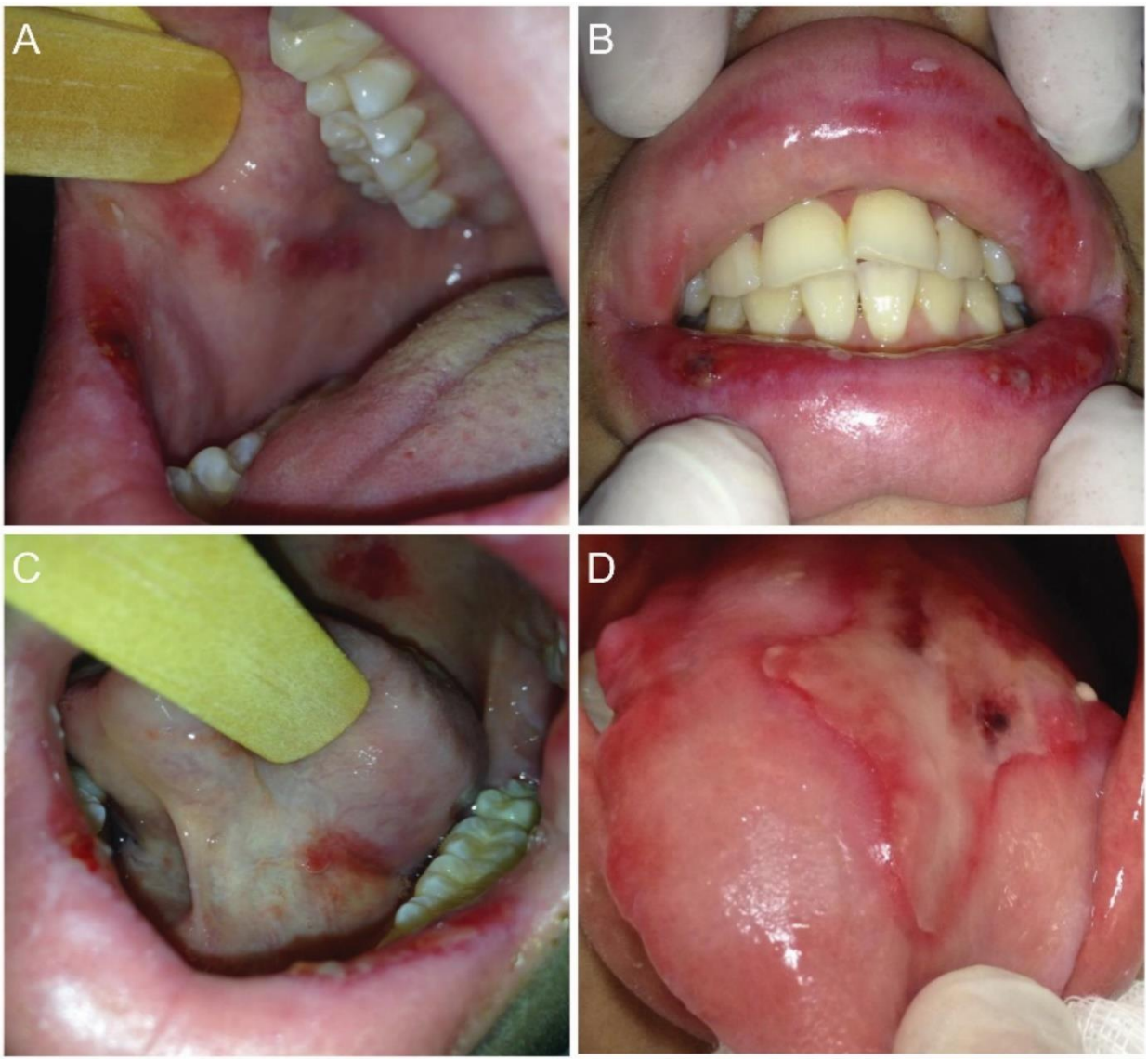

Figura 1 – Aspectos clínicos da mucosite oral induzida por quimioterapia. (A) Múltiplas úlceras na mucosa jugal direita e áreas de úlcera na mucosa do lábio inferior. (B) Lábio superior e inferior exibindo eritema e ulcerações epiteliais. (C) Úlceras no palato mole e mucosa do lábio inferior e eritema em superfície ventral da língua. (D) Úlcera extensa recoberta por membrana amarelada no dorso da língua.
Fonte: Do autor, 2023.

2.4 Infecções oportunistas associadas à mucosite oral

Segundo estimativas do Instituto Nacional de Câncer (INCA), cerca de 70% dos indivíduos com neoplasias malignas em tratamento antineoplásico apresentam complicações bucais decorrentes de toxicidade direta ou indireta (INCA, 2019), podendo levar à colonização da mucosa bucal por bactérias, vírus e fungos (MÜLLER *et al*., 2019). Embora a cavidade bucal seja normalmente colonizada por diferentes espécies de *Candida*, incluindo *C. albicans*, *C. glabrata*, *C. guillermondii*, *C. krusei*, *C. parapsilosis*, *C. pseudotropicalis*, *C. stellatoidea* e *C. tropicali* (MONTELONGO-

JAUREGUI; LOPEZ-RIBOT, 2018), a mucosite oral tem sido frequentemente associada à colonização por *C. albicans*, levando a uma condição mais grave – que é uma ameaça subsequente para indivíduos com neoplasias malignas em tratamento antineoplásico (ARRIFIN *et al*., 2018; BERGAMASCO *et al*., 2013; KURNATOWSKI; MOQBIL; KACZMARCZYK, 2014; SAUNDERS *et al*., 2020; SOUZA *et al*., 2020; VESTY *et al*., 2020).

Clinicamente, é praticamente impossível diferenciar mucosite oral infectada da não infectada, por isso o diagnóstico é desafiador (RABER-DURLACHER *et al*., 2000). No entanto, Souza (2020) detectaram 26,5% dos indivíduos em tratamento oncológico (quimioterapia, radioterapia ou quimiorradioterapia) com *Candida spp*. na saliva, com colonização por *Candida* não albicans em torno de 41,7%. Nishii *et al*. (2020) demonstraram uma alta ocorrência de candidíase oral em pacientes sob terapia antineoplásica. Os autores indicaram que contagens mais baixas de leucócitos e mucosite oral grau 2 ou superior foram positivamente correlacionados com o desenvolvimento de candidíase (NISHII *et al*., 2020).

O tratamento antineoplásico possivelmente promove uma mudança no perfil da microbiota oral do indivíduo afetado, bem como nas relações entre os microrganismos que a compõe. Bunetel *et al*. (2019) demonstraram que cepas bacterianas presentes na microbiota de indivíduos com neoplasias malignas aderem à superfície da cavidade bucal e orofaringe. Outros autores, entretanto, sugerem que tais cepas são provavelmente mais virulentas e apresentam um risco aumentado para seu hospedeiro imunocomprometido (SOUZA *et al*., 2020). Nesse caso, a triagem microbiológica dos pacientes é necessária antes e durante o tratamento antineoplásico, a fim de prevenir infecções oportunistas, principalmente colonizadas por espécies de *Candida* (SOUZA *et al*., 2020).

2.5 Patobiologia da mucosite oral

A patogênese da mucosite oral é multifacetada. Evidências acumuladas apoiam o conceito de que a mucosite oral resulta do impacto cumulativo de uma série de vias biológicas que se originam na submucosa e atingem o epitélio bucal (FIGURA 2).

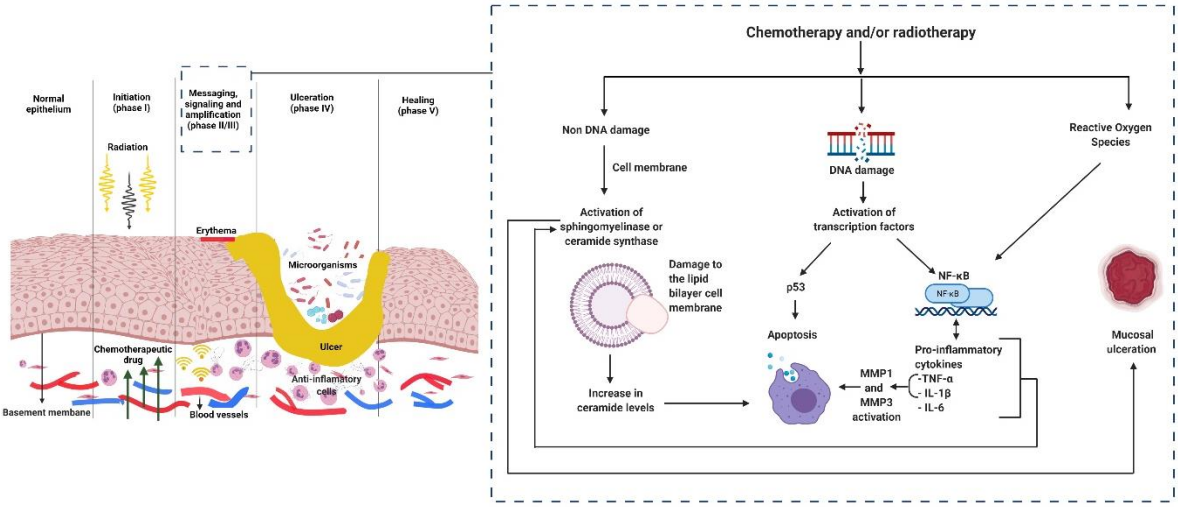

Figura 2 – Modelo dos mecanismos da mucosite oral. Os principais processos biológicos associados à patogênese da mucosite oral podem ser divididos arbitrariamente em cinco fases: iniciação (fase I: 0 a 2 dias), resposta ao dano primário (mensagens e sinalização) (fase II: 2 a 3 dias), amplificação (fase III: 2 a 10 dias), ulceração (fase IV: 10 a 15 dias) e cicatrização (fase V: 15 a 21 dias).
Fonte: SHETTY *et al*., 2022, p. 101300.

Uma sequência de cinco fases foi empregada para descrever as etapas biológicas da mucosite oral: iniciação, regulação positiva e ativação levando à geração de mensageiros, amplificação de sinal, ulceração com inflamação e cicatrização (CINAUSERO *et al*., 2017; SONIS, 2004; VILLA; SONIS, 2015). Na maioria das vezes, essa ordem é independente do regime antineoplásico empregado ou do tecido alvo envolvido (SONIS *et al*., 2004).

A fase de iniciação é caracterizada por danos diretos ao DNA causados pelos regimes antineoplásicos e subsequentes quebras de fita que resultam em morte clonogênica das células epiteliais da camada basal. Ainda mais significativo do ponto de vista do dano tecidual final é a geração de espécies reativas de oxigênio (ROS). Outras células normais apoptóticas ou necróticas por quimioterapia e/ou radioterapia podem liberar moléculas padrão associadas a danos endógenos que também desempenhar um papel integral no início da toxicidade (SONIS *et al*., 2004; SONIS, 2010).

A segunda fase é a geração da mensagem, que envolve a regulação positiva de fatores de transcrição, incluindo fator nuclear kappa B (NF-κB) e STAT3 (*Signal Transducer and Activator of Transcription 3*), e a ativação de várias citocinas (SONIS, 2007). Especificamente, a via NF-κB demonstra a complexidade do processo que leva à ulceração (CURRA *et al*., 2015; LOGAN *et al*., 2007). O NF-κB pode executar uma gama de 200 genes envolvidos em funções pró e anti-apoptóticas. A ativação do NF-

κB, o mediador central da indução de genes pró-inflamatórios, leva à produção de citocinas inflamatórias, quimiocinas e moléculas de adesão. A ativação de fatores de transcrição influencia a formação de citocinas pró-inflamatórias, como TNF-α, IL-1β e IL-6, que iniciam a sinalização ectomesenquimal que reoxigena as células epiteliais, exacerbando os danos às células epiteliais basais, ao tecido e ao endotélio (ZELOVÁ; HOŠEK, 2013).

Os sinais são amplificados devido a danos nos tecidos, apoptose, permeabilidade vascular e ativação de enzimas (ex., ciclooxigenase-2). As citocinas pró-inflamatórias fornecem um feedback positivo, intensificando a resposta ao dano primário. O TNF-α é um eficiente ativador de NF-κB e também inicia a sinalização da proteína quinase ativada por mitógeno (MAPK), levando à ativação de JNK (c-Jun N-terminal quinase) que, por sua vez, regula a atividade transcricional de AP1 (*Activator protein 1*). Essa via complexa resulta na ativação da caspase-3 e morte celular (SONIS, 2004; VILLA; SONIS, 2015).

As alterações teciduais resultam na perda do epitélio, produzindo lesões dolorosas, que podem concomitantemente causar infiltração bacteriana, fúngica e/ou viral e influxo de macrófagos e outras células inflamatórias, caracterizando a fase ulcerativa. Após a cessação dos estímulos dos regimes antineoplásicos, i.e., quimioterapia e/ou radioterapia, o processo de cicatrização pode ser estabelecido (CINAUSERO *et al*., 2017; NAPEÑAS *et al*., 2007; SONIS, 2004; VILLA; SONIS, 2015).

As vias moleculares e celulares que levam à mucosite oral não são claras. Estudos anteriores sugeriram que a mucosite resulta de uma sequência dinâmica de três eventos distintos na mucosa oral: toxicidade e morte de queratinócitos, vigilância imune da mucosa prejudicada e alterações significativas na flora oral (CHIAPPELLI, 2005). Embora seja aceito que o microbioma desempenha um papel na suscetibilidade e nos desfechos dos indivíduos com mucosite oral, além de ser modificado por drogas antineoplásicas, há uma falta de compreensão do mecanismo do efeito da microbiota (BOWEN *et al*., 2019). Considerando que a mucosite oral está associada a grandes mudanças no ambiente/comunidade microbiana oral, é provável que ocorra a translocação de bactérias bucais disbióticas para o intestino. Isso, por sua vez, poderia contribuir para alterações patológicas no intestino e ativação de respostas imunes sistêmicas e, portanto, afetar negativamente a mucosite oral (AL-QADAMI *et al*., 2022).

Abordagens baseadas em células para o manejo da inflamação surgiram recentemente e apresentam uma mudança de paradigma no tratamento da mucosite.

A inibição de citocinas pró-inflamatórias, fator de necrose tumoral alfa (TNF-α), interleucina (IL-)1β, IL-6 e IL-8; e vias de sinalização de fator nuclear kappa B (NF-κB) parecem ser promissoras no manejo da mucosite oral (BOWEN *et al*., 2019; SANTOS FILHO *et al*., 2018). Pesquisa utilizando camundongos transgênicos que expressam a proteína nuclear Smad7 (*SMAD family member 7*) em queratinócitos mostrou que antagonizar o fator de crescimento transformador beta 1 (TGF-β1) e NF-κB efetivamente previne a mucosite oral induzida por radioterapia (HAN *et al*., 2013). Da mesma forma, terapias anti-inflamatórias baseadas em anticorpos contra quimiocinas, CXCL4 e CXCL9, foram avaliadas *in vitro* e *in vivo*, indicando um conhecimento mais sofisticado dos mecanismos imunológicos para a etiopatogênese da mucosite. Anti-CXCL4 e anti-CXCL9 provaram ser potenciais candidatos terapêuticos para promover a restituição da mucosa (GAO *et al*., 2014; LU *et al*., 2015).

2.6 Papel dos leucócitos e neutrófilos na mucosite oral

Recentemente, estudos revelaram que os leucócitos são células importantes no reparo tecidual (CASTANHEIRA; KUBES, 2019). Os neutrófilos são a população de leucócitos predominante no sangue humano e estão entre as primeiras células recrutadas quando um dano tecidual acontece (BURGENER *et al*., 2019). Também, são capazes de neutralizar uma infecção por meio de fagocitose e destruição de patógenos por mecanismos que envolvem a degranulação e formação de redes extracelulares de neutrófilos (NET) (CASTANHEIRA; KUBES, 2019). NET são redes fibrosas constituídas por componentes nucleares e por componentes granulares que desempenham função antimicrobiana (BRINKMANN *et al*., 2004). Essas redes se projetam da membrana de neutrófilos ativados em resposta à infecção e ao processo inflamatório estéril (FUCHS *et al*., 2007). Sabe-se que os neutrófilos e NET medeiam o dano ao tecido durante a inflamação aguda e crônica, desde trombose a neoplasias malignas (CASTANHEIRA; KUBES, 2019; MANDA *et al*., 2014). Também, a falha na produção efetiva de NET é considerada um dos mecanismos envolvidos nas imunodeficiências primárias e secundárias (HAZELDINE *et al*., 2014; PAPAYANNOPOULOS, 2018). Ostafin *et al*. (2021) relataram que, no curso das leucemias infantis agudas, os neutrófilos diminuíram a capacidade de liberar NET, o que, consequentemente, aumentou o risco de complicações infecciosas. Nos últimos

anos, as investigações revelaram que a NET desempenha um papel antimicrobiano relevante na patogênese da periodontite e artrite reumatoide (OLIVEIRA *et al*., 2022), úlceras aftosas e doença de Behçet (MOHANTY *et al*., 2015) e líquen plano oral (JABLONSKA *et al*., 2020). Entretanto, a compreensão do envolvimento de NET na etiopatogênese da mucosite oral ainda não foi explorada.

2.7 Manejo da mucosite oral

Diversas terapias têm sido utilizadas a fim de atenuar a gravidade da mucosite oral decorrente de regimes antineoplásicos, como por exemplo cuidados bucais básicos, agentes anti-inflamatórios, terapia de fotobiomodulação (TFBM), crioterapia, antimicrobianos, agentes de revestimento, anestésicos, analgésicos, fatores de crescimento e citocinas, e agentes naturais/fitoterápicos (ELAD *et al*., 2020). No entanto, ainda existem situações clínicas para as quais não há recomendações (ELAD *et al*., 2020). Por exemplo, evidências apoiam o uso de crioterapia oral para prevenção de mucosite oral em indivíduos que recebem transplante autólogo de células-tronco hematopoiéticas com protocolos de condicionamento de alta dose de melfalano bem como para aqueles que recebem quimioterapia com 5-fluorouracil (CORREA *et al*., 2020). Enquanto isso, a TFBM se tornou uma modalidade de tratamento reconhecida no manejo de indivíduos com mucosite oral (BOWEN *et al*., 2019; ELAD *et al*., 2018; NUNES *et al*., 2020). Os efeitos clínicos incluem analgesia, anti-inflamatório, estimulação da regeneração tecidual, neovascularização e cicatrização acelerada de feridas (ANDERS; LANZAFAME; ARANY, 2015; MARTINS *et al*., 2019; PASSARELLA; KARU, 2014).

2.8 Qualidade de vida de pacientes com mucosite oral

A Organização Mundial da Saúde (OMS) define a qualidade de vida como um parâmetro de natureza multidimensional, que envolve a saúde física e psicológica, o nível de independência, as relações sociais, as crenças pessoais e a relação do indivíduo com o meio ambiente (WHO, 1995). Pesquisas de qualidade de vida também podem proporcionar um tratamento mais eficaz aos pacientes com câncer, pois podem

orientar os profissionais de saúde em sua conduta, de forma que priorizem sua recuperação (MAHAKWE *et al*., 2021). De acordo com Martins *et al*. (2021), poucos estudos avaliaram as medidas de qualidade de vida relacionadas à saúde bucal (OHRQoL) dos pacientes e a percepção dos sintomas relacionados à mucosite oral. Observou-se que a radioterapia está associada à diminuição da OHRQoL e que a mucosite oral está associada ao comprometimento da qualidade de vida dos indivíduos (MARTINS *et al*., 2021).

O índice *Oral Health Impact Profile* (OHIP) tem como objetivo avaliar o impacto de problemas bucais na qualidade de vida, a partir da percepção dos indivíduos sobre disfunções, desconfortos e incapacidades decorrentes de problemas na boca. Originalmente, esse índice era composto por 49 itens, referentes a problemas de pronúncia, sensação de paladar, dor na boca, dor ao se alimentar, desconforto com a condição bucal, tensão nervosa, alimentação prejudicada, necessidade de interromper as refeições, dificuldade para relaxar, constrangimento, irritação com outras pessoas, dificuldade de fazer tarefas rotineiras, vida insatisfatória e incapacidade funcional para realizar atividades diárias. Posteriormente, foi criado um formulário simplificado do OHIP-49, composto por 14 itens, sob o nome de *Oral Health Impact Profile – short-form* (OHIP-14) (SLADE, 1997). O instrumento OHIP-14 foi avaliado em pacientes com mucosite oral induzida por quimiorradioterapia. Dor, limitações físicas e distúrbios psicológicos foram os fatores predominantes (BARKOKEBAS *et al*., 2015).

2.9 Relação entre ansiedade, depressão e mucosite oral

Nos últimos anos, houve um aumento exponencial na prevalência, mensuração e experiência de transtornos de ansiedade e depressão entre indivíduos que recebem terapia antineoplásica (BERGEROT *et al*., 2017; DUC *et al*., 2017; MITCHELL *et al*., 2011; RICHARDSON; BROADBENT; MORTON, 2019; WEN; XIAO; YANG, 2019). Transtornos psicológicos e psiquiátricos não reconhecidos e não tratados podem ter implicações adversas para a qualidade de vida a longo prazo, adesão ao tratamento, uso de serviços de saúde, bem como mortalidade (WAKEFIELD *et al*., 2015; WANG *et al*., 2020). A incidência de ansiedade e depressão entre pacientes com câncer é de cerca de 10% e 16,5%, respectivamente (MITCHELL *et al*., 2011). A incidência documentada de depressão entre aqueles submetidos a regimes quimioterápicos varia

entre 17% e 45% (BERGEROT *et al*., 2017; DUC *et al*., 2017; MITCHELL *et al*., 2011). A depressão não só prejudica substancialmente a qualidade de vida, como também pode aumentar a taxa de recorrência do câncer e o risco de morte (BRAVERY; LOUGHNAN; MURPHY, 2020; DUC *et al*., 2017).

Estudos apontam que a magnitude da mucosite oral na qualidade de vida vai além das complicações biológicas dos problemas de saúde bucal devido ao impacto nos domínios físico, emocional, psicológico e psiquiátrico do indivíduo acometido, incluindo não apenas os transtornos de ansiedade, mas também tendências depressivas (AL-RUDAYNI *et al*., 2020; GUTIÉRREZ-VARGAS *et al*., 2016; JEHN *et al*., 2019). Assim, uma ligação bidirecional entre mucosite oral e sintomas psiquiátricos como ansiedade e depressão tem sido sugerida na literatura (CHAITANYA *et al*., 2016). Indivíduos com mucosite oral desencadeada por regimes de quimioterapia e radioterapia têm maior risco de desenvolver sintomas de raiva, ansiedade e depressão, enquanto a ansiedade especialmente tem sido associada a uma maior probabilidade de incidência e maior gravidade da mucosite oral (CHAITANYA *et al*., 2016; DODD *et al*., 2001). Além disso, considerando que a mucosa oral é muito responsiva a efeitos emocionais como estresse, ansiedade e depressão, como observado em indivíduos com líquen plano oral, úlceras aftosas recorrentes e síndrome da ardência bucal (PORRAS-CARRIQUE *et al*., 2022; SOUZA *et al*., 2012; YANG *et al*., 2018), supõe-se que os transtornos de ansiedade e depressão possam atuar de forma sinérgica, refletindo a natureza multifatorial da mucosite oral e participar agravando as lesões.

A literatura descreve alguns instrumentos de avaliação de ansiedade e depressão, como a Escala de Ansiedade de Hamilton, o Inventário de Ansiedade STAI I e II, os Inventários de Ansiedade e Depressão de Beck e a Escala de Ansiedade e Depressão Hospitalar (*Hospital Anxiety and Depression Scale* – HADS) (VODERMAIER; MILLMAN, 2011). Inicialmente, a HADS foi desenvolvida para identificar sintomas de ansiedade e/ou depressão em pacientes de hospitais de clínicas não psiquiátricas, sendo posteriormente utilizada em outros tipos de pacientes, inclusive ambulatoriais. Um ponto importante que diferencia a HADS das demais escalas é que, para evitar a interferência de transtornos somáticos no escore da escala, foram excluídos todos os sintomas de ansiedade e/ou depressão relacionados a doenças físicas (MARCOLINO *et al*., 2007).

3 OBJETIVOS

3.1 Objetivo geral

Investigar ansiedade, depressão, qualidade de vida, o perfil de citocinas pró-inflamatórias e formação de NET em pacientes submetidos a esquemas quimioterápicos e associações com mucosite oral.

3.2 Objetivos específicos

a) Realizar pesquisas eletrônicas em múltiplas bases de dados e complementadas com um escrutínio manual das listas de referências dos artigos incluídos e pesquisas de literatura cinzenta para examinar a associação de ansiedade e/ou depressão e mucosite oral relacionada a regimes antineoplásicos;

b) Avaliar o perfil de citocinas pró-inflamatórias e a formação de NET em amostras salivares de pacientes em quimioterapia e suas associações com a mucosite oral;

c) Analisar sintomas de ansiedade e depressão e qualidade de vida em pacientes em quimioterapia e suas associações com a mucosite oral.

4 METODOLOGIA EXPANDIDA

4.1 Capítulo 1: revisão sistemática da literatura

4.1.1 Protocolo e registro da revisão sistemática

A presente revisão foi conduzida de acordo com os critérios propostos pelo *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) (PAGE *et al*., 2020). Um protocolo foi elaborado e registrado no *National Institute for Health Research International Prospective Register of Systematic Reviews* (PROSPERO; https://www.crd.york.ac.uk/prospero/) sob o número de registro CRD42022328816.

4.1.2 Critérios de elegibilidade

Para responder à seguinte pergunta: “entre os indivíduos em terapia antineoplásica, qual a frequência de ansiedade e depressão e seu impacto na gravidade da mucosite oral?”, investigou-se com base no referencial PECO: P (população): participantes que estiveram ou estão em terapia antineoplásica; E (exposição): ansiedade e/ou depressão; C (comparação): não aplicável; O (resultado): mucosite oral.

Os critérios de inclusão foram: estudos observacionais (transversais, caso-controle e coorte) que analisassem a influência de sinais e sintomas de ansiedade e/ou depressão na frequência de mucosite oral (entre indivíduos com e sem mucosite oral) ou na gravidade da doença (indivíduos com diferentes graus de mucosite que receberam alguma terapia antineoplásica). Não foram impostas restrições quanto ao idioma, região geográfica ou período de publicação. Quando os achados foram aparentemente derivados da mesma população do estudo, foram escolhidos aqueles relatados mais recentemente ou aqueles que forneceram os dados mais completos. O uso da mesma população em diferentes estudos foi determinado verificando o nome e afiliação do(s) autor(es), local onde o estudo foi realizado, origem dos participantes, período de recrutamento e/ou contato com os autores do estudo, se necessário.

Os critérios de exclusão foram estudos que mencionavam mucosite oral, mas cujo objetivo não era analisar associações de sua frequência/gravidade com ansiedade e/ou depressão, investigações sobre qualidade de vida (já que, se havia algum domínio sobre estado emocional, incluindo depressão e/ou ansiedade, os resultados precisariam ser desagregados), bem como estudos com dados subjetivos derivados de métodos inconsistentes aplicados para medir ansiedade e/ou depressão (ou seja, estudos que não utilizaram um instrumento de avaliação validado ou uma escala psicométrica consolidada). Também foram excluídos artigos de revisão, relatos de casos ou séries de casos, editoriais, cartas ao editor, opiniões de especialistas, capítulos de livros, resumos de conferências/reuniões, estudos experimentais em animais e estudos *in vitro*.

4.1.3 Fontes de informação e estratégia de busca

As buscas eletrônicas foram realizadas nas seguintes bases de dados: PubMed (National Library of Medicine), Embase (Elsevier), Ovid (Wolters Kluwer), Scopus (Elsevier) e Web of Science (Clarivate Analytics) em 22 de março de 2022. Os esquemas de busca empregados em bases de dados com operadores booleanos combinando termos e palavras-chaves (TABELA 1).

Tabela 1 – Estratégia de busca empregada para identificar artigos em bases de dados eletrônicas

PubMed, Web of Science, and Ovid	(oral mucositis OR stomatitis OR stomatitides OR oral mucositides OR oromucositis OR oromucositides) AND (depression OR depressive OR depressive disorder OR emotional OR anxiety disorder OR anxiety OR anxieties OR angst OR hypervigilance OR nervousness OR anxiousness OR mania OR psychosis OR bipolar disorder OR schizophrenia OR neurocognitive disorder OR delirium)
Scopus	(“oral mucositis”) AND (depression OR depressive OR “depressive disorder” OR emotional OR “anxiety disorder” OR anxiety OR anxieties OR angst OR hypervigilance OR nervousness OR anxiousness OR mania OR psychosis OR “bipolar disorder” OR schizophrenia OR “neurocognitive disorder” OR delirium)
Embase	(“oral mucositis” OR stomatitis OR stomatitides OR “oral mucositides” OR oromucositis OR oromucositides) AND (depression OR depressive OR “depressive disorder” OR emotional OR “anxiety disorder” OR anxiety OR anxieties OR angst OR hypervigilance OR nervousness OR anxiousness OR mania OR psychosis OR “bipolar disorder” OR schizophrenia OR “neurocognitive disorder” OR delirium)

Fonte: Do autor, 2022.

Foram aplicados ajustes no esquema de busca devido à especificidade de cada base de dados. As buscas de literatura cinzenta também foram realizadas por meio do Open Grey, ProQuest e Google Scholar, com a busca limitada aos primeiros 200 registros de acesso em cada banco de dados (HADDAWAY *et al*., 2015). Além disso, foi realizado um escrutínio manual através do cruzamento das listas de referências dos artigos incluídos. Referências duplicadas em diferentes bancos de dados foram encontradas e removidas usando o programa EndNote (EndNote®, Clarivate Analytics, Toronto, Canadá).

4.1.4 Processo de seleção

Dois autores (J.A.A.A. e F.V.H.) filtraram independentemente os resumos dos títulos. Os artigos com títulos e resumos que atendiam aos critérios de elegibilidade foram incluídos imediatamente. O texto completo dos artigos sem informações suficientes nos títulos/resumos foi recuperado para auxiliar os dois autores na arbitragem independente sobre inclusão ou exclusão. Na segunda etapa, dois autores avaliaram os textos completos e os que atenderam aos critérios de elegibilidade foram

incluídos. As discrepâncias foram resolvidas por consenso ou em consulta com dois outros autores (T.A.S. e R.A.M.).

4.1.5 Processo de coleta de dados e itens

Os dados dos estudos selecionados foram extraídos por um autor (J.A.A.A.) e dois outros autores (T.A.S. e R.A.M.) checaram a extração. Os seguintes itens foram coletados: sobrenome do primeiro autor, país, ano de publicação, desenho do estudo, tamanho da amostra, método de recrutamento dos participantes, doença de base (tipo de malignidade ou doença subjacente que levou ao TCTH, idade e sexo dos participantes, regime terapêutico empregado, sistema de gradação usado para mucosite oral, instrumento empregado para mensurar ansiedade e/ou depressão, desfecho investigado, bem como análise estatística, resultados gerais, direção do efeito (se estatisticamente significativo) e força dos resultados. Caso fossem necessários mais esclarecimentos, os autores foram contatados por e-mail.

4.1.6 Avaliação do risco de viés

Dois autores (J.A.A.A. e L.G.A.) avaliaram a qualidade metodológica de todos os estudos usando o *Critical Appraisal Checklist* (MOOLA; MUNN; TUFANARU, 2020) do *Joanna Briggs Institute* da Universidade de Adelaide, Austrália. Os estudos incluídos foram avaliados de acordo com os parâmetros de cada tipo de estudo, ou seja, transversal e coorte. Para cada parâmetro, o estudo incluído foi classificado como “sim”, “não”, “incerto” ou “não aplicável”. Possíveis discrepâncias entre os dois autores foram resolvidas por discussão com um terceiro autor (T.A.S.) até chegar a um consenso.

4.1.7 Análise dos dados

Os dados foram tabulados no Microsoft Office Excel 2019 (Microsoft® software, Redmond, WA, EUA) e analisados descritivamente.

4.2 Capítulos 2 e 3: estudo longitudinal prospectivo

4.2.1 Considerações éticas

O estudo foi submetido à Diretoria de Ensino, Pesquisa e Extensão e aos serviços de Oncologia, Hematologia e Odontologia do HC-UFMG. Inicialmente, o projeto foi submetido ao Comitê de Ética em Pesquisa da UFMG, obedecendo ao exigido pela legislação brasileira do Conselho Nacional de Saúde sobre diretrizes e normas regulamentadoras de pesquisa envolvendo seres humanos (Resolução 466/2012) e foi realizado de acordo com os princípios éticos da Declaração de Helsinque (BELSEY, 1978). O estudo foi aprovado pelo Comitê de Ética em Pesquisa da UFMG (Número do Parecer: 5.904.127 e CAAE: 64244422.9.0000.5149) (ANEXO A).

Todos os participantes receberam informações detalhadas sobre a pesquisa. Os sujeitos adultos selecionados para o estudo, que concordaram em participar, assinaram o Termo de Consentimento Livre e Esclarecido (TCLE).

Uma vez identificada a necessidade de tratamento odontológico dos pacientes, eles foram informados, orientados sobre o assunto e esclarecidos que, caso desejassem, o atendimento odontológico era garantido no HC-UFMG.

4.2.2 Delineamento do estudo

Trata-se de um estudo longitudinal, prospectivo, monocêntrico, realizado entre 2021 e 2023 nos serviços de Onco-Hematologia e Transplante de Células-Tronco Hematopoiéticas do HC-UFMG, Belo Horizonte, Minas Gerais. O presente estudo seguiu a lista de verificação e a declaração do *Strengthening the Reporting of Observational studies* (STROBE) (KNOTTNERUS; TUGWELL, 2008).

4.2.3 Participantes e critérios de elegibilidade

Foram considerados os seguintes critérios de inclusão para os participantes:

a) Adultos (≥18 anos) de ambos os sexos, segundo os critérios de admissão do HC-UFMG, ou seja, aqueles com tumores sólidos malignos de qualquer tipo histopatológico localizados em qualquer região do corpo, ou com doenças hematológicas e/ou linfoides;

b) Indivíduos em tratamento quimioterápico (QUADRO 1) e aqueles submetidos a TCTH (autólogo ou alogênico);

c) Indivíduos com capacidade de cooperar com o tratamento, i.e., com capacidade mental e física para tomar decisões para aceitar participar da pesquisa.

Os seguintes critérios de exclusão foram listados:

a) Pacientes com neoplasias de glândulas salivares ou síndrome de Sjögren ou doenças crônicas com envolvimento salivar (ex., histoplasmose, linfoma MALT, lúpus eritematoso sistêmico, artrite reumatoide, amiloidose), programados para receber outro tipo de terapia antineoplásica (ex., radioterapia ou quimiorradioterapia);

b) Indivíduos que não completaram quatro consultas regulares para coleta de dados.

Quadro 1 – Principais quimioterápicos utilizados no serviço de Onco-Hematologia do HC-UFMG

Doença	**Agentes quimioterápicos**
Leucemia linfocítica aguda	Metotrexato, Doxorrubicina, Citarabina, Vincristina, Daunorrubicina, Etoposídeo, 6-Mercaptopurina
Leucemia mieloide aguda	Metotrexato, Doxorrubicina, Citarabina, Daunorrubicina, Etoposídeo, 6-Mercaptopurina
Osteossarcoma	Metotrexato, Doxorrubicina, Vincristina, Etoposídeo
Linfoma de Burkitt	Metotrexato, Doxorrubicina, Citarabina, Vincristina, Etoposídeo

Fonte: NUNES *et al.*, 2020, p. 1857.

4.2.4 Coleta de dados

Os pacientes foram acompanhados dentro da sequência de ciclos de quimioterapia e foram avaliados em quatro momentos: D0 (antes da quimioterapia), D3 (início da imunossupressão), D10 (período nadir) e D15 (recuperação da medula

óssea). Dados sobre sexo, idade, doença de base e tipo de TCTH (autólogo ou alogênico) foram registrados. Concomitantemente, dados dos hemogramas foram obtidas dos prontuários para mensuração da contagem absoluta de neutrófilos (valores de referência: 2,0 a 7,0 x 10^3/μL). Informações sobre desfechos relacionados à sobrevida também foram registradas.

4.2.5 Exame clínico bucal – definição da mucosite oral e gradação

Os exames clínicos bucais foram realizados por dois dentistas calibrados (J.A.A.A. e F.V.H.). A mucosite oral foi avaliada diariamente, do D1 ao D15. Foi utilizada a escala da OMS para avaliação dos graus de mucosite oral: grau 0 (sem lesões), grau 1 (eritema sem lesões), grau 2 (úlceras, mas o indivíduo conseguia se alimentar), grau 3 (úlceras dolorosas, mas o indivíduo estava capaz de consumir alimentos líquidos com analgesia de suporte) e grau 4 (suporte parenteral/enteral necessário individual e analgesia contínua) (WHO, 1979). Dados sobre odinofagia também foram registrados.

As informações sobre a localização anatômica da(s) lesão(es) de mucosite oral e orofaríngea foram consideradas da seguinte forma: lábios, mucosa labial, comissura labial, mucosa jugal, vestíbulo bucal, soalho da boca, língua (borda lateral, dorso e ventre), trígono retromolar, palato duro/mole e orofaringe. A localização anatômica não foi analisada em termos do número de pacientes, mas sim em termos do número de lesões apresentadas, ou seja, o mesmo paciente pode ser acometido em mais de um sítio anatômico.

Todos os indivíduos incluídos receberam instruções abrangentes sobre higiene bucal, consistindo em escovação diária com cerdas macias e bochechos com digluconato de clorexidina 0,12% antes e durante a quimioterapia. Como padrão de atendimento no serviço, todos os pacientes também receberam fotobiomodulação profilática e terapêutica nas regiões oral e orofaríngea seguindo o protocolo previamente descrito por Nunes *et al*. (2020).

4.2.6 Avaliação da qualidade de vida, ansiedade e depressão

Os instrumentos foram administrados nos dias D0 e D15.

4.2.6.1 *Oral Health Impact Profile* (OHIP-14)

Foi utilizada a versão atual do OHIP-14 (ANEXO B) que possui sete domínios/dimensões, em 14 questões de impactos nas atividades diárias como resultado de problemas bucais: limitação funcional, dor física, desconforto psicológico, atividade física, deficiência psicológica e deficiência social. O índice fornece uma medida abrangente de disfunção, desconforto e incapacidade auto-relatados decorrentes de condições bucais, cujas dimensões são baseadas no modelo conceitual de saúde bucal de Locker *et al.* (2002). Os itens referem-se à frequência de eventos relacionados à saúde bucal. As respostas são avaliadas em uma escala Likert de 5 pontos: 0 = nunca; 1 = quase nunca; 2 = ocasionalmente; 3 = com bastante frequência; 4 = muito frequentemente/todos os dias. As pontuações do OHIP-14 podem variar de 0 a 56 e são calculadas pela soma dos valores ordinais dos 14 itens (SLADE, 1994). Para a escala, uma pontuação baixa indica uma boa qualidade de vida, enquanto uma pontuação alta indica pior qualidade de vida (BEZINELLI, 2016).

4.2.6.2 *World Health Organization Quality of Life* (WHOQOL-BREF)

Consiste na versão abreviada do questionário de qualidade de vida desenvolvido pela OMS, o WHOQOL-100. Baseia-se nos domínios saúde física, psicológico, relações sociais e ambiente. Dentro deste domínio são avaliadas diversas características associadas a qualidade de vida, como atividades diárias, mobilidade, dores e desconfortos, pensamentos positivos e negativos, relações pessoais, recursos financeiros, segurança e transporte. O questionário contém um total de 26 questões. Para fornecer uma avaliação ampla e abrangente, um item de cada uma das 24 facetas contidas no WHOQOL-100 foi incluído. Além disso, foram incluídos dois itens da faceta qualidade de vida geral e saúde geral. Os quatro escores de domínio denotam uma percepção individual de qualidade de vida em cada domínio particular. As pontuações do domínio são escaladas em uma direção positiva (i.e., pontuações mais altas denotam maior qualidade de vida). A pontuação média dos itens dentro de cada domínio é usada para calcular a pontuação do domínio. Os escores médios são então

multiplicados por 4 para tornar os escores dos domínios comparáveis aos escores usados no WHOQOL-100 (ANEXO C).

4.2.6.3 *Hospital Anxiety and Depression Scale* (HADS)

É um método de avaliação por meio de um questionário que possui 14 itens, sendo sete voltados para avaliação da ansiedade (HADS-A) e sete para a depressão (HADS-D). Cada um de seus itens pode ser pontuado de zero a três, perfazendo uma pontuação máxima de 21 pontos para cada escala (MARCOLINO, 2007; ZIGMOND; SNAITH, 1983) (ANEXO D).

4.2.7 Coleta de saliva

Amostras de saliva foram coletadas dos participantes em quatro momentos de avaliação clínica (D0, D3, D10 e D15), seguindo o protocolo de Gonçalves *et al*. (2015). Os pacientes foram instruídos a não comer ou beber líquidos 30 minutos antes do procedimento. Todas as coletas foram realizadas no período da manhã. A coleta da saliva não estimulada foi realizada em ambiente com luz artificial, com o paciente sentado com os olhos abertos, cabeça levemente inclinada para baixo, sem falar, abrir a boca ou deglutir a saliva durante o tempo da coleta, antes do atendimento clínico. Toda a saliva produzida, em um intervalo de 5 minutos, foi coletada em um tubo estéril milimetrado tipo Falcon. Imediatamente após a coleta, o material foi transportado em gelo, distribuídas em alíquotas e congeladas a -80°C. As amostras foram mantidas em Biorepositório conforme regulamentação vigente e descartadas após o término das análises.

4.2.7.1 ELISA

O ELISA (*enzyme-linked immunosorbent assay*) foi utilizado para quantificar os níveis de citocinas pró-inflamatórias na saliva, nomeadamente IL-1, IL-6, IL-8, TNF-α e TGF-β1. Os kits comerciais de ELISA foram utilizados de acordo com as instruções do fabricante (DuoSet® ELISA; R&D Systems, Minneapolis, MN, EUA). A densidade óptica

foi determinada em 450-nm usando um leitor FlexStation 3 Microplate (Molecular Devices, San Jose, CA, EUA).

4.2.7.2 Análise das NET

Para a quantificação das NET na saliva, foram utilizados o anticorpo anti-MPO e o kit de quantificação de DNA PicoGreen® dsDNA Assay Kit (Invitrogen, EUA). A co-localização do DNA extracelular com histonas, elastase de neutrófilos e mieloperoxidase confirmou as características clássicas das NET e foram determinadas por análise espectrofluorométrica (excitação de 484 nm e emissão de 520 nm) em leitor automatizado (OLIVEIRA *et al*., 2021). Foram comparadas as quantificações realizadas entre os tempos avaliados, relacionando-as com os parâmetros clínicos e sorológicos (contagem de neutrófilos) dos pacientes sob regimes antineoplásicos.

O kit de ensaio Quant-iT™ PicoGreen® dsDNA (Invitrogen, Carlsbad, CA, EUA) foi usado para quantificar os níveis das NET identificando o complexo mieloperoxidase (MPO)-DNA na saliva de acordo com o método publicado anteriormente (OLIVEIRA *et al*., 2021). Resumidamente, 50 µL de cada amostra foram colocados em uma placa preta de fundo transparente de 96 poços coberta com anticorpo anti-MPO (PA5-16672; diluição 1:500, Invitrogen, Carlsbad, CA, EUA). A quantidade de DNA ligado ao MPO foi quantificada com o kit Quant-iT™ PicoGreen®, de acordo com as instruções do fabricante. A intensidade da fluorescência (excitação em 488 nm e emissão em comprimento de onda de 525 nm) foi determinada com um FlexStation 3 Microplate Reader (Molecular Devices, San Jose, CA, EUA). Para todos os ensaios, dois poços replicados foram configurados para cada amostra.

4.2.8 Análise estatística

Foram utilizados os softwares *Statistical Package for the Social Sciences* (SPSS) (versão 25.0, Armonk, NY, EUA) e *GraphPad Prism* (versão 8.0, San Diego, CA, EUA). Os dados clínico-patológicos foram analisados de forma descritiva. O teste de Shapiro-Wilk demonstrou que os dados seguiram uma distribuição não normal. Assim, os dados não paramétricos foram submetidos ao teste de comparações múltiplas de Kruskal-

Wallis e ao teste de Mann-Whitney. O teste qui-quadrado (teste exato de Fisher e Pearson) foi usado para comparações intergrupos. O teste de Wilcoxon foi utilizado para avaliações dependentes. Os coeficientes de correlação de postos de Spearman foram calculados para determinar a força das correlações entre os questionários empregados. Os dados da matriz de correlação foram obtidos e analisados usando a linguagem de programação R (R Core Team, Viena, Áustria). Para todas as análises, o nível de significância foi adotado em $p<0,05$.

5 ARTIGOS

5.1 Capítulo 1: revisão sistemática sobre ansiedade e depressão de indivíduos em regimes antineoplásicos que desenvolveram mucosite oral. Os métodos e resultados são apresentados no manuscrito intitulado "***Association of anxiety and depression with oral mucositis: a systematic review***" que foi publicado no periódico *Oral Diseases* (fator de impacto: 4.06; ISSN: 1354-523X; estrato A1).

Association of anxiety and depression with oral mucositis: a systematic review

Abstract

Objective: Anxiety and depression are frequent conditions among individuals undergoing antineoplastic therapy, but their relationship with oral mucositis is unclear. This systematic review evaluated the potential association of anxiety and depression with frequency and severity of chemo/radiotherapy-induced oral mucositis.

Materials and Methods: Electronic searches were undertaken in five databases supplemented by manual scrutiny and gray literature searches in three other databases. The risk of bias was assessed using the Joanna Briggs Institute tool.

Results: Eight observational studies conducted on 954 individuals (male-to-female ratio: 1.1:1; age range: six-82 years). Three (37.5%) studies included patients with solid tumors, two (25%) studies included hematopoietic/lymphoid tissue tumors, and two (25%) studies comprised mixed types of malignant neoplasms. Eight different instruments were used to assess oral mucositis, while seven different instruments were used to evaluate anxiety and depression. Associations of anxiety and/or depression with oral mucositis severity were reported in six (75.0%) studies. Oral mucositis-related symptoms, especially pain, were linked with depression in three (37.5%) studies.

Conclusion: A relatively low number of cases and data heterogeneity hamper definitive conclusion about the potential association between anxiety/depression and oral mucositis. Further studies that could guide more personalized treatments are warranted to investigate this plausible bidirectional interaction.

Keywords: antineoplastic therapy; anxiety; depression; mental health; oral mucositis; psycho-oncology.

1. Introduction

Oral mucositis (OM) is a side effect associated with regimens of chemotherapy (CT), radiotherapy (RT), and chemoradiotherapy (CCRT) (Elad et al., 2020; Elad et al., 2022; Shetty et al., 2022). OM is characterized by erythematous and/or ulcerated lesions in the oral mucosa and oropharynx (Shetty et al., 2022; Villa & Sonis, 2020). The pathogenesis of OM comprises epithelial and submucosal injury, activation of pro-inflammatory pathways, and subsequent oral microbiota changes (Bowen et al., 2019; Elad et al., 2022; Villa & Sonis, 2015). The overall incidence of OM in individuals undergoing CT and/or RT varies from 60% to 90% (Cinausero et al., 2017; Pacheco, Cavacas, Mascarenhas, Oliveira, & Zagalo, 2021). The risk of developing OM is related to the volume of the organ exposed to irradiation, doses of melphalan and methotrexate (antineoplastic drugs), myeloablative conditioning therapy, and conventional RT (Wardill et al., 2020).

OM has been recognized as one of the most bothersome outcomes in patients undergoing antineoplastic therapy, as it increases the risk of systemic infections and causes pain requiring high doses of opioids and antimicrobials, enteral feeding, and extension of hospitalization (Elad et al., 2020; Elad et al., 2022; Sonis, 2021). Therefore, OM can increase treatment costs, morbidity, and mortality (Rodrigues-Oliveira et al., 2021). Furthermore, OM can lead to avoidance of social eating and social isolation (Pateman, Ford, Batstone, & Farah, 2015), affecting the general well-being of these patients with a direct impact on their quality of life (Al-Rudayni, Gopinath, Maharajan, & Menon, 2020). Current OM management focuses on relieving symptoms and reducing opportunistic infections (Elad et al., 2020). However, other aspects of the care of these patients, including behavioral or psychiatric symptoms, are overlooked.

The documented incidence of anxiety and depression among cancer patients is around 10.0% and 16.5%, respectively (Mitchell et al., 2011). Nevertheless, many patients with anxiety and depression are not properly diagnosed and the frequency of these symptoms within the context of OM may be underestimated (Chen, Lai, Liao, Lin, & Chang, 2010; Chen et al., 2015). OM can cause pain and psychological distress among other effects that might underlie the development of anxiety and depression (Dodd et al., 2001). Conversely, anxiety and depressive symptoms can worsen OM (Chaitanya et al., 2016; Dodd et al., 2001). Furthermore, these conditions share biological mechanisms (e.g., inflammation) that can ‘feed’ each other. A similar scenario

is observed in other oral diseases such as oral lichen planus, recurrent aphthous ulcers, and burning mouth syndrome (De Porras-Carrique, González-Moles, Warnakulasuriya, & Ramos-García, 2022; de Souza et al., 2012; Yang, Liu, Shi, & Zhang, 2018).

The purpose of the current systematic review was to investigate the link between anxiety/depression and OM among individuals undergoing antineoplastic therapy.

2. Materials and Methods

2.1 Eligibility criteria

The answer to the following question: “among individuals undergoing antineoplastic therapy, what is the frequency of anxiety and depression and their impact on the severity of OM?”, was investigated based on the PECO framework: P (population): participants who are undergoing or underwent antineoplastic therapy; E (exposure): anxiety and/or depression; C (comparison): not applicable; O (outcome): OM.

Inclusion criteria were as follows: observational studies (cross-sectional, case-control, and cohort) that analyzed the influence of signs and symptoms of anxiety and/or depression on the frequency of OM (between individuals with and without OM) or on the severity of OM (individuals with different grades of OM who received any antineoplastic therapy). No restrictions regarding language, geographic region, or publication period were imposed. When findings were apparently derived from the same study population, those most recently reported or those that provided more complete data were chosen. The use of the same population in different studies was determined by verifying the name and affiliation of the author(s), location where the study was conducted, source of participants, period of recruitment, and/or contacting the authors of the study if necessary.

Exclusion criteria were studies that mentioned OM but whose objective was not to analyze associations of its frequency/severity with anxiety and/or depression, investigations on quality of life (since, if there was any domain of emotional state, including depression and/or anxiety, the results would need to be disaggregated), as well as studies with subjective data derived from inconsistent methods applied to measure anxiety and/or depression (i.e., studies that did not use a validated assessment instrument or a consolidated psychometric scale). Review articles, case reports or case series, editorials, letters to the editor, expert opinions, book chapters,

conference/meeting abstracts, experimental animal studies, and *in vitro* studies were also excluded.

2.2 Information sources and search strategy

Electronic searches were undertaken in the following databases: PubMed (National Library of Medicine), Embase (Elsevier), Ovid (Wolters Kluwer), Scopus (Elsevier), and Web of Science (Clarivate Analytics) on March 22, 2022. The search schemes employed in databases with Boolean operators combining terms and keywords are described in **Supplementary File 1**. Adjustments were applied to the search scheme due to the specificity of each database. Gray literature searches were also performed through Open Grey, ProQuest, and Google Scholar, with the search limited to the first 200 hit records in each database (Haddaway, Collins, Coughlin, & Kirk, 2015). Additionally, a manual scrutiny was performed by cross-checking the reference lists of the included articles. Duplicate references across different databases were found and removed using the EndNote program (EndNote®, Clarivate Analytics, Toronto, Canada).

2.3 Selection process

Two authors (J.A.A.A. and F.V.H.) independently filtered the title abstracts. Articles with titles and abstracts that fulfilled the eligibility criteria were immediately included. The full text of articles without sufficient information in the titles/abstracts was retrieved to assist the two authors in independent arbitration about inclusion or exclusion. In the second step, two authors assessed the full texts and those meeting the eligibility criteria were included. Discrepancies were resolved by consensus or in a consultation with two senior authors (T.A.S. and R.A.M.).

2.4 Data collection process and items

Data from selected studies were extracted by one author (J.A.A.A.) and two senior authors (T.A.S. and R.A.M.) double-checked the extraction. The following items were collected: first author’s last name, country, year of publication, design, setting, sample size, participant recruitment method, baseline disease (type of malignancy or underlying disease that led to hematopoietic stem cell transplantation (HSCT), age and sex of participants, therapeutic regimen employed, grading system used for OM, instrument employed to measure anxiety and/or depression, outcome investigated, as

well as statistical analysis, overall results, direction of the effect (if statistically significant), and strength of the association. If further clarifications were necessary, authors were contacted via e-mail.

2.5 Study risk of bias assessment

Two authors (J.A.A.A. and L.G.A.) assessed the methodological quality of all studies using the Critical Appraisal Checklist (Moola, Munn, & Tufanaru, 2020) of the Joanna Briggs Institute from the University of Adelaide, Australia. The included studies were assessed according to the parameters of each type of study, i.e., cross-sectional and cohort. For each parameter, the included study was classified as “yes”, “no”, “unclear”, or “not applicable”. Possible discrepancies between the two authors were resolved by discussion with a third author (T.A.S.) until reaching a consensus.

2.6 Data analysis

Data were tabulated in Microsoft Office Excel 2019 (Microsoft® software, Redmond, WA, USA) and analyzed descriptively.

2.7 Protocol and registration

This systematic review was performed in compliance with the criteria proposed by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Page et al., 2021). A protocol was drafted and registered with the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/) under the registration number CRD42022328816.

3. Results

3.1 Study selection

The initial electronic search strategy yielded 1,332 records. No additional studies were identified through the manual search or the gray literature. After exclusion of duplicates, 790 references were screened based on title/abstract and 32 of those had their full text retrieved for analysis. Eight studies met the inclusion criteria (Chaitanya et al., 2016; Chen, Lai, Liao, Lin, & Chang, 2010; Chen et al., 2015; Cheng et al., 2011; Dodd et al., 2001; Fall-Dickson et al., 2008; Kushner et al., 2008; Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002). A flowchart depicting the search of

articles and the selection process is shown in **Figure 1**. **Supplementary File 2** shows all articles excluded after reading the full text, with their respective reasons for exclusion.

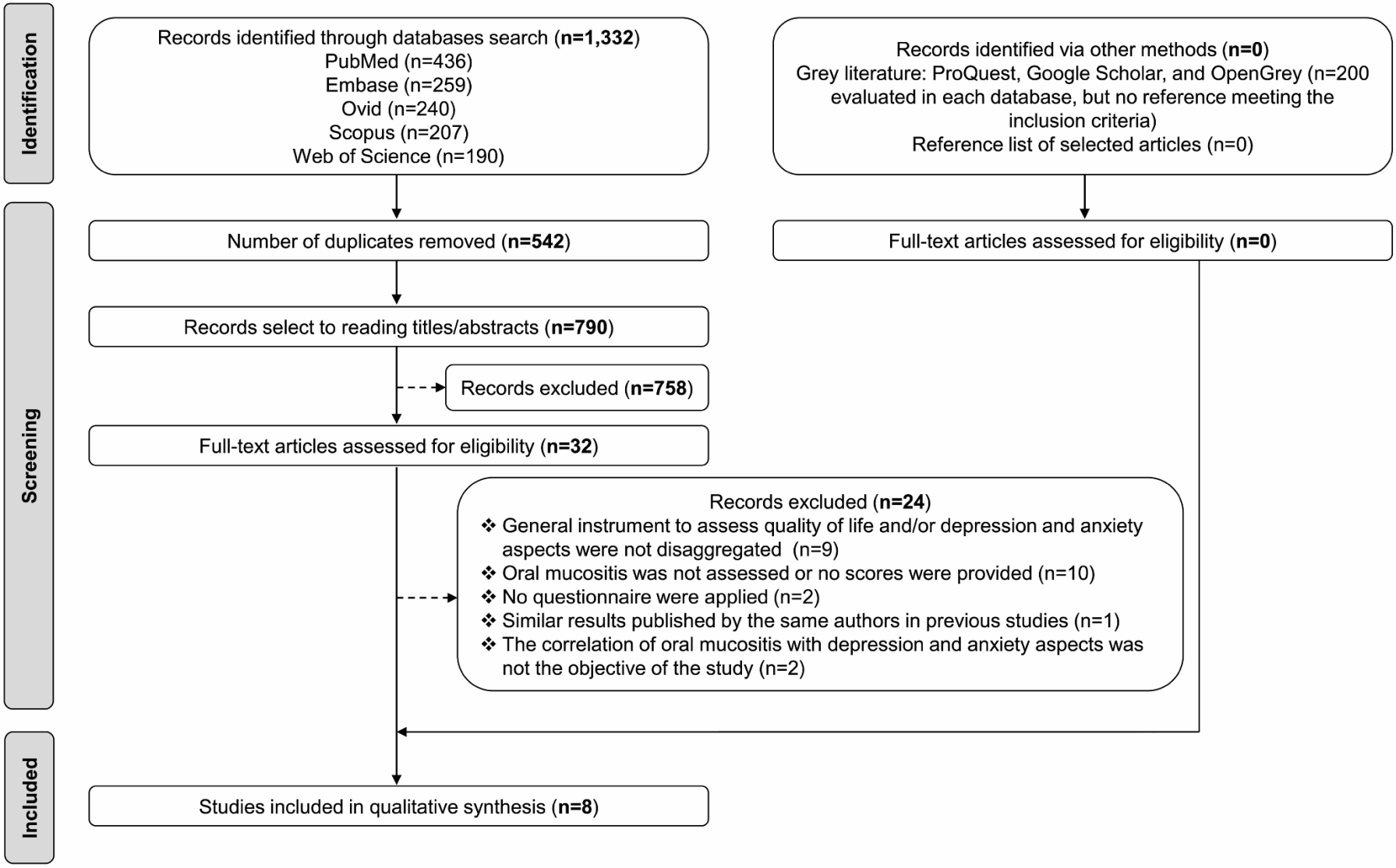

Figure 1 – Flowchart illustrating the search process.

3.2 Study characteristics

The characteristics of the included studies are summarized in **Table 1**. The studies were from the United States (Dodd et al., 2001; Fall-Dickson et al., 2008), Canada (Kushner et al., 2008), Germany (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002), Taiwan (Chen, Lai, Liao, Lin, & Chang, 2010; Chen et al., 2015), Hong Kong (Cheng et al., 2011), and India (Chaitanya et al., 2016). The studies were reported in English and published between 2001 and 2016.

A total of 954 participants were evaluated across all studies and the sample sizes ranged from 32 to 455 participants. The male-to-female ratio was 1.1:1. The mean/median age of the individuals was reported in seven studies and ranged from six to 82 years. With the exception of one study conducted on pediatric individuals (six to 18 years) (Cheng et al., 2011), the remainder included adults and older adults. Regarding underlying diseases, solid tumors were included as the only disease in three studies (Chen, Lai, Liao, Lin, & Chang, 2010; Chen et al., 2015; Fall-Dickson et al., 2008), whereas two reported individuals with different tumors of hematopoietic/lymphoid tissues (Kushner et al., 2008; Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002). Two studies reported patients with mixed types of malignant neoplasms (Dodd et al., 2001; Cheng et al., 2011). In one study, the description of malignant neoplasms was not provided (Chaitanya et al., 2016). The studies included regimens such as CT, RT, CCRT, or a combination of these. Only one did not identify which CT regimen had been employed for antineoplastic therapy (Kushner et al., 2008). In parallel with the regimen used in the treatment, mouthwashes with saline and sodium bicarbonate were reported, in addition to lip lubricants, ice chips, and candies or chewing gum used to stimulate saliva production (Cheng et al., 2011; Dodd et al., 2001; Fall-Dickson et al., 2008).

Table 1. Characteristics of source of patients, recruitment period, methods applied in the anamnesis, main results, and conclusions of the studies included in the present systematic review

Author(s)/year of publication and country	Study design/study sample	Baseline disease	Age (mean, range) and sex	Therapeutic regimen used (*n*)	Analysis/grading system for OM (*n*)	Instruments used to measure psychiatric/psychological disorders	Overall results and concluding remarks	
Dodd *et al.* (2001); USA	Longitudinal study: 77 participants from 23 private offices and outpatient clinics in community and teaching hospitals	Breast cancer: 45.4% Colorectal cancer: 29.9% Lung cancer: 5.2% NHL: 5.2% Other cancers: 14.3%	55 (NI) years ♂: 23 ♀: 54	CT: 77 *At least three cycles of doxorubicin, bleomycin, etoposide, fluorouracil, MTX, paclitaxel, or fludarabine*	OAG 28 participants developed OM and 49 did not Mean (± SD) score: 13.30±2.70 Mean (± SD) number of days to onset of OM: 20.20±15.80	POMS short form[1]	Participants with OM Time 1 (beginning of CT)/Time2 (during the 3rd cycle of CT; mean ± SD): *Anxiety:* 5.46±4.79/6.79±6.56 *Depression:* 3.43±4.76/7.57±8.23 *Anger:* 2.50±4.22/5.07±6.06 *Vigor:* 7.89±5.09/5.36±5.64 *Fatigue:* 7.54±5.86/11.54±5.85 *Confusion:* 4.22±4.42/4.57±5.45 *Total mood disturbance:* 15.26±20.40/30.18±28.58	Participants without OM Time 1 (beginning of CT)/Time 2 (during the 3rd cycle of CT; mean ± SD): *Anxiety:* 4.89±4.50/4.58±4.85 *Depression:* 3.69±5.25/4.31±5.82 *Anger:* 3.21±4.96/3.53±5.61 *Vigor:* 9.76±5.05/8.29±5.48 *Fatigue:* 5.19±4.67/7.69±5.23 *Confusion:* 2.75±3.15/3.15±3.48 *Total mood disturbance:* 9.98±20.54/14.97±24.71 **Concluding remarks:** Individuals who had OM experienced a significant increase in mood disturbances compared to those who did not experience OM. Individuals with OM reported higher levels of all six

							subscales and total scores of mood disorders than those without OM			
Schulz-Kindermann *et al*. (2002); Germany	Prospective longitudinal study: 63 participants from the BMT-center of a university hospital	AML: 22.2% ALL: 9.5% CML: 49.2% Myeloma: 12.7% Other: 6.4%	40.2 (19-61) years ♂: 41 ♀: 22	PBSCT: 12 BMT: 51 TBI (no/yes): 36/27 *(conditioning used: busulfan, cyclophosphamide, and/or melphalan)*	<u>Mucositis Index</u> <u>Mean (± SD, min-max) OM scores:</u> *Time 1:* 5.33±3.86 (0-16.00) *Time 2:* 13.90±5.14 (0-25.30) *Time 3:* 5.93±6.08 (0-23.00)	BDI[2] and NRS[3]	<u>Time 0 (prior to treatment; mean ± SD; min-max)</u> *BDI depression:* 7.25±4.88 (0-24.00)	<u>Time 1 (days 0 to +7 after BMT; mean ± SD; min-max)</u> *Anxious mood:* 1.47±1.39 (0-6.00) *Depressive mood:* 1.54±1.39 (0-6.00)	<u>Time 2 (days 8 to 14; mean ± SD; min-max)</u> *Anxious mood*: 1.47±1.47 (0-6.00) *Depressive mood:* 1.60±1.56 (0-6.00)	<u>Time 3 (days 15 to 21; mean ± SD; min-max)</u> *Anxious mood*: 1.62±1.51 (0-6.00) *Depressive mood:* 1.60±1.45 (0-6.00)
							Concluding remarks: BDI-depression contributed to the prediction of mouth pain in week 1 with positive correlations for depression (p=0.34)			
Fall-Dickson *et al*. (2008); USA	Descriptive, correlational, cross-sectional study: 32 participants from two urban national cancer institute-designed comprehensive cancer centers with established HSCT programs	Breast cancer: 100%	49.4 (32-64) years ♀: 32	SX + CT: 26 SX + CT + RT: 3 SX + CT + RT + HT: 1 SX + CT + HT: 2 *(conditioning used: doxorubicin, cyclophosphamide, paclitaxel,* cancer: *adriamycin, cytoxan, neo taxol, 5-FU, docetaxel, MTX)* *Tamoxifen:* 3 *BMT:* 0 *Peripheral blood:* 28	<u>OAG and OMI-20</u> 31/97% participants had OM <u>OAG mean (± SD) score:</u> 13.0±2.4) <u>Severity of OM (OMI-20):</u> 5.8 *Normal:* ~60.9% *Mild:* ~32.4% *Moderate:* ~5.1% *Severe:* ~1.4%	STAI[4] and BDI[2]	<u>Time 1:</u> The correlations between overall oral pain intensity (VAS) and state anxiety (r=-0.02) and trait anxiety (r=-0.13) were extremely weak and did not reach significance. Depression was correlated with state anxiety (r=0.42, p<0.05) and moderately correlated with trait anxiety (r=0.54, p<0.01) <u>Multiple regression analysis predicting overall intensity of OM-related acute oral pain</u> *OM severity:* R=0.831 (R^2=0.691; p=0.225) *Depression:* R=0.838 (R^2=0.702; p=0.325) *State anxiety:* R=0.839 (R^2=0.704; p=0.721) **Concluding remarks:** In the OM scenario, oral pain was not significantly correlated with state of anxiety or depression. Oral sensory and affective pain intensity most accurately predicted overall intensity of oral pain			

				BM + peripheral blood: 4						
Kushner *et al*. (2008); Canada	Longitudinal study: 34 participants from a referral hospital	ALL: 24% AML: 29% CML: 18% MS: 9% NHL: 6% Other hematological disorders: 15%	44.2 (23-61) years ♂: 20 ♀: 14	CT + TBI: 28 CT alone: 6	<u>VAS-OMAS (mean ± SD)</u> *Baseline:* 0 (13.9±3.6 at day 3) for erythema and 0 (11.3±4.3 at day 3) for ulceration *Day 7 after BMT:* 48.1±7.1 for erythema and 42.1±8.1 for ulceration *Day 14 after BMT:* 50.3±7.7 for erythema and 58.9±7.8 for ulceration *Day 21 after BMT:* 24.7±7.6 for erythema and 33.2±9.1 for ulceration *Day 28/discharge):* 23.5±7.8 for erythema and 30.2±10.1 for ulceration <u>PROMS (mean ± SD)</u> *Baseline:* 7.8±2.3 *Day 7 after BMT:* 44.7±5.1 *Day 14 after BMT:* 39.8±5.3 *Day 21 after BMT:* 28.7±6.5 *Day 28/discharge:* 9.2±1.9 *Day 60 after BMT:* 7.3±2.1	CES-D[5,6]	<u>CES-D (mean ± SD)</u> *Baseline:* 13.4±1.7 *Day 7:* 21.6±1.5 *Day 14:* 20.7±1.7 *Day 21:* 18.1±2.5 *Day 28/discharge:* 17.8±2.5 *Day 60:* 13.4±2.0 Spearman correlation coefficients between PROMS scores and CES-D scores during BMT treatment: *Day 7 after transplantation: p*=0.51 *Day 14 after transplantation: p*=0.39 *Day 21 after transplantation: p*=0.40 *Day28/discharge: p*=0.28 **Concluding remarks:** Although CES-D demonstrated minimal depressive symptoms at baseline, the PROMS scores were significantly correlated with symptoms of depression, consistent with the new instrument's discriminant validity and with the premise that symptoms of OM are powerful stressors compromising quality of life. This correlation was most pronounced on days 7 and 14		
Chen *et al.* (2010); Taiwan	Prospective study: 76 participants from one outpatient radiation department of a medical center	Oral cavity cancer: 100%	48.9 (30-71) years ♂: 70 ♀: 6	RT: 26 (mean total RT dose: 6291.85 cGy) CCRT: 50	<u>SSS</u> <u>Mean (±SD) OM scores:</u> *Time 1*: 3.20±1.9 *Time 2*: 5.37±2.40 *Time 3*: 7.29±2.38 *Time 4*: 2.81±1.68	HADS[7] – depression subscale	<u>Time 1 (pre-treatment; mean ± SD</u> *Depression:* 6.24±2.99 *RT only:* 5.75±3.62 *CCRT:* 6.44±2.71	<u>Time 2 (1 month after receiving RT/CCRT; mean ± SD)</u> *Depression:* 7.61±4.19 *RT only:* 6.75±3.77 *CCRT:*7.97±4.35	<u>Time 3 (2 months after receiving RT/CCRT; mean ± SD)</u> *Depression:* 9.70±4.06 *RT only:* 8.56±4.24 *CCRT:* 10.18±3.94	<u>Time 4 (3 months after receiving RT/CCRT; mean ± SD)</u> *Depression:* 4.91±3.43 *RT only:* 3.31±2.68 *CCRT:* 5.58±3.52

								Concluding remarks: The mean scores for levels of depression were moderate, with a score of 7 or higher at 1 month and 2 months after the beginning of RT. There was no significant difference in the levels of depression between the two treatment groups across time. Changes in patients' symptoms during the study period were positively correlated with changes in radiation dose and level of depression
Cheng *et al*. (2011); Hong Kong	Prospective cohort study: 140 participants from the children's cancer center of a university-affiliated hospital and two pediatric departments of two regional hospitals	Solid tumors: 44.3% Hematological malignancies: 55.7%	11.8 (6-18) years ♂: 88 ♀: 52	CT: 140 (*etoposide:* 18 *MTX:* 25 *Cytarabine:* 13 *Adriamycin:* 39 *Other anthracyclines:* 13 *Combined etoposide, MTX, cytarabine and/or adriamycin:* 32)	OMQD MTS-C (daily from day 1 to day 14) Absence of OM (<2): 83 participants Presence of OM (≥2): 57 participants; of these, 32 and 25 patients reported a maximum MTS score of 2 (non-severe OM) and 3-4 (severe OM) as the worst OM across 14 days, respectively. *Mean time to onset of OM after the beginning of CT*: 4.7±2.7 days *Mean duration of OM:* 6.3±4 days *Peak occurrence of OM:* 7.5±2.6 day	CSAS-C[8] short form	Time 1 (on day 1) *Mean (±SD; min-max) anxiety level of MTS<2:* 15.48±2.9 (14.84-16.11) *Mean (±SD; min-max) anxiety level of MTS≥2:* 18.18±3.4 (17.29-19.08) A higher level of anxiety (adjusted RR = 1.46; 95% CI = 1.23-1.73) was significantly associated with a higher probability of OM after controlling for the chemotherapy regimen (p<0.01). Multivariate ordinal logistic analysis, adjusted RR (95% CI) for mean anxiety level to predict AUC of the MTS groups: 1.37 (1.20–1.55). Cox proportional hazards regression analysis, hazard ratio (95% CI) for mean anxiety level to predict time in days to onset of MTS≥: 1.27 (1.18-1.37) **Concluding remarks:** The increased level of anxiety may be a risk factor for OM (after controlling for CT); however, anxiety was not reported to confound symptom reporting or assessment accuracy in OM
Chen *et al.* (2015); Taiwan	Longitudinal study: 77 participants from the head and neck outpatient radiation department of one medical center	Oral cavity cancer: 100%	51.6 (31-82) years ♂: 70 ♀: 7	RT: 33 (mean total RT dose: 6545.45 cGY) CCRT: 44	WHO Prevalence of severe OM: *RT only* *T0:* 0% *T1:* 0% *T2:* 12.1% *T3:* 63.6% *T4:* 69.7% *T5:* 84.8% *CCRT* *T0:* 2.3% *T1:* 6.8% *T2:* 27.3% *T3:* 59.1% *T4:* 84.1% *T5:* 90.9%	HADS[7] – depression subscale	Time 0 (RT began, day 1; mean ± SD) *Depression:* 6.69±3.53 *RT only:* 6.91±3.63 *CCRT:* 6.52±3.49 Time 4 (4-week after the beginning of RT; mean ± SD) *Depression:* 7.01±3.54 *RT only:* 7.11±3.42 *CCRT:* 6.86±3.66 Time 8 (8-week after the beginning of RT; mean ± SD) *Depression:* 7.92±3.71 *RT only:* 7.12±3.80 *CCRT:* 8.52±3.57 **Concluding remarks:** Changes in depression followed the slope of OM-related symptoms, with the lowest depression score at T0, peaking at T8, with statistically significant differences (p<0.001) among time points, especially from the beginning of RT

					T6: 87.9% *T7:* 45.5% *T8:* 3.0%	*T6:* 86.4% *T7:* 75.0% *T8:* 56.8%				
Chaitanya *et al*. (2016); India	Randomized cross-sectional study: 455 participants from outpatient and inpatient clinics of four hospitals	Cancer (NI): 100%	NI (20-80) years ♂: 187 ♀: 268	CT: 121 CCRT: 128 RT (within 14 days): 118 RT (after 14 days): 88	OM scale designed by the authors Prevalence of OM: *CT* *None:* 38.0 % *Mild:* 40.5 % *Moderate:*	*CCRT* *None:* 22.7 % *Mild:* 37.5 %	*RT (within 14 days)* *None:* 72.0 %	*RT (after 14 days)* *None:* 47.7 %	HADS[7]	Anxiety *Borderline:* n=181 *Abnormal:* n=149 *No anxiety:* n=125 Depression *Borderline:* n=140 *Abnormal:* n=234 *No anxiety:* n=81 Anxiety + depression: n=124 Borderline anxiety + established depression: n=89 Borderline anxiety + borderline depression: n=65 Borderline depression only: n=49 Borderline anxiety only: n=27 Established anxiety and borderline depression: n=23 Established depression only: n=21 Not anxious or depressed: n=56 Individuals undergoing RT (within 14 days since initiation of therapy) had established anxiety in 20/34 cases (58.8%). Group of individuals undergoing RT (14 days after initiation of therapy), 19/40 (47.5%) individuals had severe OM. In groups of individuals undergoing CT and CCRT, 25 (47.2%) and 20 (40%) patients with borderline anxiety had mild OM (p=0.01). Group RT (within 14 days of initiation of therapy) had established depression in 31/55 (56.4%) cases, followed by group RT (14 days after initiation of therapy) with 21/53 (39.6%) individuals revealing severe OM. In the CT and CCRT groups, mild OM was associated with abnormal depression and moderate OM was associated with established depression (p=0.02) **Concluding remarks:** Individuals who underwent RT 14 days after the sessions had severe OM and more pronounced anxiety and depression. However, they was closely followed by individuals undergoing CCRT and individuals undergoing RT (within 14 days), but less observed in the group of individuals undergoing CT

21.5 %	*Mode rate:* 39.8 %	*Mild:* 22.9 % *Mode rate:* 5.1%	*Mild:* 27.3 % *Mode rate:* 25.0 %

Note: 5-FU, 5-fluorouracil; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; AUC, area under the ROC curve; BDI, Beck Depression Inventory; BMT, bone marrow transplantation; CCRT, concurrent chemoradiation therapy; CES-D, Center for Epidemiologic Studies Depression; CI, confidence interval; CML, chronic myeloid leukemia; CSAS-C, Chinese version of the State Anxiety Scale for Children; CT, chemotherapy; HADS, Hospital Anxiety and Depression Scale; HSCT, hematopoietic stem cell transplantation; HT, hormonal therapy; max, maximum; min, minimum; MS, myelodysplastic syndrome; MTS, Mouth and Throat Soreness; MTX, methotrexate; NHL, non-Hodgkin lymphoma; NI, not informed; NRS, Numerical Rating Scale; OAG, Oral Assessment Guide; OM, oral mucositis; OMI-20, Oral Mucositis Index-20; OMQD MTS-C, Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire; PBSCT, peripheral blood stem cell transplantation; POMS, Profile of Mood States; PROMS, Patient-Reported Oral Mucositis Symptom; RR, relative risk; RT, radiotherapy; SD, standard deviation; SSS, Symptoms Severity Scale; STAI, State-Trait Anxiety Inventory; SX, surgery; TBI, total body irradiation; VAS, Visual Analog Scale; VAS-OMAS, Visual Analog Scale-Oral Mucositis Assessment Scale; WHO, World Health Organization.

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3.3 Results of individual studies

3.3.1 OM assessment/grading system and follow-up period

The following scales for OM assessment were used: the Oral Assessment Guide (OAG) plus the Oral Mucositis Index-20 (OMI-20) in one study (12.5%) (Fall-Dickson et al., 2008), the Visual Analog Scale - Oral Mucositis Assessment Scale (VAS-OMAS) plus the Patient-Reported Oral Mucositis Symptom (PROMS) in another study (12.5%) (Kushner et al., 2008). Five studies used one scale: the World Health Organization (WHO) (Chen et al., 2015), the Mucositis Index (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002), the OAG (Dodd et al., 2001), the Mouth and Throat Soreness-Related Questions of the Oral Mucositis Daily Questionnaire (OMQD MTS-C) (Cheng et al., 2011), and the Symptom Severity Scale (SSS) (Chen, Lai, Liao, Lin, & Chang, 2010) (12.5% for each). One study assessed OM using its own scale (12.5%) (Chaitanya et al., 2016). Six (75.0%) of the eight studies described the calibration of the researchers responsible for assessing the OM grades (Chen et al., 2015; Chen, Lai, Liao, Lin, & Chang, 2010; Cheng et al., 2011; Fall-Dickson et al., 2008; Kushner et al., 2008; Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002).

One study evaluated the oral mucosa once at baseline and updated with the CT cycle (Dodd et al., 2001). Another evaluated it daily from day 1 to day 14 (Cheng et al., 2011), while another study assessed it once within the antineoplastic therapy regimen (but did not specify the day) (Chaitanya et al., 2016). In one study, OM was assessed at three time points (before RT and then 4 and 8 weeks after initiation of RT) (Chen, Lai, Liao, Lin, & Chang, 2010). Another study evaluated the oral mucosa at nine time points: baseline (before RT) and 1, 2, 3, 4, 5, 6, 7, and 8 weeks after initiation of RT (Chen et al., 2015). Among the studies that included patients undergoing bone marrow transplantation (BMT)/HSCT, one evaluated the OM of individuals at three-time points (days 0 to +7 after BMT, days 8 to 14, and days 15 to 21) (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002), another assessed it on day +7 (±24 hours) (Fall-Dickson et al., 2008), and still another evaluated OM at seven time points (baseline, days 7, 14, 21, 28/discharge, and day 60) (Kushner et al., 2008).

3.3.2 Instruments used to measure anxiety and depression disorders

Three (37.5%) investigations relied on the Hospital Anxiety and Depression Scale (HADS) (Chaitanya et al., 2016; Chen et al., 2015; Chen, Lai, Liao, Lin, & Chang, 2010) and two (25.0%) on the Beck Depression Inventory (BDI) (Fall-Dickson et al., 2008;

Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002). Two studies also used a second tool, namely the Numerical Rating Scales (NRS) (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002) and the State-Trait Anxiety Inventory (STAI) (Fall-Dickson et al., 2008), respectively. Other studies (n=3; 12.5% for each) employed the following instruments: the Profile of Mood States (POMS) (Dodd et al., 2001), the Center for Epidemiologic Studies Depression (CES-D) (Kushner et al., 2008), and the short form of the Chinese version of the State Anxiety Scale for Children (CSAS-C) (Cheng et al., 2011).

Regarding the frequency of the instruments used, one study evaluated the patients prior to treatment, on days 0 to +7 after BMT, on days 8 to 14, and on days 15 to 21 (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002). Another study assessed patients at baseline and on days 7, 14, 21, 28/discharge, and 60 (Kushner et al., 2008). One study assessed individuals during pre-treatment and 1, 2, and 3 months after receiving antineoplastic therapy (Chen, Lai, Liao, Lin, & Chang, 2010), while another evaluated individuals when antineoplastic therapy was started (day 1) and at 4 and 8 weeks after initiation of the antineoplastic regimen (Chen et al., 2015). An investigation evaluated individuals at two time points: the beginning of CT and during the third cycle of CT (Dodd et al., 2001). Of the other three studies, one reported that data were collected on day +7 (±24 hours) (Fall-Dickson et al., 2008), another collected them once (day 1) (Cheng et al., 2011), and the third also applied the instrument once within the antineoplastic therapy regimen, but did not provide information on the specific day (Chaitanya et al., 2016).

3.3.3 OM related to anxiety and/or depression disorders

One study found an association between CT and CCRT regimens, anxiety, and mild OM (p=0.01). Also, CT and CCRT regimens were associated with mild OM and depression, while moderate OM was associated with depression (p=0.02) (Chaitanya et al., 2016). Another study found that an increased level of anxiety may be a risk factor for CT-related OM, but anxiety was not perceived as a confounder for symptom reporting and assessment accuracy in OM (Cheng et al., 2011). Among individuals undergoing CT regimens, those who had OM experienced a significant increase in mood disorders, including anxiety and depression, compared to those who did not have OM (Dodd et al., 2001). Regarding individuals undergoing BMT/HSCT, a study showed that OM scores

were significantly correlated with symptoms of depression, especially on days 7 (p=0.51) and 14 (p=0.39) after the beginning of antineoplastic regimens (Kushner et al., 2008).

In patients undergoing RT, changes in depression symptoms were observed after a substantial increase of OM-related symptoms (e.g., mouth pain, dry mouth, eating difficulties, swallowing difficulties, taste changes, and speech difficulties), with the lowest depression score at baseline and a later peak at 8 weeks (p<0.001) (Chen et al., 2015). Another investigation found no differences in changes of symptom severity in individuals who received RT or CCRT, but patients in the CCRT group tended to have depression, with a peak in severity at 2 and 3 months after the initiation of RT. Changes in OM symptoms over the study period were positively correlated with changes in radiation dose (p<0.0001) and level of depression (p<0.0001) (Chen, Lai, Liao, Lin, & Chang, 2010).

While one study demonstrated that depression contributed to oral pain at the beginning of the antineoplastic regimen (p=0.34) (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002), another found that oral pain was not significantly correlated with anxiety or depression (Fall-Dickson et al., 2008).

3.4 Risk of bias in individual studies

Of the two cross-sectional studies included, only one presented an issue about the objective and standard criteria used for measurement of the condition studied (i.e., the authors did not use a validated instrument to assess OM) and also did not provide information on the identified confounding factors **(Supplementary File 3; Figure 2A)**. The major methodological issues of the cohort studies involved the lack of similarity in the allocation of participants to the two groups studied, confounding factors, and strategies employed to address incomplete follow-up **(Supplementary File 4; Figure 2B)**.

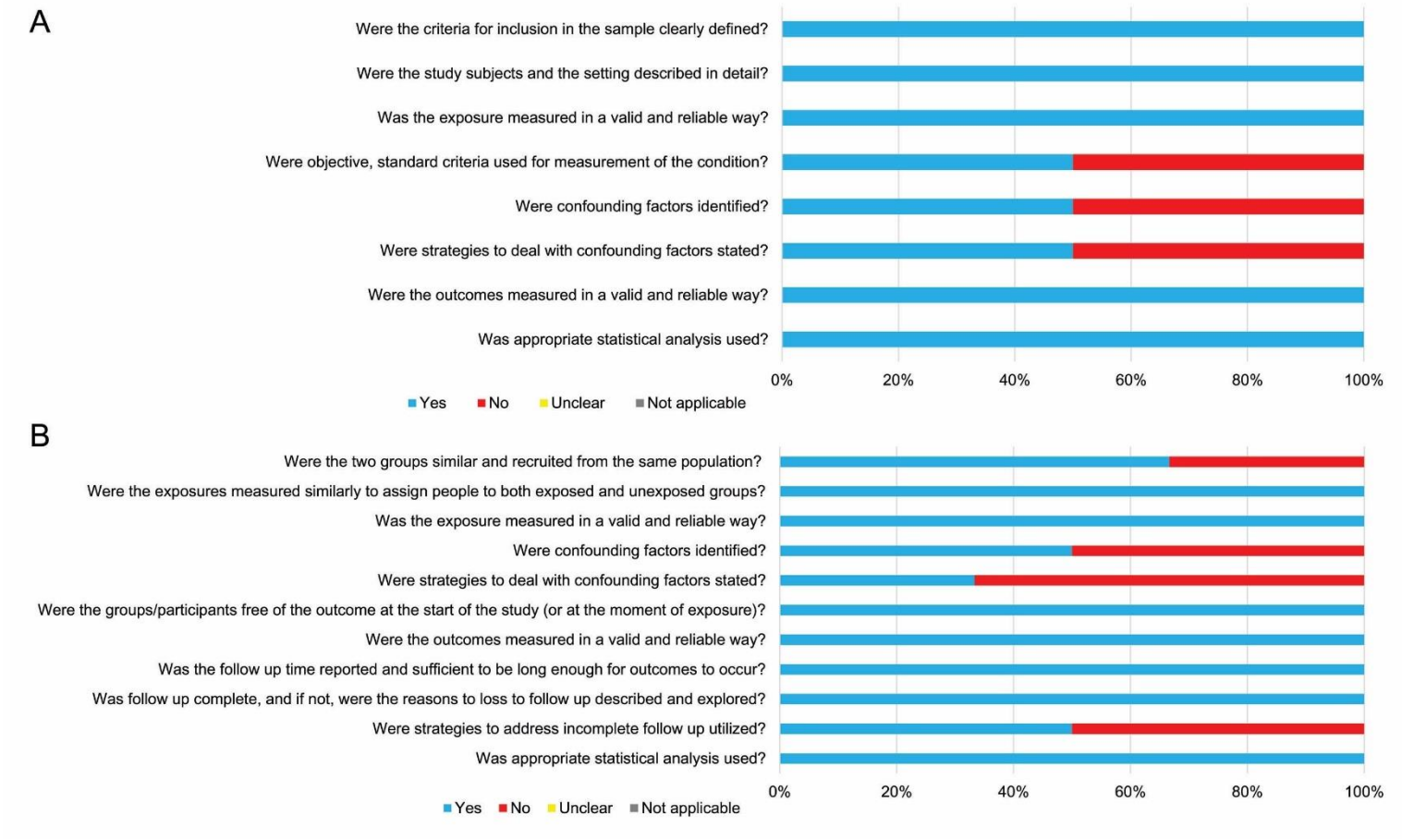

Figure 2 – Quality assessment of the included **(A)** cross-sectional and **(B)** cohort studies.

4. Discussion

The eight observational studies included in this systematic review reported heterogeneous data regarding clinicodemographic aspects, antineoplastic regimens, and methods of assessment of exposure and outcome. Associations of anxiety and/or depression with the severity of OM were pointed out in 75.0% of the studies (Chaitanya et al., 2016; Chen, Lai, Liao, Lin, & Chang, 2010; Chen et al., 2015; Cheng et al., 2011; Dodd et al., 2001; Kushner et al., 2008). Based on the limited data available, we could not draw definite conclusions about this intriguing and complex relationship.

While anxiety and depressive disorders tend to have a long-term course, the related symptoms may fluctuate over time depending on multiple factors, including general health and psychosocial stressors, among others (Wang, Ding, Yang, Hao, & Wang, 2020). For instance, distress symptoms (e.g., pain, nausea/vomiting, dyspnea, and lack of appetite) and anxiety and depression appear to be associated with cancer-related fatigue (Oh & Seo, 2011). A relationship between fatigue and OM was observed among patients undergoing chemotherapy (Dodd et al., 2001). Likewise, a third of adults with cancer have difficulty performing basic activities of daily living (Neo, Fettes, Gao, Higginson, & Maddocks, 2017). This has been linked to depression symptoms, particularly in the onco-geriatric patients (Couderc et al., 2022). In cases in which patient's food intake is unfeasible due to the severity of the OM, the patient may receive tube or parenteral feeding, which impact on the quality of life of patients (Ojo, Keaveney, Wang, & Feng, 2019). Importantly, the literature on OM does not clearly disentangle symptoms from disorders, partly explaining the current findings. The levels of anxiety and depression symptoms fluctuate during the antineoplastic treatment according to the severity of OM, implying that these symptoms occur in response to OM (Chaitanya et al., 2016; Chen et al., 2015). Pain is a major feature of OM. Besides causing psychological distress, pain shares neurobiological mechanisms with psychiatric disorders (Goesling, Clauw, & Hassett, 2013). Within these circumstances, OM-induced pain might be a trigger of psychiatric symptoms (Dodd et al., 2001; Jehn et al., 2019). Thus, the adoption of a holistic approach in the context of a multidisciplinary team of healthcare providers allows for support in the physical and mental aspects of the disabling process, avoiding a focus restricted to the disease or injury (Elad et al., 2020; Elad et al., 2022; Zadik et al., 2019).

On the contrary, a bi-directional Mendelian randomization analysis revealed significant effects of psychiatric features, including major depressive disorder, on

mouth ulcers in the European population (Wang, Ding, Yang, Hao, & Wang, 2020). This latter observation is supported by studies with other oral diseases whose course is influenced by the presence of psychiatric disorders (De Porras-Carrique, González-Moles, Warnakulasuriya, & Ramos-García, 2022; Yang, Liu, Shi, & Zhang, 2018). Furthermore, compelling evidence indicates that a key factor for the appearance of anxiety and depression in the population undergoing antineoplastic therapy is the presence of pre-existing mental health problems (Niedzwiedz, Knifton, Robb, Katikireddi, & Smith, 2019).

As mentioned above, symptoms of anxiety and/or depression in cancer patients can be influenced by multiple factors, including, but not limited to, individual aspects, social and contextual factors, and antineoplastic treatment (Baliousis, Rennoldson, & Snowden, 2016; Niedzwiedz, Knifton, Robb, Katikireddi, & Smith, 2019). Specific antineoplastic regimens increase the severity of anxiety and/or depression disorders more often than other treatments (Anderson et al., 2021; de Farias Gabriel et al., 2022; Wardill et al., 2020). It remains to be investigated whether these same regimens affect the incidence and/or severity of OM compared to others.

Individuals with OM are rarely evaluated by mental health professionals even if a change in their emotional state is confirmed (Chaitanya et al., 2016; Chen, Lai, Liao, Lin, & Chang, 2010; Chen et al., 2015; Cheng et al., 2011). Given their potential impact on quality of life and even course of the disease, recognition and treatment of psychiatric symptoms should be a priority. Of note, psychological intervention, particularly cognitive behavioral therapy, has been effective in improving the anxiety and depression symptoms of cancer patients (Osborn, Demoncada, & Feuerstein, 2006). The definition of an algorithm model for cancer treatment including anxiety/depression diagnosis and OM assessment risk is needed (Al-Rudayni, Gopinath, Maharajan, & Menon, 2020; Owen, Klapow, Hicken, & Tucker, 2001; Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002).

Previous studies have examined the psychometric properties of existing tools used to screen anxiety and depression in patients undergoing antineoplastic therapy (Mahakwe, Johnson, Karlsson, & Nilsson, 2021; Shunmugasundaram, Rutherford, Butow, Sundaresan, & Dhillon, 2020; Vodermaier & Millman, 2011; Vodermaier, Linden, & Siu, 2009; Yeh, Chung, Hsu, & Hsu, 2014). In general, HADS is the instrument most frequently employed for anxiety and depression assessment in individuals diagnosed with cancer (Vodermaier & Millman, 2011). Studies have

demonstrated that severe OM was associated with higher HADS scores among patients at the beginning (Chaitanya et al., 2016) and at the end of RT (Chen et al., 2015). Also, the BDI, a self-reported depression scale, has adequate reliability and validity and is feasible for evaluating patients with cancer (Pettersson, Boström, Gustavsson, & Ekselius, 2015; Vodermaier, Linden, & Siu, 2009). Although a low mean score on the BDI depression scale was observed in patients undergoing high-dose CT for BMT/PBSCT, significant association of BDI with pain and OM was seen in the first weeks of treatment (Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002). Other instruments have been used to measure anxiety and/or depression in the population at risk for OM, including the POMS short form, NRS, STAI, CES-D, and CSAS-C. A recent systematic review indicated that HADS, BDI, CES-D, and quick inventory of depressive symptomatology self-report (QIDS-SR) were the measures most frequently used to identify anxiety and/or depression in individuals diagnosed with head and neck cancer (Shunmugasundaram, Rutherford, Butow, Sundaresan, & Dhillon, 2020). Each scale has its particularities that may restrain the researcher and clinician from using it in the cancer population as opposed to the general population (Shunmugasundaram, Rutherford, Butow, Sundaresan, & Dhillon, 2020). As such, for the assessment of anxiety through a self-reported instrument, the STAI has been found to be satisfactorily applicable to adults with OM undergoing autologous HSCT (Fall-Dickson et al., 2008).

Of clinical relevance, recent literature has indicated salivary molecules (e.g., cortisol, melatonin, α-amylase) as auxiliary factors in the diagnosis of stress, anxiety or depression (Chojnowska, Ptaszyńska-Sarosiek, Kępka, Knaś, & Waszkiewicz, 2021). Furthermore, salivary and serum biomarkers (e.g., epidermal growth factor, C-reactive protein) have also been suggested as tools for the assessment of OM risk (Normando et al., 2017). Future studies should link these sets of salivary/serum biomarkers defining shared and/or overlapping pathophysiological mechanisms.

Although the strength of this review relies on the search performed in multiple databases and in the gray literature, caution should be taken when interpreting its results. There are few studies specifically investigating anxiety and depression within the context of antineoplastic-induced OM. Sample sizes were small and the confidence intervals were large, resulting in uncertainty about the magnitude of effect (Visentin, Cleary & Hunt, 2020). There was also a high degree of data heterogeneity among included studies regarding clinical parameters, psychometric instruments and

antineoplastic therapeutic regimens (Cheng et al., 2011; Kushner et al., 2008; Schulz-Kindermann, Hennings, Ramm, Zander, & Hasenbring, 2002), making meta-analysis unfeasible. Furthermore, the identification of anxiety and depression relied on self-report questionnaires and not on formal psychiatric assessment. Finally, most studies were conducted in high-income countries and the setting was largely restricted to academic centers, precluding the generalizability of the results.

5. Conclusion

In summary, patients undergoing antineoplastic regimens are vulnerable to anxiety and depression. OM causes and/or aggravates these symptoms by inducing pain and worsening patients' perception of their quality of life. Moreover, the effects of psychiatric disorders increasing the susceptibility to OM cannot be ruled out. The bidirectional relationship between anxiety/depression and OM remains to be fully understood, and further mechanistic and longitudinal studies with standardized instruments, larger samples, and appropriated control groups are warranted.

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Supplementary files

Association of anxiety and depression with oral mucositis: a systematic review

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Supplementary File 1. Search strategy employed to identify articles in electronic databases

PubMed, Web of Science, and Ovid	(oral mucositis OR stomatitis OR stomatitides OR oral mucositides OR oromucositis OR oromucositides) AND (depression OR depressive OR depressive disorder OR emotional OR anxiety disorder OR anxiety OR anxieties OR angst OR hypervigilance OR nervousness OR anxiousness OR mania OR psychosis OR bipolar disorder OR schizophrenia OR neurocognitive disorder OR delirium)
Scopus	(“oral mucositis”) AND (depression OR depressive OR “depressive disorder” OR emotional OR “anxiety disorder” OR anxiety OR anxieties OR angst OR hypervigilance OR nervousness OR anxiousness OR mania OR psychosis OR “bipolar disorder” OR schizophrenia OR “neurocognitive disorder” OR delirium)
Embase	(“oral mucositis” OR stomatitis OR stomatitides OR “oral mucositides” OR oromucositis OR oromucositides) AND (depression OR depressive OR “depressive disorder” OR emotional OR “anxiety disorder” OR anxiety OR anxieties OR angst OR hypervigilance OR nervousness OR anxiousness OR mania OR psychosis OR “bipolar disorder” OR schizophrenia OR “neurocognitive disorder” OR delirium)

Supplementary File 2. Articles excluded with reasons for exclusion after reading the full text

Articles	Reasons for exclusion
1. Syrjala KL, Chapko ME. Evidence for a biopsychosocial model of cancer treatment-related pain. Pain. 1995;61(1):69-79	The main outcome analyzed was cancer-related pain. Oral mucositis was not assessed. Anxiety and depression were not assessed as independent outcomes
2. Zaniboni A, Labianca R, Marsoni S, et al. GIVIO-SITAC 01: A randomized trial of adjuvant 5-fluorouracil and folinic acid administered to patients with colon carcinoma--long term results and evaluation of the indicators of health-related quality of life. Gruppo Italiano Valutazione Interventi in Oncologia. Studio Italiano Terapia Adiuvante Colon. Cancer. 1998;82(11):2135-2144	A general quality of life questionnaire was employed. The emotional domain was assessed, but data on anxiety and depression were not disaggregated
3. Moinpour CM, Sawyers Triplett J, McKnight B, et al. Challenges posed by non-random missing quality of life data in an advanced-stage colorectal cancer clinical trial. Psychooncology. 2000;9(4):340-354	A general quality of life questionnaire was employed. The emotional domain was assessed, but data on anxiety and depression were not disaggregated. No grading of oral mucositis was provided
4. Goldberg SL, Chiang L, Selina N, Hamarman S. Patient perceptions about chemotherapy-induced oral mucositis: implications for primary/secondary prophylaxis strategies. Support Care Cancer. 2004;12(7):526-530	No questionnaire was applied. Evaluation of anxiety was not performed with an appropriate psychometric instrument
5. Cheng KK. Oral mucositis and quality of life of Hong Kong Chinese patients with cancer therapy. Eur J Oncol Nurs. 2007;11(1):36-42	A general quality of life questionnaire was employed. Anxiety and depression were not assessed
6. Brown CG, McGuire DB, Peterson DE, Beck SL, Dudley WN, Mooney KH. The experience of a sore mouth and	No scale for anxiety and depression was used

associated symptoms in patients with cancer receiving outpatient chemotherapy. Cancer Nurs. 2009;32(4):259-270	
7. Chen AM, Jennelle RL, Grady V, et al. Prospective study of psychosocial distress among patients undergoing radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys. 2009;73(1):187-193	Oral mucositis was not assessed
8. Molassiotis A, Brearley S, Saunders M, et al. Effectiveness of a home care nursing program in the symptom management of patients with colorectal and breast cancer receiving oral chemotherapy: a randomized, controlled trial. J Clin Oncol. 2009;27(36):6191-6198	This was a clinical trial study. No grading of oral mucositis was provided
9. Kim JW, Cha Y, Kim SJ, et al. Association of oral mucositis with quality of life and symptom clusters in patients with solid tumors receiving chemotherapy. Support Care Cancer. 2012;20(2):395-403	A general quality of life questionnaire was employed. The emotional domain was assessed, but data on anxiety and depression were not disaggregated
10. Oton-Leite AF, Corrêa de Castro AC, Morais MO, Pinezi JC, Leles CR, Mendonça EF. Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. Head Neck. 2012;34(3):398-404	Oral mucositis was not assessed along with anxiety domain
11. Chen SC, Lai YH, Liao CT, et al. Supportive care needs in newly diagnosed oral cavity cancer patients receiving radiation therapy. Psychooncology. 2013;22(6):1220-1228	Oral mucositis was not assessed along with anxiety and depression domains

12. Likhacheva A, Jhingran A, Bodurka DC, Sun C, Sam M, Eifel PJ. Prospective study of symptom assessment among patients with cervical cancer during concurrent chemoradiotherapy with weekly cisplatin or every-3-week cisplatin and 5-fluorouracil. Int J Gynecol Cancer. 2013;23(8):1520-1527	Oral mucositis was not assessed
13. Loo WT, Liu Q, Yip MC, et al. Status of oral ulcerative mucositis and biomarkers to monitor posttraumatic stress disorder effects in breast cancer patients. Int J Biol Markers. 2013;28(2):168-173	The emotional domain was assessed, but data on anxiety and depression were not disaggregated
14. Ip WY, Epstein JB, Lee V, et al. Oral mucositis in paediatric patients after chemotherapy for cancer. Hong Kong Med J. 2014;20 Suppl 7:4-8	Similar results published by the authors in previous studies (Cheng KK, Lee V, Li CH, et al. Impact of oral mucositis on short-term outcomes in paediatric and adolescent patients undergoing chemotherapy. Support Care Cancer. 2013;21:2145-52; Cheng KK, Lee V, Li CH, et al. Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. Oral Oncol. 2011;47:153-162)
15. Murthy V, Kumar DP, Budrukkar A, Gupta T, Ghosh-Laskar S, Agarwal J. Twice-weekly palliative radiotherapy for locally very advanced head and neck cancers. Indian J Cancer. 2016;53(1):138-141	No questionnaire was applied. Evaluation of anxiety was not performed with an appropriate psychometric instrument
16. Huang BS, Wu SC, Lin CY, Fan KH, Chang JT, Chen SC. The effectiveness of a saline mouth rinse regimen and education programme on radiation-induced oral mucositis and quality of life in oral cavity cancer patients: A	A general quality of life questionnaire was employed. The socio-emotional domain was assessed, but data on anxiety and depression were not disaggregated

randomised controlled trial. Eur J Cancer Care (Engl). 2018;27(2):e12819	
17. Yenugadhati N, Albalawi AN, Qureshey AT, et al. Associated factors for oral health problems in a sample of Saudi cancer patients. Cancer Manag Res. 2018;10:1285-1293	Oral mucositis was not assessed
18. Jehn P, Stier R, Tavassol F, et al. Physical and psychological impairments associated with mucositis after oral cancer treatment and their impact on quality of life. Oncol Res Treat. 2019;42(6):342-349	Oral mucositis was subjectively evaluated; no grading of oral mucositis was provided
19. Willershausen I, Schmidtmann I, Azaripour A, Kledtke J, Willershausen B, Hasenburg A. Association between breast cancer chemotherapy, oral health and chronic dental infections: a pilot study. Odontology. 2019;107(3):401-408	Oral mucositis was not assessed
20. Oba MK, Innocentini LMAR, Viani G, et al. Evaluation of the correlation between side effects to oral mucosa, salivary glands, and general health status with quality of life during intensity-modulated radiotherapy for head and neck cancer. Support Care Cancer. 2021;29(1):127-134	A general quality of life questionnaire was employed
21. Reeve BB, McFatrich M, Mack JW, et al. Validity and reliability of the pediatric patient-reported outcomes version of the Common Terminology Criteria for Adverse Events. J Natl Cancer Inst. 2020;112(11):1143-1152	The correlation of oral mucositis with depression and anxiety aspects was not the objective of the study
22. Das S, Lahiri D, Dam A, et al. Definitive concurrent chemoradiation versus laryngectomy and postoperative	A general quality of life questionnaire was used. Oral mucositis was not assessed along with the quality of life questionnaire

radiation using IMRT in locally advanced laryngeal cancer: experience from a regional cancer centre of Eastern India. J Radiother Pract. 2021;20(1):71-77	
23. Yang P, Liu J, Yong H, Ma J, Gao X. Effect of cetuximab combined with IMRT and concurrent chemotherapy in treating locally advanced nasopharyngeal carcinoma. J BUON. 2021;26(1):138-144	A general quality of life questionnaire was employed. The emotional domain was assessed, but data on anxiety and depression were not evaluated
24. Yuce Sari S, Beduk Esen CS, Yazici G, Yuce D, Cengiz M, Ozyigit G. Do grape and black mulberry molasses have an effect on oral mucositis and quality of life in patients with head and neck cancer? Support Care Cancer. 2022;30(1):327-336	A general quality of life questionnaire was employed. The emotional domain was assessed, but data on anxiety and depression were not disaggregated

Supplementary File 3. Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies

Author(s) (year of publication)	**Items**							
	Were the criteria for inclusion in the sample clearly defined?	*Were the study subjects and the setting described in detail?*	*Was the exposure measured in a valid and reliable way?*	*Were objective, standard criteria used for measurement of the condition?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the outcomes measured in a valid and reliable way?*	*Was appropriate statistical analysis used?*
Fall-Dickson *et al*. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chaitanya *et al*. (2016)	Yes	Yes	Yes	No	No	No	Yes	Yes

Supplementary File 4. Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies

Author(s) (year of publication)	**Items**										
	Were the two groups similar and recruited from the same population?	*Were the exposures measured similarly to assign people to both exposed and unexposed groups?*	*Was the exposure measured in a valid and reliable way?*	*Were confounding factors identified?*	*Were strategies to deal with confounding factors stated?*	*Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?*	*Were the outcomes measured in a valid and reliable way?*	*Was the follow up time reported and sufficient to be long enough for outcomes to occur?*	*Was follow up complete, and if not, were the reasons for loss to follow up described and explored?*	*Were strategies to address incomplete follow up utilized?*	*Was appropriate statistical analysis used?*
Dodd *et al*. (2001)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Schulz-Kinderman n *et al*. (2002)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Kushner *et al*. (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chen *et al*. (2010)	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Cheng *et al*. (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Chen *et al*. (2015)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes

5.2 Capítulo 2: análise do perfil de citocinas pró-inflamatórias e a formação de redes extracelulares de neutrófilos em amostras salivares de pacientes submetidos à quimioterapia e associações com mucosite oral. Os métodos e resultados são apresentados no manuscrito intitulado ***"Salivary cytokine profile and neutrophil extracellular traps in patients with chemotherapy-induced oral mucositis"*** e serão submetidos ao periódico *Supportive Care in Cancer* (fator de impacto: 3.1; ISSN: 0941-4355; estrato A2).

Salivary cytokine profile and neutrophil extracellular traps in patients with chemotherapy-induced oral mucositis

Abstract

Purpose: Inflammation plays a crucial role in the pathogenesis of oral mucositis (OM). This study examined the profile of salivary pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, and TGF-β1) and the formation of neutrophil extracellular traps (NET) in patients with and without OM.

Methods: Sixty adult patients diagnosed with hematolymphoid diseases and undergoing a chemotherapy/conditioning regimen for hematopoietic stem-cell transplantation were enrolled. Saliva samples were collected on days D0/baseline, D3, D10, and D15. Cytokine levels were analyzed by ELISA and NET formation by identification of the myeloperoxidase-DNA complex.

Results: About 43.3% of the patients developed OM. The concentration levels of pro-inflammatory cytokines revealed differences between individuals with and without OM. Significantly higher concentrations of IL-6 and TNF-α and lower concentrations of TGF-β1 were observed in those who had OM. There was a slight decrease in NET formation among those who experienced OM. However, no statistical differences of cytokine concentrations and NET levels with clinical variables and OM severity were identified.

Conclusions: Special attention should be given to IL-6, TNF-α and TGF-β1 levels in saliva, which may be non-invasive biomarkers in the development of chemotherapy-induced OM. It is suggested that NET-mediated tissue damage may also contribute to the establishment of OM.

Keywords: Chemotherapy; Cytokines; Inflammation; Neutrophil extracellular traps; Oral mucositis; Saliva.

Introduction

Oral mucositis (OM) represents an inflammatory condition of the oral and oropharyngeal mucosa resulting from antineoplastic therapy, typically manifesting as atrophy, erythema, and ulcerations [1]. Estimates indicate a prevalence of OM between 14% and 100% resulting from chemotherapy, radiotherapy, and/or chemoradiotherapy [2]. OM can impar nutritional intake and impose a major worsening of health-related quality of life [1,2]. Chemotherapy-associated immunosuppression also increases the risk of fungal infections, which may occur in parallel with OM [3].

The pathogenesis of OM is not fully understood and encompasses a five-stage multifactorial sequence: initiation, primary damage response, signal amplification, ulceration, and healing [4]. In this complex sequence of events, the production of the inflammatory cascade mediated by reactive oxygen species (ROS), in particular activated innate immune responses, plays a central role in the pathogenesis of chemotherapy-induced OM [5–7]. Emerging evidence has also demonstrated that the microbiome and neuroimmune signaling can trigger the onset of OM [8].

Current literature has identified salivary cytokines as biomarkers to predict the risk of OM occurrence and assess its severity in individuals undergoing antineoplastic therapy [9,10]. Some studies have suggested a role for tumor necrosis factor (TNF) in the pathogenesis of OM, particularly for chemoradiotherapy-induced OM [11,12]. TNF is a pleiotropic cytokine released mainly by activated macrophages with relevant role in diverse cellular events, including cell proliferation, differentiation, and apoptosis [13]. Other pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6 and IL-8, have also been associated with the severity of OM induced by radiotherapy or chemoradiotherapy [10,14]. IL-6 is a pro-inflammatory cytokine with multiple effects, including immunocompetence, and in combination with TNF-α and IL-1, contributes to acute inflammation [10]. Besides, transforming growth factor beta (TGF-β) is a pleiotropic cytokine with important anti-inflammatory and immunosuppressive properties, in which the activation of TGF-β signaling is

linked to the development of OM [15]. Despite consistent results on salivary cytokines involved in radiotherapy- or chemoradiotherapy-induced OM [9], there are still no definitive conclusions about chemotherapy-induced OM. In part, this is due to the heterogeneity of the chemotherapeutic agents available and the limited number of enrolled participants in the studies [9,10].

Neutrophils play a crucial role in the pathophysiology of chemotherapy-induced OM [16,17]. Neutrophils are activated in the blood shortly after chemotherapy [18], and influence the release of circulating vascular endothelial growth factors, which stimulate tumor angiogenesis and the release of IL-1, IL-6, and TNF-α [17]. The main microbicidal mechanisms of neutrophils are degranulation, phagocytosis, cytokine secretion, and formation of extracellular traps [19]. Neutrophil extracellular traps (NET) are composed of DNA containing histones and granule-derived enzymes [19,20]. NET formation not only serves as a mechanism of defense to immobilize invading microorganisms, but also responds to sterile stimuli. Inflammatory cytokines, such as TNF-α [21], IL-8 [22], and IL-1β [23] can stimulate neutrophils to form NET. From a clinical point of view, NET formation during chemotherapy confers resistance to treatment via TGF-β activation [24]. In recent years, investigations have revealed that NET play a relevant antimicrobial role in the pathogenesis of periodontitis and rheumatoid arthritis [25], aphthous ulcers and Behçet disease [26], and oral lichen planus [27]. Nevertheless, the contribution of NET formation in the context of chemotherapy-induced OM is unexplored.

The aim of the present study was to evaluate the content of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF-α, and TGF-β1) and NET formation in salivary samples from individuals undergoing chemotherapy and their associations with experience of OM.

2. Methods

2.1. Study design, setting, and ethical approval

This was a prospective longitudinal study performed between 2021 and 2023 at the onco-hematology and hematopoietic stem-cell transplantation (HSCT) services of the Hospital das Clínicas, Belo Horizonte, Brazil. The guidelines for Strengthening the Reporting of Observational studies in Epidemiology were followed [28]. The study was approved by the Institutional

Ethics Committee (Protocol No. 5904127). Patients signed an informed consent form and their anonymity was preserved in accordance with the Declaration of Helsinki.

2.2. Participants and eligibility requirements

A total of 60 adults (≥18 years) of both sexes diagnosed with hematolymphoid diseases and undergoing a chemotherapy/conditioning regimen for HSCT, that required hospitalization of the patient, were included. Hematolymphoid malignancies were categorized according to the 2017 classification of Tumors of Hematopoietic and Lymphoid Tissue of the World Health Organization (WHO) [29]. The chemotherapy regimens for each group of conditions are shown in **Supplementary Table 1**.

The exclusion criteria were as follows: individuals with salivary gland neoplasms or chronic diseases with salivary involvement, those who had received radiotherapy or chemoradiotherapy, and those with refractory diseases.

2.3. Data collection

Patients were followed within the sequence of chemotherapy cycles and were evaluated at four-time points: D0 (before chemotherapy), D3 (onset of immunosuppression), D10 (nadir period), and D15 (bone marrow recovery). Data on sex, age, underlying disease, and type of HSCT (autologous or allogeneic) were recorded. At the same time, blood samples were obtained from the medical records for measurement of absolute neutrophil counts. Information on survival-related outcomes (alive with disease or if the individual had died) was also registered.

2.4. Clinical oral examination – definition of OM and staging

Clinical oral examinations were performed by two calibrated dentists (J.A.A.A. and F.V.H.). OM was evaluated daily, from D1 until D15. The WHO scale for assessment of grades of OM severity was used: grade 0 (no lesions), grade 1 (erythema without lesions), grade 2 (ulcers, but individual was able to eat), grade 3 (painful ulcers, but individual was able to consume liquid food with supportive analgesia), and grade 4 (individual required parenteral/enteral support and continuous analgesia) [30]. Data on odynophagia were also recorded. The

anatomical sites involved were divided into lips/labial mucosa, buccal mucosa, vestibule, retromolar trigone, tongue (dorsal, ventral and/or lateral border), floor of the mouth, hard/soft palate, and oropharynx.

All included individuals had comprehensive instructions on oral hygiene consisting of daily toothbrushing with soft brushes and mouthwashes with 0.12% chlorhexidine digluconate prior to and during chemotherapy. As a standard of care in the service, all patients also received prophylactic and therapeutic photobiomodulation in the oral and oropharyngeal regions following the protocol previously described elsewhere [31].

2.5. Identification of OM-associated oral candidiasis infections

Clinically suspected candidiasis infections associated with OM were confirmed by cytopathological examination and treated with fluconazole 100 mg (once a day for at least two weeks).

2.6. Saliva sample collection, quantification of inflammatory cytokines and NET assessment

Saliva samples were obtained early in the morning using the unstimulated technique for 5 minutes in sterile 50 mL tubes, as described elsewhere [32]. Samples were collected on days D0, D3, D10, and D15 and stored at -80°C.

Salivary concentrations of IL-1, IL-6, IL-8, TNF-α, and TGF-β1 were measured by means of an enzyme-linked immunosorbent assay (ELISA)-based capture assay using commercially available kits (DuoSet® ELISA; R&D Systems, Minneapolis, MN, USA). The tests were performed according to the manufacturer's instructions. The optical density was determined at 450-nm using a FlexStation 3 Microplate Reader (Molecular Devices, San Jose, CA, USA).

The Quant-iT™ PicoGreen® dsDNA assay kit (Invitrogen, Carlsbad, CA, USA) was used to quantify NET levels by identifying the myeloperoxidase (MPO)-DNA complex in saliva according to previous published method [25]. Briefly, 50 µL of each sample were placed in a 96-well clear-bottom black plate covered with anti-MPO antibody (PA5-16672; dilution 1:500, Invitrogen, Carlsbad, CA, USA). The amount of DNA bound to MPO was quantified using the Quant-iT™ PicoGreen® kit, according to the manufacturer's instructions. Fluorescence intensity (excitation at 488-nm and emission at 525-nm wavelength) was

determined with a FlexStation 3 Microplate Reader (Molecular Devices, San Jose, CA, USA). For all assays, two replicate wells were set up for each sample.

2.7. Data analysis

The Statistical Package for the Social Sciences (SPSS) (version 25.0, Armonk, NY, USA) and the GraphPad Prism (version 8.0, San Diego, CA, USA) software were used. Descriptive analysis was applied to clinicodemographic data. Non-parametric data were submitted to the Kruskal-Wallis multiple comparison test and Mann-Whitney test. The Wilcoxon test was used for dependent assessments. For all analyses, the level of significance was set at <0.05.

3. Results

3.1. Clinicodemographic profile and outcomes

The survey comprised 30 men and 30 women with a mean age of 44.2 (±16.2) years (range: 18–74 years). The most common diseases were myeloid leukemia (30.0%) and lymphoid leukemia (26.7%). Forty-two (70%) patients underwent chemotherapy as the main treatment and 18 (30%) underwent HSCT (*n*=15 autologous and *n*=3 allogeneic). With regard to survival-related outcomes, 41 (68.3%) patients survived and 19 (31.7%) died **(Table 1)**.

Table 1. Clinicodemographic profile and outcomes of patients undergoing chemotherapy or hematopoietic stem-cell transplantation (HSCT) affected by oral mucositis (OM)

Variables	n (%)
Sex	
Male	30 (50.0)
Female	30 (50.0)
Age (years), mean ± SD, range	44.2 ± 16.2 (18–74)
Underlying disease	
Myeloid leukemia	18 (30.0)
Lymphoid leukemia	16 (26.7)
Multiple myeloma	10 (16.7)
Non-Hodgkin lymphoma	9 (15.0)
Hodgkin lymphoma	2 (3.3)
Other hematological diseases	5 (8.3)
Treatment	
Chemotherapy (alone)	42 (70.0)
Autologous HSCT	15 (25.0)
Allogeneic HSCT	3 (5.0)
OM grade	
0	34 (56.7)
1	12 (20.0)
2	7 (11.7)
3	6 (10.0)
4	1 (1.6)
Anatomical location affected by OM	
1 site	9 (34.6)
2 sites	7 (26.9)
3 sites	4 (15.4)
>3 sites	6 (23.1)
Topographical anatomy affected by OM*	
Hard/soft palate	12 (19.7)
Buccal mucosa	12 (19.7)
Lips/labial mucosa	10 (16.4)
Tongue (dorsal, ventral and/or lateral border)	9 (14.7)
Floor of the mouth	9 (14.7)
Oropharynx	4 (6.6)
Retromolar trigone	3 (4.9)
Vestibule	2 (3.3)
Odynophagia	
Yes	14 (23.3)
No	46 (76.7)

OM-related oral candidiasis	
Yes	12 (20.0)
No	48 (80.0)
Outcomes	
Alive with disease	41 (68.3)
Died	19 (31.7)

Note: SD, standard deviation.
*The unit of analysis was not the number of individuals, since each individual evaluated could have been affected at more than one anatomical site.

3.2. OM assessment

Twenty-six (43.3%) patients experienced some degree of OM; of these, the majority exhibited grade 1 (*n*=12/46.1%). Male and female patients were equally affected with OM and no differences in the grades of OM were observed either. Individuals with lymphoma (*n*=10/38.4%) were the most affected by OM, followed by individuals with leukemia (*n*=8/30.8%) and those undergoing HSCT (*n*=8/30.8%). In nine (34.6%) cases, one anatomical site was affected, followed by seven (26.9%) cases at two sites, and four (15.4%) at three sites. Six (23.1%) patients had more than three sites affected. The hard/soft palate (19.7%), buccal mucosa (19.7%), and lips/labial mucosa (16.4%) were the most affected sites. Odynophagia occurred in 14 (23.3%) patients and OM-related oral candidiasis occurred in 12 patients (20%) **(Table 1)**.

3.3. Cytokine profile between patients with and without OM

The IL-1 concentration was higher in patients with OM than in those without OM at baseline (D0) and on days D10 and D15 **(Figure 1A)**. There was a significant increase in IL-6 concentration from baseline to day D15 ($p<0.05$). Individuals with OM had significantly higher concentrations of IL-6 compared to individuals without OM on days D10 ($p=0.02$) and D15 ($p=0.008$) **(Figure 1B)**. There was a significant increase in IL-8 concentration from baseline to day D15 ($p=0.009$). Individuals with OM had a lower concentration of IL-8, albeit not significant, compared to individuals without OM on day D3 ($p>0.05$). In contrast, individuals with OM had significantly higher concentrations of IL-8 compared to those without OM on day D15 ($p=0.03$) **(Figure 1C)**.

There was a significant increase in TNF-α concentration from baseline to day D15 ($p=0.02$). Compared to the beginning of the chemotherapy cycle (D3), there was a significantly higher concentration of TNF-α on day D15 ($p=0.03$). In addition, individuals with OM had significantly higher concentration of TNF-α compared to those without OM on day D10 ($p=0.02$) **(Figure 1D)**. Regarding TGF-β1 concentration, there was a significant decrease between days D0 and D15 ($p<0.05$). Individuals with OM exhibited lower concentrations of TGF-β1 than those without OM at all time-points, but a statistically significant difference was observed only on day D10 **(Figure 1E)**. No statistical differences of the

concentrations of IL-1, IL-6, IL-8, TNF-α, and TGF-β1 with clinical variables were identified (p>0.05).

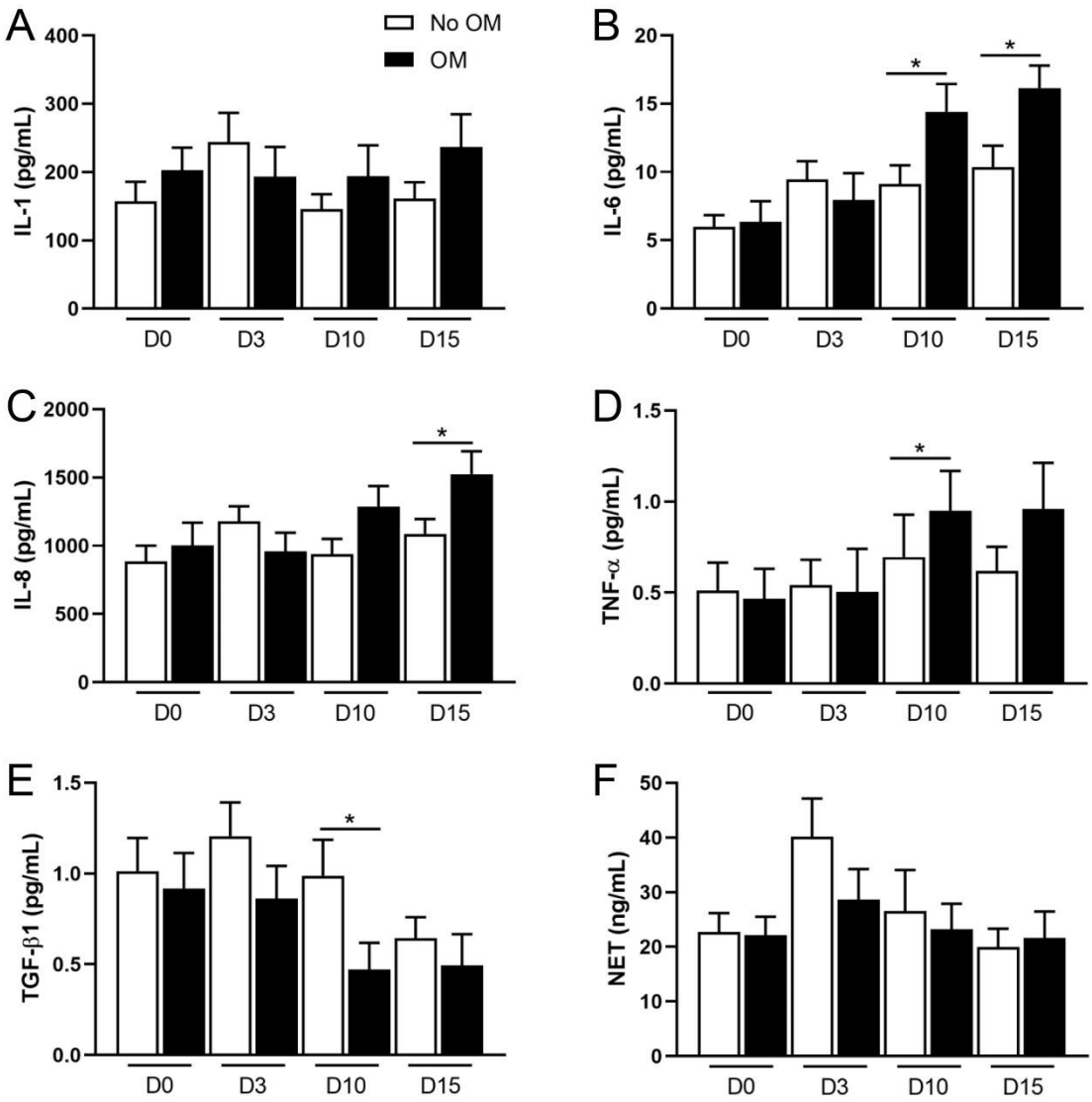

Figure 1 – Salivary concentration of (A) interleukin (IL)-1, (B) IL-6, (C) IL-8, (D) tumor necrosis factor-alpha (TNF-α), (E) transforming growth factor-beta 1 (TGF-β1), and (F) neutrophil extracellular traps (NET) in individuals with and without oral mucositis (OM) on days D0, D3, D10, and D15. *p<0.05; the Mann-Whitney test was employed to determine a statistically significant difference between groups.

3.4. Salivary NET formation and plasma neutrophil count

Compared to baseline, there was a significant increase in NET formation on D3 (p=0.04), but its concentration decreased on days D10 and D15 (p<0.05). Individuals with OM had a lower formation of NET, albeit not significant,

compared than those without OM on days D0, D3, and D10 (p>0.05) **(Figure 1F)**. Also, no statistical differences were identified for NET formation and clinical variables (p>0.05).

As expected, the patients' mean neutrophil count was 3.45×10^3/µL on day D0. The count reduced significantly to 1.36×10^3/µL on day D10, indicating the nadir period. A significant association was observed between the presence of OM and severe neutropenia. Individuals with OM exhibited a more severe neutropenia than individuals without OM (p=0.04) **(Figure 2)**.

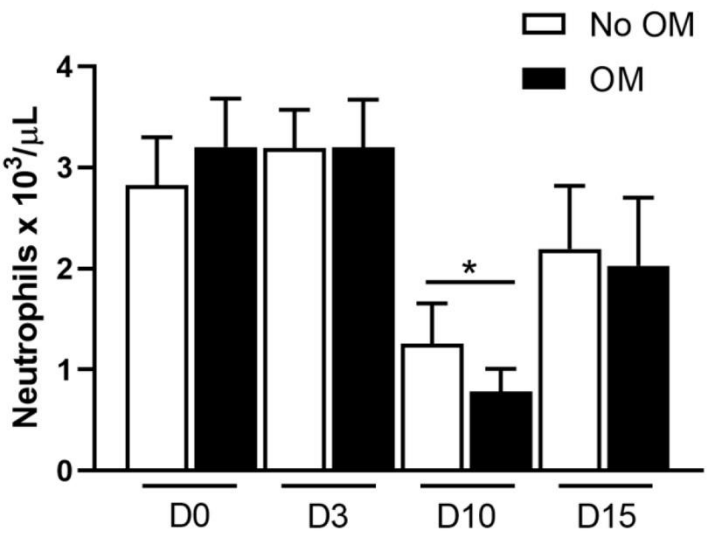

Figure 2 – Mean values of neutrophils from individuals with and without oral mucositis (OM) on days D0, D3, D10, and D15. *p<0.05; the Mann-Whitney test was employed to determine a statistically significant difference between groups.

Discussion

Chemotherapy-induced OM occurred in nearly 43% of the patients analyzed in this study. The assessment of salivary pro-inflammatory cytokines levels, IL-1, IL-6, IL-8, TNF-α, and TGF-β1, differentiated patients with and without OM. Particular attention should be paid to salivary IL-6, TNF-α, and TGF-β1, which may be non-invasive biomarkers in predicting the development of OM in individuals undergoing chemotherapy. Additionally, we provided, for the first time, some insights into NET-mediated tissue damage in chemotherapy-induced OM.

Over the last few decades, a growing number of studies have attempted to investigate the role of inflammatory cytokines related to the complex pathogenesis of OM, with the goal of expanding new therapeutic options to attenuate its severity [9,10]. Various mediators can affect the occurrence of OM *in situ*; however, the evidence in the literature that interprets the balance of cytokine subclasses according to the different stages of OM development is still limited [9,10]. Saliva has potential for use in laboratory diagnostics because this biomaterial permits repeated, non-invasive, and stress-free sampling, which is particularly important for patients with cancer [10,14]. The concentration of some biomarkers in saliva is correlated with their blood levels, allowing one to use saliva in the assessment of chemotherapy- and radiotherapy-induced OM [9,10]. It is widely known that saliva plays an important role in protecting the oral mucosa. Changes in salivary flow rate or salivary components, however, result in diminished salivary defense mechanisms and may affect oral/mucosal homeostasis and influence the severity of OM [33].

The content of pro-inflammatory TNF-α and IL-6 were significantly higher, while the level of TGF-β1 was statistically lower in the analyzed patients with OM, particularly in the nadir period. The five-phase model of OM documented by Sonis [4] entails the production of ROS as a first step in initiation of OM. ROS is able to activate NF-κB, producing IL-6 [34] and TNF-α [35] in alveolar macrophages, whereas clinical inhibition of mitochondrial ROS production hinders the expression of IL-6 and TNF-α [36]. It is well known that TNF-α plays a significant role in mediating acute inflammation. TNF-α levels in OM consistently increased in some studies [12,14], decreased in others [11], and were significantly associated with the severity related to chemoradiotherapy-induced OM [14]. Consistent with our data, mean salivary TNF-α concentrations were previously found to be higher at day D9 than at baseline among patients receiving conditioning chemotherapy for HSCT [37]. Interestingly, salivary TNF-α levels were higher one year after chemotherapy-induced OM among children with acute lymphoblastic leukemia than in controls, despite the fact that measured concentrations were low [38]. However, the long-term rescue of pro-inflammatory salivary cytokines in adults who have had chemotherapy-induced OM remains to be defined.

As shown in former studies, salivary IL-6 production appears to be an important step in the development of OM [9,10]. Herein, a significant augment in IL-6 values was observed from baseline to day D15. Although no association was observed with grades of OM, patients with OM exhibited significantly increased concentrations of IL-6 compared to those without OM. Such findings corroborate data from patients receiving high-doses of chemotherapy, among whom a positive correlation between elevated levels of IL-6 in serum and OM was detected [11,39]. Furthermore, salivary IL-6 concentrations were found to increase two-fold after 96 hours of chemotherapy conditioning [40]. It has been postulated that IL-6 is an initiator cytokine, whose levels are elevated in the pathway of chemotherapy-induced OM before other cytokines can enter the inflammatory cascade, highlighting a key point between direct cytotoxic damage and indirect tissue injury [5]. In this sense, blocking IL-6 production can prevent the release of other inflammatory cytokines by infiltrating immune cells. Of note, ongoing clinical trials have focused on IL-6 therapy, which may be a promising approach for the management of chemotherapy-induced OM [6].

An important growth factor analyzed in this study was TGF-β1. It controls cellular homeostasis and proliferation, wound healing, immunosuppression, and angiogenesis [41]. A decline in TGF-β1 expression was observed over the analyzed period, particularly among patients with OM. In contrast, the level of TGF-β1 was significantly higher in patients with severe radiotherapy-induced OM [42]. Lundberg et al. [43] found no significant association between OM severity and TGF-β1. Previous literature has suggested that TGF-β contributes to the pathogenesis of OM [15]. Conversely, some authors claim that TGF-β1 cannot be considered an efficient predictive biomarker, but it can be useful in monitoring head and neck radiotherapy [9]. Alternatively, TGF-β1 production is genetically regulated and individuals who have the variant allele at the single nucleotide polymorphism in the *TGFB1* gene tend to exhibit a higher concentration of serum TGF-β1 [43].

This study also identified that the inflamed mucosa generated higher NET in patients with OM than in uninvolved patients. Consistent with this finding, high levels of IL-6, IL-8, and TNF were detected in the saliva of patients with OM. Activation of neutrophils may be attributed, at least in part, to these cytokines [21,22,25]. Neutrophils can release NET to exacerbate tissue damage during

inappropriate inflammation and plays an important role in the pathogenesis of immune-mediated diseases [44]. For instance, high levels of NET expression have been observed in the saliva of patients with periodontitis and rheumatoid arthritis [25]. In oral lichen planus, on the other hand, the increased generation of NET is not due to the alteration of neutrophils, but to the aggregation of more neutrophils and the action of inflammatory factors [27]. It might be speculated that, in the context of OM, there is a positive feedback loop mediation, by means of which, pro-inflammatory NET promotes neutrophil recruitment and NET production; an assumption that should be examined in further research.

Important points and limitations should be recognized in this study. Despite the indisputable advantages, the use of saliva in diagnosis also has some drawbacks. The cytokine profile of saliva depends on the type of salivary gland involved in saliva secretion [45]. About 70% of non-stimulated saliva is produced in the submandibular glands, making the non-stimulated saliva composition very similar to blood plasma [46]. In general, cytokine concentrations are generally higher in saliva than in blood [37,40]; although there are divergent results regarding cytokine levels between the two fluids [10]. Since salivary hypofunction may occur in patients receiving antineoplastic therapy [47], efforts were made to standardize saliva sampling at all time-points. It is important to emphasize that we did not focus on the relationship between salivary gland function and the evaluated cytokines. Due to ethical issues, there is no control group of individuals who are not receiving oral health care to mitigate the onset of OM (e.g., basic oral care, photobiomodulation therapy); thus, larger randomized controlled studies are warranted. Considering that no associations were observed between cytokine/NET values and clinical variables, the multiple factors involved in the patient undergoing chemotherapy, including aging, medications, dietary supplements, as well as oral and systemic diseases cannot be ruled out. At this time, it is important to emphasize the careful selection of the patients undergoing chemotherapy in the current study.

5. Conclusion

In summary, salivary pro-inflammatory cytokines, TNF-α and IL-6 were elevated, whereas TGF-β1 was decreased, revealing a significant association with the development of chemotherapy-induced OM. A shift in circulating NET

levels suggests a possible contribution to the development of OM, as illustrated in **Figure 3**. Further studies with a large sample are needed to better understand the role of pro-inflammatory cytokines and NET formation in influencing the underlying disease and how they can be effectively targeted in a therapeutic context in chemotherapy-induced OM.

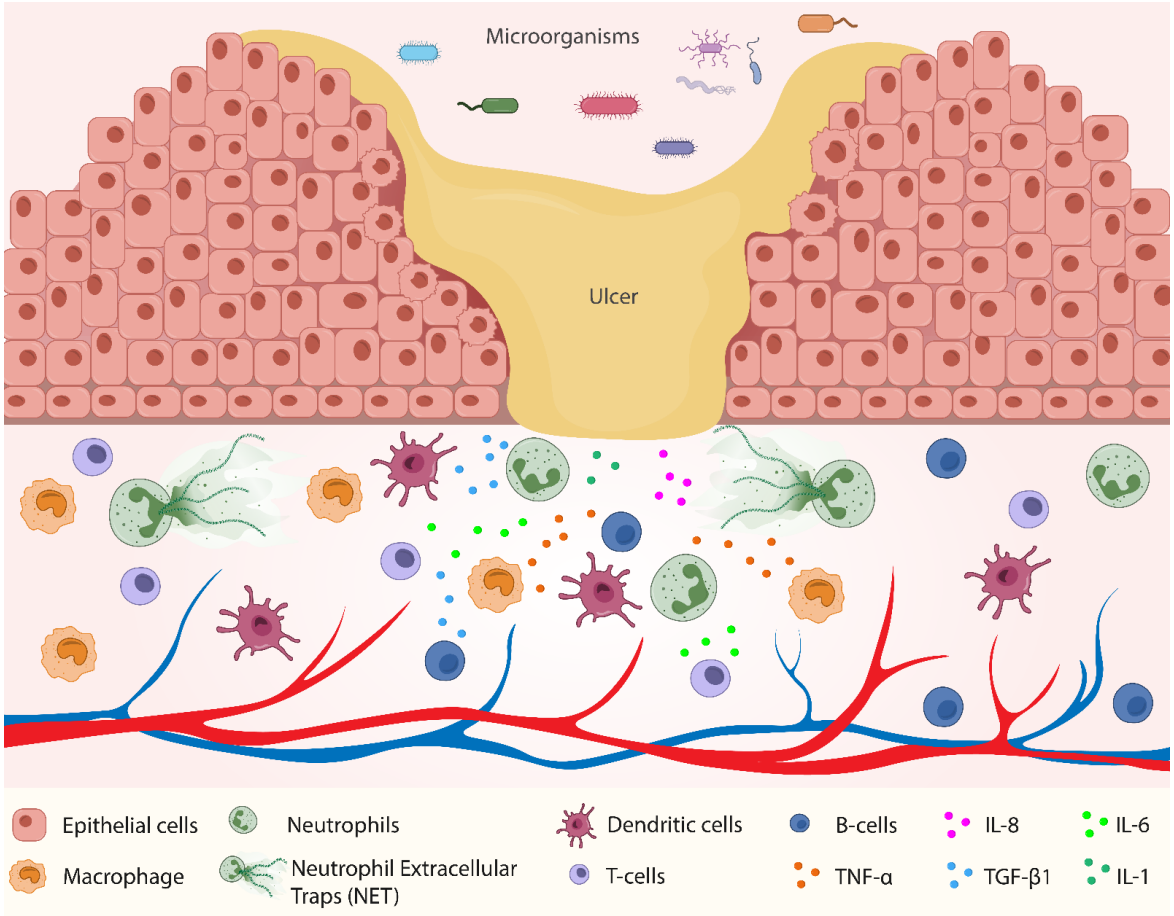

Figure 3 – Schematic presentation of pro-inflammatory cytokine concentration and neutrophil extracellular trap formation in the chemotherapy-induced oral mucositis etiopathogenesis. The ulceration-phase of oral mucositis exhibits high concentration of IL-6 and TNF-α and low concentration of TGF-β1. A possible NET release is suggested based on the stimulation of pro-inflammatory cytokines, possibly reflecting on neutrophil recruitment and NET formation.

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Supplementary Table 1. Chemotherapeutic agents used in hematolymphoid malignancies/hematopoietic stem-cell transplantation (HSCT) treatment

Outcomes	Chemotherapeutic agents
Leukemias	Bortezomib, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, etoposide, fludarabine, imatinib, MADIT (methotrexate, cytarabine, dexamethasone), methotrexate, mitoxantrone hydrochloride, vincristine, sorafenib, tioguanine
Lymphomas	Cisplatin, cyclophosphamide, cytarabine, doxorubicin, ifosfamide, gemcitabine, methotrexate, rituximab, vincristine, vinorelbine
HSCT	Busulfan, carboplatin, etoposide, fludarabine, melphalan, methotrexate, thymoglobulin

5.3 Capítulo 3: análise de ansiedade/depressão, qualidade de vida relacionada à saúde geral e bucal de pacientes em tratamento quimioterápico e associações com mucosite oral. Os métodos e resultados são apresentados no manuscrito intitulado ***"Influence of anxiety/depression on oral mucositis and related quality of life"*** submetido ao periódico *Oral Diseases* (fator de impacto: 4.06; ISSN: 1354-523X; estrato A1).

Influence of anxiety/depression on oral mucositis and related quality of life

Abstract

Objective: The impact of anxiety and depression on chemotherapy-induced oral mucositis has been barely explored in the literature. This study aimed to investigate anxiety/depressive symptoms, health-related quality of life and oral health-related quality of life and their association with oral mucositis among patients undergoing chemotherapy.

Materials and Methods: A prospective longitudinal study was conducted at a Brazilian referral center. The Hospital Anxiety and Depression Scale (HADS), World Health Organization Quality of Life-BREF (WHOQOL-BREF), and Oral Health Impact Profile questionnaire (OHIP-14) were applied at D0 (before chemotherapy) and D15 of chemotherapy. Clinicodemographic data and oral mucositis severity scores were assessed.

Results: Thirty-seven patients (mean age: 45.9 years) were included in the study. Nearly 38% of patients developed oral mucositis and had higher anxiety/depression scores at baseline. Oral mucositis had a negative impact on oral health-related quality of life regarding functional limitation, physical pain, physical disability, and handicap.

Conclusion: Anxiety/depressive symptoms are associated with oral mucositis that affects overall health and oral health-related quality of life.

Keywords: anxiety; chemotherapy; depression; mental health; oral health-related quality of life; oral mucositis; quality of life

1. Introduction

Oral mucositis (OM) is one of the most frequent side effects associated with chemotherapy, radiotherapy, and chemoradiotherapy (Elad et al., 2022). Estimates indicate an incidence of OM between 40% and 84% among patients undergoing chemotherapy and/or hematopoietic stem cell transplantation (HSCT) (Berger et al., 2018). The pathogenesis of OM encompasses a complex cascade of biological events involving inflammation, oral microbiome-host interactions, and neuroimmune signaling (Bowen et al., 2019).

OM is clinically characterized by erythematous and/or ulcerative lesions with different degrees of severity affecting the oral cavity and oropharynx (Elad et al., 2022). The pain provoked by OM is often described as excruciating (Christoforou et al., 2019). It negatively affects dietary intake and oral hygiene, and increases the risk of local/systemic infection (Cinausero et al., 2019). OM progression can lead to the interruption of antineoplastic therapy, impacting patient outcomes (Cinausero et al., 2019) and oral health-related quality of life (OHRQoL) (Barkokebas et al., 2015). The influence of OM on quality of life appears to extend beyond oral complications and involves physical, functional, and emotional aspects (Al-Rudayni et al., 2020).

Anxiety and depressive symptoms are documented in 10% to 16% of cancer patients independently of disease and treatment (Grassi et al., 2023; Mitchell et al., 2011). There is growing evidence that anxious or depressive states contribute to the onset of OM among individuals receiving antineoplastic therapy (de Arruda et al., 2022). Moreover, ‘distress’ and ‘neuroticism’ measured at the time of cancer diagnosis are consistent indicators of long-term emotional vulnerability and putative contributors to worse outcomes (Cook et al., 2018). Conversely, given its pain/discomfort and inflammatory basis, OM seems to contribute to anxiety and depression (Christoforou et al., 2019; McFarland et al., 2022; Bauer & Teixeira, 2019). This bidirectional interaction remains to be fully understood, including the pathophysiological mechanisms linking anxiety/depression and OM (Al-Rudayni et al., 2020; Chaitanya et al., 2016; de Arruda et al., 2022; Dodd et al., 2001; Fall-Dickson et al., 2008).

The purposes of the present study were i) to evaluate anxiety and depressive symptoms, health-related quality of life, and OHRQoL among patients undergoing chemotherapy; and ii) to investigate whether anxiety/depressive symptoms can contribute to OM and influence the perception of quality of life.

2. Materials and methods

2.1. Study design, setting, and ethical issues

This was a prospective longitudinal study carried out between 2021 and 2023 at Hospital das Clínicas, Belo Horizonte – a public referral service supported by the Brazilian Public Health System. The sample of this study consisted of patients undergoing chemotherapy at the onco-hematology and hematopoietic stem cell transplantation services. The guidelines for Strengthening the Reporting of Observational studies in Epidemiology were followed (Knottnerus & Tugwell, 2008). The study was approved by the Institutional Ethics Committee (No. 5.904.127) and the patient's identity remained anonymous in accordance with the Declaration of Helsinki.

2.2. Patients and eligibility criteria

Adults of both sexes aged ≥18 years who had received a diagnosis of hematolymphoid disease or HSCT and had undergone cycles of chemotherapy were selected. The diagnosis of hematolymphoid diseases was confirmed according to the 2017 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues (Swerdlow et al., 2017). The diagnosis of non-malignant cases in patients with HSCT was defined according to the 11th revision of the International Statistical Classification of Diseases (ICD-11) of the WHO (Harrison et al., 2021). The chemotherapy protocols used for each type of disease are depicted in **Supplementary Table 1**.

Exclusion criteria were as follows: individuals who received radiotherapy or concomitant chemoradiotherapy, those who were discharged before day 15, those with refractory disease, and those who were unable to understand and/or complete the questionnaires. Individuals with incomplete/illegible medical records were excluded as well.

2.3. Data collection

Patients were followed during each chemotherapy cycle, regardless of the duration of the chemotherapy protocol. Patients were assessed before (day 0) and on day 15 of the chemotherapy regimen. Data regarding sex, age, and underlying disease were recorded.

OM was evaluated by two calibrated dentists (J.A.A.A. and F.V.H.). The WHO scale was used to grade the measurements: grade 0 (no mucositis), grade 1 (erythema without lesions), grade 2 (ulcers, but able to eat), grade 3 (painful ulcers, but able to consume liquid food with supportive analgesia), and grade 4 (requires parenteral or enteral support and continuous analgesia) (WHO, 1979). Information about the anatomical location of the OM lesion was considered as follows: lips/labial mucosa, tongue (dorsal, ventral and lateral border), floor of the mouth, buccal mucosa, vestibule, retromolar trigone, hard/soft palate, and oropharynx. Information about dysphagia and survival-related outcomes (alive with disease or died) were also recorded.

During hospitalization, all patients received guidance on oral hygiene, including counseling about tooth brushing with soft brushes and mouthwashes with 0.12% chlorhexidine digluconate. As standard of care in the unit, all patients also received prophylactic and therapeutic photobiomodulation in the oral and oropharyngeal regions, as described elsewhere (Nunes et al., 2020).

2.4. Instruments

2.4.1. Anxiety and depression assessment tool

The Hospital Anxiety and Depression Scale (HADS), a self-report questionnaire designed to screen anxious and depressive states in patients in non-psychiatric settings, was administered (Zigmond & Snaith, 1983). The HADS consists of two subscales: HADS-A, designed to detect anxious states, and HADS-D, designed to detect depressive states. Participants responded to each item by considering how they felt and/or behaved during the past week. Each subscale consists of seven items with a 4-point ordinal response format. In each subscale, scores range from 0 to 21, with higher scores indicating higher levels of anxious or depressive state. HADS has been previously cross-culturally validated in the Brazilian population (Botega et al., 1995).

2.4.2. Quality of life assessment tool

The World Health Organization Quality of Life-BREF (WHOQOL-BREF), a self-administered instrument, consists of 24 items distributed across four domains plus two general items that describe overall quality of life and general health (Skevington et al., 2004). The domains represent physical health (seven

items), psychological health (six items), social relationships (three items), and environment (eight items). The four domain scores can range 0 to 100, and higher scores are indicative of better quality of life. The general facet is scored on a scale of 2 to 10. The items inquire ‘how much’, ‘how completely’, ‘how often’, ‘how good’, or ‘how satisfied’ the respondent felt in the last two weeks. The instrument has been translated into Portuguese, with validation for the Brazilian population (Fleck et al., 2000).

2.4.3. OHRQoL assessment tool

Participants' OHRQoL was assessed using the short version of the Oral Health Impact Profile questionnaire (OHIP-14), which has been previously validated in Brazil (Oliveira & Nadanovsky, 2005). The items of the OHIP-14 are grouped into seven subscales: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. There are two questions in each domain, each with five answer alternatives as follows: 0 = ‘never’, 1 = ‘hardly ever’, 2 = ‘occasionally’, 3 = ‘fairly often’, and 4 = ‘very often’. The overall score corresponds to the sum of the 14 questions' scores and ranges from 0 to 56, with higher scores indicating a worse OHRQoL (Oliveira & Nadanovsky, 2005).

2.5. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY: IBM Corp.) was used for statistical analysis of the data. Descriptive and bivariate analyses were carried out. Since the Shapiro-Wilk test demonstrated that the data followed a non-normal distribution, the Mann-Whitney test was used to evaluate associations between clinicodemographic variables and the sum of the scores for the domains of the questionnaires applied on days 0 and 15. The chi-square test (Fisher and Pearson's exact test) was used for intergroup comparisons. Spearman's rank correlation coefficients were calculated to determine the strength of the correlations between the questionnaires employed. The correlation matrix data were obtained and analyzed using the R programming language (R Core Team, Vienna, Austria). The level of significance was set at 95% for all analyses.

3. Results

Of the 60 individuals initially screened, 23 were excluded for the following reasons: 10 did not respond to the three questionnaires (i.e., unwillingness to participate), eight were discharged before day 15 (e.g., short-term chemotherapy), and five died due to complications of the baseline disease. Thus, a total of 37 individuals, 21 (56.7%) women and 16 (43.3%) men, were enrolled in the study. The clinicodemographic data of the patients are summarized in **Table 1**. The mean age of the patients was 45.9 years (range: 19 to 70 years). The most common diseases were acute myeloid leukemia (32.4%) and acute lymphoblastic leukemia (29.8%).

Table 1. Clinicodemographic data and outcomes of patients undergoing chemotherapy

Variables	n (%)
Sex	
Male	16 (43.2)
Female	21 (56.8)
Age (median; mean ± SD; range)	49; 45.9 ± 15.6; 19–70
Baseline disease	
Acute myeloid leukemia	12 (32.4)
Acute lymphocytic leukemia	11 (29.8)
Diffuse large B-cell lymphoma	2 (5.4)
Burkitt lymphoma	2 (5.4)
Mantle cell lymphoma	2 (5.4)
Hodgkin lymphoma	1 (2.7)
Chronic myeloid leukemia	1 (2.7)
Plasma cell leukemia	1 (2.7)
Multiple myeloma (HSCT)	5 (13.5)
Grade of oral mucositis	
0	23 (62.2)
1	8 (21.6)
2	3 (8.1)
3	3 (8.1)
Anatomical location*	
Tongue	6 (24.0)
Buccal mucosa	6 (24.0)
Hard/soft palate	5 (20.0)
Lips/labial mucosa	3 (12.0)
Floor of the mouth	3 (12.0)
Vestibule	1 (4.0)
Retromolar trigone	1 (4.0)
Dysphagia	
Yes	8 (21.6)
No	29 (78.4)
Outcome	
Alive	25 (67.6)
Died	12 (32.4)

Note: HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
*The unit of analysis was not the number of individuals, since each individual evaluated could have been affected at more than one anatomical site.

Female patients had significantly higher anxiety scores than male patients on D0 and D15 (p=0.001 and p=0.02, respectively). At baseline, individuals with leukemia/lymphoma had higher HADS-D scores than patients undergoing HSCT (p=0.03). Patients were followed up for a total of 15 days. Compared to those who survived, those who died had higher HADS-A (median: 7 and 5) and HADS-D (median: 6 and 5) scores on D0 and D15, respectively (**Table 2**).

Table 2. Hospital Anxiety and Depression Scale (HADS) and its subscales of anxious states (HADS-A) and depressive states (HADS-D) and clinical aspects and outcomes of patients (n=37) with malignant neoplasms/hematopoietic stem cell transplantation (HSCT) under chemotherapy regimens

Variables	**HADS-A**				**HADS-D**			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	3 (0–10)	**0.01**	3 (0–13)	**0.02**	2 (0–12)	0.15	3 (0–13)	0.36
Female	7 (1–16)		8 (0–16)		5 (0–15)		4 (0–13)	
Age								
≤49 years	7 (1–16)	0.24	4 (0–16)	0.76	5 (0–15)	0.36	4 (0–13)	0.53
≥50 years	4 (0–16)		5 (0–14)		3 (0–12)		3 (0–13)	
Baseline disease								
Leukemia/lymphoma	5 (0–16)	0.49	4.5 (0–16)	0.86	5 (0–15)	**0.03**	4 (0–13)	0.11
HSCT	3.5 (0–16)		3.5 (2–14)		1 (0–4)		1 (0–7)	
Outcome								
Alive	4 (0–16)	0.381	4 (0–15)	0.199	4 (0–15)	0.589	3 (0–13)	0.230
Died	7 (0–16)		6 (2–16)		5 (0–13)		5 (1–13)	

Note: HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
Bold means statistically significant at $p<0.05$.

Fourteen (37.8%) patients experienced some degree of OM. OM healing time was 7.8 (±1.7) days. Tongue and buccal mucosa (24.0% each), followed by hard/soft palate (20.0%), were the sites most affected by OM. Dysphagia occurred in eight patients (21.6%), all of whom also experienced OM. Regarding survival-related outcomes, 25 (67.6%) patients survived and 12 (32.4%) died.

Patients who experienced OM had higher HADS-A and HADS-D scores at baseline compared to those who did not develop OM (p=0.01 and p=0.04, respectively). When comparing the D0 and D15 HADS-A and HADS-D scores of individuals who developed OM, no significant changes were observed, suggesting that the OM experience did not worsen anxiety/depression symptoms in our sample (p>0.05). Similar results were also obtained when analyzing HADS-A and HADS-D scores at baseline and at D15 among patients who did not develop OM (**Figure 1**).

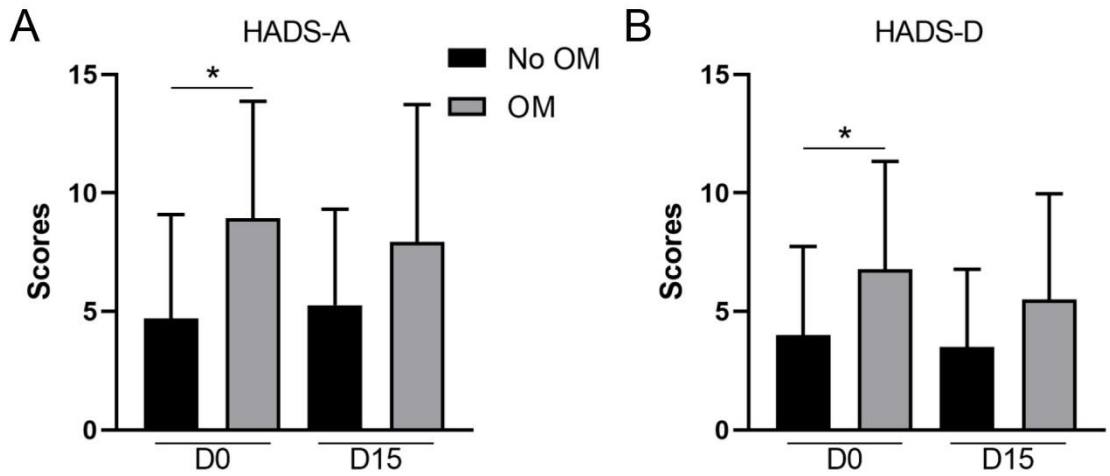

Figure 1 – Perception of oral mucositis (OM) based on the anxious (HADS-A) and depressive (HADS-D) states subscales of the Hospital Anxiety and Depression Scale (HADS) among patients (n=37) undergoing chemotherapy regimens.

OM negatively impacted quality of life. Patients who did not develop OM had significantly better scores in the social relationships (p=0.01) and environment (p=0.03) domains (WHOQOL-BREF) than those who experienced OM (**Figure 2**). Moreover, individuals with OM had a negative impact on the functional limitation (p=0.03), physical pain (p=0.04), physical disability (p=0.01), and handicap (p=0.03) domains of the OHIP-14 (**Figure 3**).

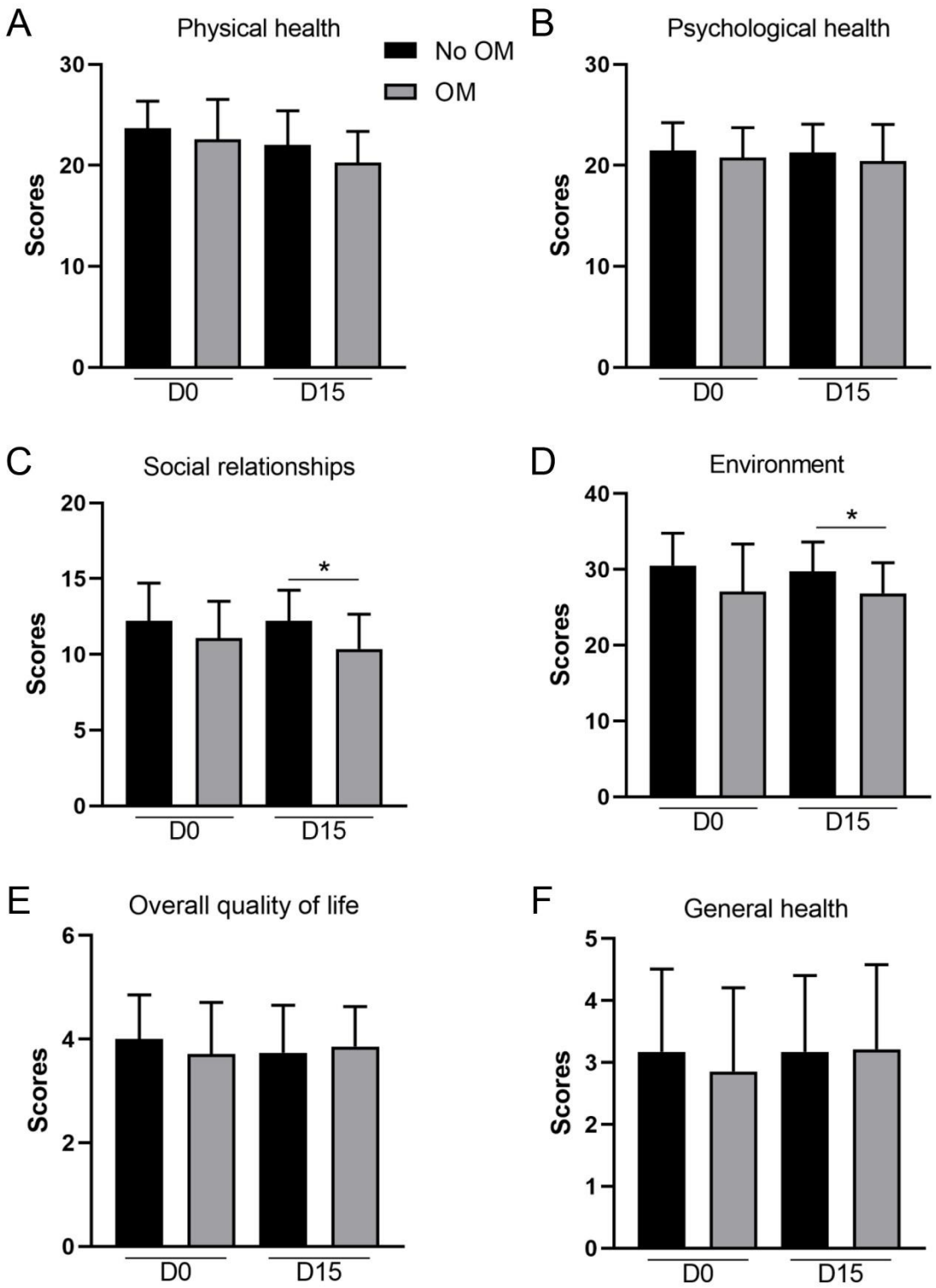

Figure 2 – Perception of oral mucositis (OM) based on the domains of the World Health Organization Quality of Life-BREF (WHOQOL-BREF) among patients (*n*=37) undergoing chemotherapy regimens.

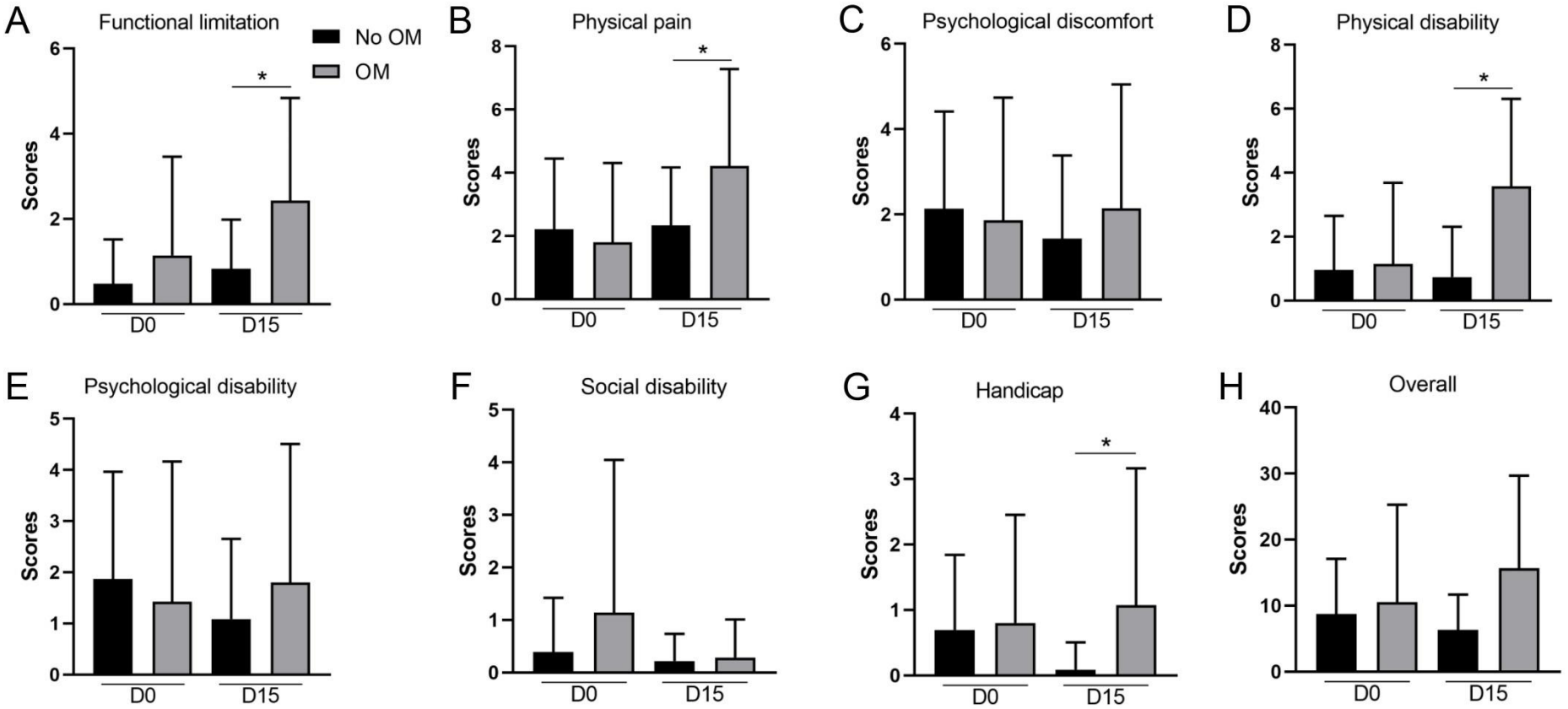

Figure 3 – Perception of oral mucositis (OM) based on the domains of the Oral Health Impact Profile (OHIP-14) among patients (*n*=37) undergoing chemotherapy regimens.

Regarding the WHOQOL-BREF instrument, participants obtained the best scores in the environment domain, while the worst scores were observed for the social domain, both on D0 and D15. The scores of all domains were lower on D15 than on D0. Male patients exhibited significantly higher scores in the social relationships (D15) (p=0.04) and general health (D0 and D15) domains than did female patients (p=0.01 and p=0.04, respectively). Patients with leukemia/lymphoma had significantly higher scores than those undergoing HSCT (p=0.02) in the social relationships domain on D0 (**Table 3**).

Female patients had significantly higher OHIP-14 scores in the psychological discomfort domain both on D0 (p=0.02) and D15 (p=0.03) (**Table 4**).

Correlations between the HADS, WHOQOL-BREF, and OHIP-14 instruments at the D0 and D15 time-points are detailed in **Supplementary Figure 1**. As expected, HADS and WHO scores showed an inverse correlation, while for HADS and WHOQOL-BREF there was a positive association.

Table 3. World Health Organization Quality of Life-BREF (WHOQOL-BREF) and clinical aspects of patients (n=37) with malignant neoplasms/hematopoietic stem cell transplantation (HSCT) under chemotherapy regimens

Variables	***Physical health***				***Psychological health***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	24 (16–28)	0.65	23 (18–26)	0.12	23 (14–25)	0.41	22 (13–27)	0.09
Female	24 (15–28)		21 (14–28)		21.5 (16–25)		20.5 (16–25)	
Age								
≤49 years	24 (16–28)	0.98	22 (18–28)	0.23	22 (16–25)	0.17	21 (13–27)	1.00
≥50 years	24 (15–28)		21 (14–26)		21.5 (14–24)		21 (13–25)	
Baseline disease								
Leukemia/lymphoma	24 (15–28)	0.35	21 (15–28)	0.41	22 (16–25)	0.09	21 (13–27)	0.81
HSCT	22.5 (16–26)		19.5 (14–28)		20 (14–23)		21 (17–24)	

Variables	***Social relationships***				***Environment***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	12 (8–15)	0.47	13 (10–15)	**0.04**	31 (18–37)	0.25	29 (26–35)	0.33

Female	12 (3–14)		10.5 (6–14)		30 (19–36)		28.5 (19–34)	
Age								
≤49 years	13 (6–15)	0.27	12 (7–15)	0.20	30 (19–37)	0.59	28 (19–35)	0.68
≥50 years	12 (3–14)		11.5 (6–14)		30.5 (18–35)		29.5 (23–33)	
Baseline disease								
Leukemia/lymphoma	13 (6–15)	**0.02**	12 (6–15)	0.39	30 (18–37)	0.66	29 (19–35)	0.86
HSCT	10 (3–13)		11 (7–14)		31 (24–36)		29 (23–33)	

Variables	***Overall quality of life***				***General health***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	4 (2–5)	0.14	4 (2–5)	0.64	4 (1–5)	**0.01**	4 (2–5)	**0.04**
Female	4 (2–5)		4 (2–5)		3 (1–4)		3 (1–5)	
Age								
≤49 years	4 (2–5)	0.47	4 (2–5)	0.57	3 (1–5)	0.85	3 (1–5)	0.23
≥50 years	4 (2–5)		4 (2–5)		3 (1–5)		4 (2–5)	
Baseline disease								

Leukemia/lymphoma	4 (2–5)	0.82	4 (2–5)	0.74	4 (1–5)	0.05	3 (1–5)	0.94
HSCT	4 (2–5)		4 (2–5)		2.5 (1–3)		3 (1–5)	

Note: HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
Bold means statistically significant at $p<0.05$.

Table 4. Oral Health Impact Profile questionnaire (OHIP-14) and clinical aspects of patients (n=37) with malignant neoplasms/hematopoietic stem cell transplantation (HSCT) under chemotherapy regimens

Variables	***Functional limitation***				***Physical pain***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	0 (0–4)	0.51	1.5 (0–4)	0.84	0 (0–4)	0.20	2 (0–8)	0.80
Female	0 (0–8)		0 (0–8)		2 (0–7)		3 (0–8)	
Age								
≤49 years	0 (0–4)	0.13	0.5 (0–8)	0.69	0 (0–6)	0.15	3 (0–8)	0.66
≥50 years	0 (0–8)		1 (0–5)		3 (0–7)		2 (0–8)	
Baseline disease								
Leukemia/lymphoma	0 (0–8)	0.13	0 (0–8)	0.49	1 (0–7)	0.69	3 (0–8)	0.06
HSCT	0 (0–0)		1.5 (0–4)		0.5 (0–4)		0.5 (0–4)	

Variables	***Psychological discomfort***				***Physical disability***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	0 (0–2)	**0.02**	0 (0–5)	**0.03**	0 (0–3)	0.28	0 (0–7)	0.69

Female	2 (0–8)		2 (0–8)		0 (0–8)		0 (0–8)	
Age								
≤49 years	0 (0–6)	0.06	1 (0–8)	0.29	0 (0–6)	0.43	0.5 (0–8)	0.38
≥50 years	2 (0–8)		0 (0–5)		0 (0–8)		0 (0–7)	
Baseline disease								
Leukemia/lymphoma	1 (0–8)	0.25	1 (0–8)	0.20	0 (0–8)	1.00	0 (0–8)	0.76
HSCT	3.5 (0–7)		0 (0–7)		0 (0–2)		0.5 (0–4)	

Variables	***Psychological disability***				***Social disability***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	0 (0–4)	0.20	0 (0–4)	0.26	0 (0–3)	0.15	0 (0–2)	0.18
Female	0 (0–8)		0 (0–8)		0 (0–8)		0 (0–2)	
Age								
≤49 years	0 (0–7)	0.11	0 (0–8)	0.98	0 (0–4)	0.75	0 (0–2)	0.88
≥50 years	2 (0–8)		0 (0–4)		0 (0–8)		0 (0–2)	
Baseline disease								

Leukemia/lymphoma	0 (0–8)	0.64	0 (0–8)	0.20	0 (0–8)	0.16	0 (0–2)	0.30
HSCT	2 (0–3)		0 (0–3)		0 (0–8)		0 (0–1)	

Variables	***Handicap***				***Overall***			
	D0 (median; range)	***p* value**	**D15 (median; range)**	***p* value**	**D0 (median; range)**	***p* value**	**D15 (median; range)**	***p* value**
Sex								
Male	0 (0–3)	0.07	0 (0–2)	0.79	3 (0–14)	0.15	7.5 (0–21)	0.74
Female	0 (0–4)		0 (0–7)		9 (0–51)		8 (0–47)	
Age								
≤49 years	0 (0–4)	0.29	0 (0–7)	0.70	2 (0–33)	0.05	10 (0–47)	0.57
≥50 years	0 (0–4)		0 (0–2)		10 (0–51)		6 (0–27)	
Baseline disease								
Leukemia/lymphoma	0 (0–4)	0.24	0 (0–7)	0.29	4 (0–51)	0.40	8 (0–47)	0.28
HSCT	0.5 (0–4)		0 (0–0)		10.5 (0–22)		3 (0–18)	

Note: HSCT, hematopoietic stem cell transplantation; SD, standard deviation.
Bold means statistically significant at $p<0.05$.

4. Discussion

This study revealed that anxious and depressive symptoms may represent risk factors that contribute to the onset of OM. Nevertheless, the OM experience did not worsen these symptoms. The level of anxiety was higher among females and among patients with leukemia/lymphoma. The negative repercussions of OM on quality of life were perceived mainly regarding the functional limitations, physical pain, physical disability, and handicap domains.

Participants of this study were mostly middle-aged adult females with tumors of hematopoietic and lymphoid tissues. Female patients were also the ones with higher levels of anxiety/depression and a negative perception of their quality of life. Accordingly, high levels of distress, along with anxiety and depression, have been documented among women (Gebri et al., 2020; Wardill et al., 2020) and younger patients with cancer (Bergerot et al., 2018). A possible explanation involves female sex hormones (i.e., progesterone) (Gebri et al., 2020).

Previous studies have demonstrated an elevated level of anxiety and depression disorders among individuals receiving antineoplastic therapy (Grassi et al., 2023; Mitchell et al., 2011). Herein, patients with OM undergoing chemotherapy were more likely to have anxiety and depression than those undergoing chemotherapy and who did not develop OM, in agreement with previous studies (Chaitanya et al., 2016; Dodd et al., 2001). Moreover, OM was associated with an increase in anxiety/depression scores among patients at baseline and at the end of radiotherapy (Chaitanya et al., 2016; Chen et al., 2015). While anxiety and depressive disorders tend to have a long-term course, related symptoms may fluctuate over time and depend on multiple factors, including but not limited to diagnosis of the disease, treatment, or even anticipation of a recurrence of the condition, as well as general health and psychosocial stressors (Al-Rudayni et al., 2020; de Arruda et al., 2022). In this study, there were no significant changes in anxiety or depressive symptoms over time, a fact that may be explained in part by the short term of the investigation (15 days) and by pain-management interventions (e.g., prophylactic and therapeutic photobiomodulation therapy) in the presence of OM. It is worth mentioning that the anxiety and/or depression experienced by these individuals has been related to fear of uncontrolled pain (Christoforou et al., 2019; Elad et al., 2022; Sonis, 2021). Thus, it is possible that the health support provided by hospital-based dental service

professionals contributed to mitigating and/or preventing worsening of anxiety and depressive symptoms, especially for patients evolving with OM.

Anxiety and depression are important predictors of quality of life in cancer patients (Cook et al., 2018) and those undergoing HSCT (Di Giuseppe et al., 2020). While the key factor appears to be the presence of pre-existing mental health problems and their severity, the argument that chemotherapy induces biochemical changes in the brain, which in turn induces anxiety symptoms and impairs quality of life through specific biological mechanisms (e.g., inflammatory pathways), should be considered when studying post-chemotherapy behavioral and psychological symptoms (Ren et al., 2019). As expected, in the present study, HADS-A and HADS-D scores correlated with quality of life. Compared to a previous study that investigated general cancer populations (Quinten et al., 2015), our patients' quality of life scores were better, in addition to the fact that anxiety and depressive symptoms rates were lower than those previously reported (de Arruda et al., 2022). Emotional dimensions, functional limitation, physical pain, and physical disability were impaired. Kim et al. (2012) and Dodd et al. (2001) reported a significant deterioration of patient quality of life following OM with changes in emotional functions. Likewise, a significant impairment was observed in the physical and social domains (Cheng, 2007). Cheng et al. (2010) identified that mouth and throat pain scores were independent predictors of difficulty in chewing, swallowing, and speaking. In particular, the physical pain dimension corresponds to the feeling of pain and discomfort when eating, most commonly associated with the severity of OM (Barkokebas et al., 2015). However, it has been observed that subjective symptoms, including oral pain and oral dryness, are more common than objective signs, such as bleeding, scalloping of the tongue, and ulcerations in patients with OM (Cheng et al., 2010).

Of clinical relevance, the oral mucosa is very sensitive to emotional responses, as observed in inflammatory conditions such as oral lichen planus (De Porras-Carrique et al., 2022) and recurrent aphthous ulcers (Hariyani et al., 2020). Inflammation is an important component of OM (Sonis, 2021). Inflammation also plays a role in anxiety/depression disorders (McFarland et al., 2022; Bauer & Teixeira, 2019). OM affects not only psychosocial processes, but also the neural, neuroendocrine, and immune axes, and may further exacerbate or maintain inflammatory signaling during antineoplastic therapy (Bowen et al., 2019). Future studies targeting pro-inflammatory cytokines and their signaling pathways might represent a strategy for the definition of

shared and/or overlapping pathophysiological mechanisms linking OM with anxiety and depression.

Limitations of this study should be acknowledged. This was a convenience sample of patients treated at a single referral onco-hematology/HSCT service in Brazil. Given the severity of their underlying diseases, these patients may have more anxiety and depressive symptoms than patients with less severe conditions, limiting the generalizability of the findings. Another important point is that the preventive measures employed in our service, which may not be available in other settings, could have minimized complications. Furthermore, identification of anxiety and depression was based on self-report questionnaires and not on formal psychiatric assessment. The duration of follow-up (only 15 days) is another limitation of the study. In contrast, its strength is the longitudinal design taking into account the data at baseline and after 15 days of chemotherapy and the systematic approach/evaluation. Few studies have specifically investigated the influence of chemotherapy-induced OM on anxiety, depression, and quality of life (Al-Rudayni et al., 2020; de Arruda et al., 2022) and, to the best of our knowledge, this is the first study that has examined such issues in a Brazilian population and in Latin America in general.

While investigating quality of life and OM as an outcome measure and anxiety/depression as independent variables seems relatively straightforward, former studies have examined OM as an independent variable and anxiety/depression and quality of life as outcomes (Dodd et al., 2001; Cheng, 2010). Given the possible bi-directional effects and pre-existing vulnerability suggested by the present study, anxiety and depressive symptoms may contribute to the onset and severity of OM and negatively influence the perceptions of oral- and health-related quality of life. Taken together, the outcomes of the current study can be useful for the formulation of treatment plans, which might focus on the overall health of the oral cavity and the assessment of OM and on the adoption of scales to measure physical and mental aspects prior to and during antineoplastic therapy.

5. Conclusion

In summary, anxiety/depressive symptoms can contribute to the development of OM. Conversely, OM did not affect the severity of anxiety/depressive symptoms in this subset of patients, but negatively impacted the perceptions of OHRQoL in relation to functional limitation, physical pain, physical disability, and handicap. Future

directions for OM management might focus on systematic monitoring of mental health before and concurrently with chemotherapy in order to mitigate morbidity and mortality.

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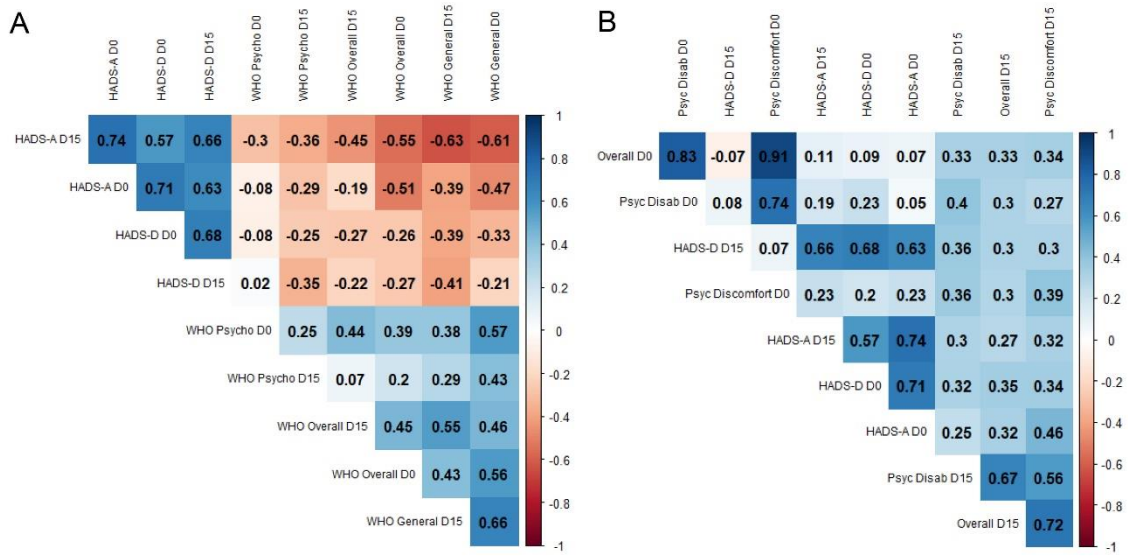

Supplementary Figure 1 – Spearman's rank correlation matrix between the questionnaires evaluated on days 0 and 15. **(A)** Hospital Anxiety and Depression Scale (HADS-A and HADS-D) versus the World Health Organization Quality of Life-BREF (WHO) and its domains (overall, general, and psychological health). **(B)** Hospital Anxiety and Depression Scale (HADS-A and HADS-D) versus the Oral Health Impact Profile (OHIP-14) and its domains (overall, psychological discomfort, and psychological disability).

6 CONSIDERAÇÕES FINAIS

Os dados dos indivíduos avaliados na análise prospectiva e na revisão sistemática demonstraram que os indivíduos submetidos a regimes antineoplásicos, particularmente quimioterapia, são vulneráveis à ansiedade e/ou depressão. A mucosite oral certamente causa e/ou agrava esses sintomas devido à dor e à inflamação relacionadas e, por sua vez, piora a percepção do paciente sobre sua qualidade de vida. Além disso, destaca-se a existência de uma relação bidirecional entre ansiedade/depressão e mucosite oral; no entanto, mais estudos mecanicistas e longitudinais com amostras robustas são necessários.

A avaliação dos níveis de citocinas pró-inflamatórias salivares, IL-1, IL-6, IL-8, TNF-α e TGF-β1, diferenciou pacientes com e sem mucosite oral. Atenção especial deve ser dada às citocinas IL-6, TNF-α e TGF-β1, que podem ser biomarcadores não invasivos na predição e/ou monitoramento da mucosite oral em indivíduos submetidos à quimioterapia. A mudança nos níveis circulantes das redes extracelulares de neutrófilos levanta questões relevantes acerca de uma possível contribuição para a patogênese da mucosite oral quimioinduzida.

Em síntese, os dados do presente estudo visam promover o desenvolvimento e implementação de ações efetivas, integradas e baseadas em evidências para a prevenção e controle da mucosite oral e/ou orofaríngea e suas complicações. Os resultados deste trabalho podem contribuir para melhor subsidiar a concepção e a qualidade da assistência integral aos pacientes em tratamento quimioterápico, colaborando principalmente para medidas preventivas, tratamento e redução de comorbidades, além de elucidar os mecanismos da doença e impacto na qualidade de vida.

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ANEXO A – Aprovação do Comitê de Ética em Pesquisa

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: TERAPIA DE FOTOBIOMODULAÇÃO NA MUCOSITE ORAL E OROFARÍNGEA EM ADULTOS: ASPECTOS CLÍNICOS, BIOQUÍMICOS, INFLAMATÓRIOS, MICROBIOLÓGICOS E AVALIAÇÃO DA QUALIDADE DE VIDA.

Pesquisador: Ricardo Alves de Mesquita

Área Temática:

Versão: 1

CAAE: 64244422.9.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.904.127

Apresentação do Projeto:

4.2 A proposta envolve ensaio clínico randomizado para avaliar os efeitos clínicos, bioquímicos, inflamatórios e microbiológicos da terapia de fotobiomodulação (TFBM) no tratamento da mucosite oral e/ou orofaríngea (MOO) induzida por quimioterápicos e pelo transplante de células tronco hematopoéticas (TCTH) em pacientes adultos. Adicionalmente, o impacto da magnitude da MOO na qualidade de vida dessa população bem como da TFBM no tratamento das lesões será avaliado por meio de três instrumentos: Oral Health Impact Profile (OHIP-14), The World Health Organization Quality of Life (WHOQOL-bref) e Hospital Anxiety and Depression Scale (HADS). No período de maio de 2022 a maio de 2023, 78 pacientes adultos de ambos os sexos em tratamento quimioterápico no serviço de Oncologia do Hospital das Clínicas da Universidade Federal de Minas Gerais (HC-UFMG), serão aleatoriamente divididos em três grupos (n=26): (1) grupo que receberá TFBM profilática intraoral a partir do primeiro dia de QT; (2) grupo que receberá TFBM profilática intraoral e em orofaringe; e (3) grupo que receberá TFBM profilática intraoral incluindo orofaringe e extraoral. Os parâmetros clínicos e inflamatórios serão avaliados por meio da investigação de citocinas inflamatórias e redes extracelulares de neutrófilos (NET) e de eosinófilos (EET) na saliva. Também será realizado isolamento e identificação de Candida spp. em amostras de saliva. Raspados da mucosa oral serão utilizados para investigação de infecção pelos vírus do herpes simples (HSV-1) e citomegalovírus (CMV). As comparações serão feitas entre os grupos com base

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BELO HORIZONTE, 20 de Fevereiro de 2023

Assinado por:
Corinne Davis Rodrigues
(Coordenador(a))

Endereço: Av. Presidente Antonio Carlos, 6627 2º. Andar Sala 2005 Campus Pampulha
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
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ANEXO B – Oral Health Impact Profile (OHIP14)

Perguntas	Respostas				
	Nunca	Raramente	As vezes	Muitas vezes	Sempre
1. Você teve problemas para falar alguma palavra por causa de problemas com sua boca ou dentes?					
2. Você sentiu que o sabor dos alimentos ficou pior por causa dos problemas com sua boca ou dentes?					
3. Você sentiu dor em sua boca ou nos seus dentes?					
4. Você se sentiu incomodado ao comer algum alimento por causa de problemas com sua boca ou dentes?					
5. Você ficou preocupado por causa de problemas com sua boca ou dentes?					
6. Você se sentiu estressado por causa de problemas com sua boca ou dentes?					
7. Sua alimentação ficou prejudicada por causa de problemas com sua boca ou dentes?					
8. Você teve que parar suas refeições por causa de problemas com sua boca ou dentes?					
9. Você encontrou dificuldade para relaxar por causa de problemas com sua boca ou dentes?					
10. Você sentiu-se envergonhado por causa de problemas com sua boca ou dentes?					
11. Você ficou irritado com outras pessoas por causa de problemas com sua boca ou dentes?					

12. Você teve dificuldades em realizar suas atividades diárias por causa de problemas com sua boca ou dentes?					
13.Você sentiu que a vida, em geral, ficou pior por causa de problemas com sua boca ou dentes?					
14.Você ficou totalmente incapaz de fazer suas atividades diárias por causa de problemas com sua boca ou dentes?					

ANEXO C – Instrumento de Avaliação de Qualidade de Vida (*World Health Organization Quality of Life* – WHOQOL-BREF)

Instruções

Este questionário é sobre como você se sente a respeito de sua qualidade de vida, saúde e outras áreas de sua vida. Por favor responda a todas as questões. Se você não tem certeza sobre que resposta dar em uma questão, escolha entre as alternativas a que lhe parece mais apropriada. Esta, muitas vezes, poderá ser sua primeira escolha. Tenha em mente seus valores, aspirações, prazeres e preocupações. Nós estamos perguntando o que você acha de sua vida, tomando como como referência as duas últimas semanas. Por exemplo, pensando nas últimas duas semanas, uma questão poderia ser:

	Nada	Muito pouco	Médio	Muito	Completamente
Você recebe dos outros o apoio de que necessita?	1	2	3	4	5

Você deve circular o número que melhor corresponde ao quanto você recebe dos outros o apoio de que necessita nestas últimas duas semanas. Portanto, você deve circular o número 4 se você recebeu "muito" apoio como abaixo.

	Nada	Muito pouco	Médio	Muito	Completamente
Você recebe dos outros o apoio de que necessita?	1	2	3	4	5

Você deve circular o número 1 se você não recebeu "nada" de apoio. Por favor, leia cada questão, veja o que você acha e circule no número e lhe parece a melhor resposta.

		Muito ruim	Ruim	Nem ruim nem boa	Boa	Muito boa
1	Como você avaliaria sua qualidade de vida?	1	2	3	4	5
		Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
2	Quão satisfeito(a) você está com a sua saúde?	1	2	3	4	5

As questões seguintes são sobre **o quanto** você tem sentido algumas coisas nas últimas duas semanas.

		Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
3	Em que medida você acha que sua dor (física) impede você de fazer o que você precisa?	1	2	3	4	5
4	O quanto você precisa de algum tratamento médico para levar sua vida diária?	1	2	3	4	5
5	O quanto você aproveita a vida?	1	2	3	4	5
6	Em que medida você acha que a sua vida tem sentido?	1	2	3	4	5
7	O quanto você consegue se concentrar?	1	2	3	4	5
8	Quão seguro(a) você se sente em sua vida diária?	1	2	3	4	5
9	Quão saudável é o seu ambiente físico (clima, barulho, poluição, atrativos)?	1	2	3	4	5

As questões seguintes perguntam sobre **quão completamente** você tem sentido ou é capaz de fazer certas coisas nestas últimas duas semanas.

		Nada	Muito pouco	Médio	Muito	Completamente
10	Você tem energia suficiente para seu dia-a-dia?	1	2	3	4	5
11	Você é capaz de aceitar sua aparência física?	1	2	3	4	5
12	Você tem dinheiro suficiente para satisfazer suas necessidades?	1	2	3	4	5
13	Quão disponíveis para você estão as informações que precisa no seu dia-a-dia?	1	2	3	4	5
14	Em que medida você tem oportunidades de atividade de lazer?	1	2	3	4	5

As questões seguintes perguntam sobre **quão bem ou satisfeito** você se sentiu a respeito de vários aspectos de sua vida nas últimas duas semanas.

		Muito ruim	Ruim	Nem ruim nem bom	Bom	Muito bom
15	Quão bem você é capaz de se locomover?	1	2	3	4	5
		Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
16	Quão satisfeito(a) você está com o seu sono?	1	2	3	4	5
17	Quão satisfeito(a) você está com sua capacidade de desempenhar as atividades do seu dia-a-dia?	1	2	3	4	5
18	Quão satisfeito(a) você está com sua capacidade para o trabalho?	1	2	3	4	5
19	Quão satisfeito(a) você está consigo mesmo?	1	2	3	4	5
20	Quão satisfeito(a) você está com suas relações pessoais (amigos, parentes, conhecidos, colegas)?	1	2	3	4	5
21	Quão satisfeito(a) você está com sua vida sexual?	1	2	3	4	5
22	Quão satisfeito(a) você está com o apoio que você recebe de seus amigos?	1	2	3	4	5
23	Quão satisfeito(a) você está com as condições do local onde mora?	1	2	3	4	5
24	Quão satisfeito(a) você está com o seu acesso aos serviços de saúde?	1	2	3	4	5

25	Quão satisfeito(a) você está com o seu meio de transporte?	1	2	3	4	5

As questões seguintes referem-se a **com que frequência** você sentiu ou experimentou certas coisas nas últimas duas semanas.

		Nunca	Algumas vezes	Frequentemente	Muito frequentemente	Sempre
26	Com que frequência você tem sentimentos negativos tais como mau humor, desespero, ansiedade, depressão?	1	2	3	4	5

Alguém lhe ajudou a preencher este questionário? .....

Quanto tempo você levou para preencher este questionário? .....

ANEXO D – Questionário Hospitalar de Ansiedade e Depressão (*Hospital Anxiety and Depression Scale* – HADS)

Este questionário ajudará o profissional da saúde a saber como você está se sentindo. Leia todas as frases e marque com um "X" a resposta que melhor corresponder a como você tem se sentido na ÚLTIMA SEMANA. Neste questionário as respostas espontâneas têm mais valor do que aquelas em que se pensa muito. Marque apenas uma resposta para cada pergunta.

A (1) Eu me sinto tenso ou contraído: 3 ( ) A maior parte do tempo 2 ( ) Boa parte do tempo 1 ( ) De vez em quando 0 ( ) Nunca	**D (8) Eu estou lento para pensar e fazer as coisas:** 3 ( ) Quase sempre 2 ( ) Muitas vezes 1 ( ) De vez em quando 0 ( ) Nunca
D (2) Eu ainda sinto gosto pelas mesmas coisas de antes: 0 ( ) Sim, do mesmo jeito que antes 1 ( ) Não tanto quanto antes 2 ( ) Só um pouco 3 ( ) Já não sinto mais prazer em nada	**A (9) Eu tenho uma sensação ruim de medo, como um frio na barriga ou um aperto no estômago:** 0 ( ) Nunca 1 ( ) De vez em quando 2 ( ) Muitas vezes 3 ( ) Quase sempre
A (3) Eu sinto uma espécie de medo, como se alguma coisa ruim fosse acontecer: 3 ( ) Sim, e de um jeito muito forte 2 ( ) Sim, mas não tão forte 1 ( ) Um pouco, mas isso não me preocupa 0 ( ) Não sinto nada disso	**D (10) Eu perdi o interesse em cuidar da minha aparência:** 3 ( ) Completamente 2 ( ) Não estou mais me cuidando como deveria 1 ( ) Talvez não tanto quanto antes 0 ( ) Me cuido do mesmo jeito que antes
D (4) Dou risada e me divirto quando vejo coisas engraçadas: 0 ( ) Do mesmo jeito que antes 1 ( ) Atualmente um pouco menos 2 ( ) Atualmente bem menos 3 ( ) Não consigo mais	**A (11) Eu me sinto inquieto, como se eu não pudesse ficar parado em lugar nenhum:** 3 ( ) Sim, demais 2 ( ) Bastante 1 ( ) Um pouco 0 ( ) Não me sinto assim

A (5) Estou com a cabeça cheia de preocupações: 3 ( ) A maior parte do tempo 2 ( ) Boa parte do tempo 1 ( ) De vez em quando 0 ( ) Raramente	**D (12) Fico esperando animado as coisas boas que estão por vir:** 0 ( ) Do mesmo jeito que antes 1 ( ) Um pouco menos do que antes 2 ( ) Bem menos do que antes 3 ( ) Quase nunca
D (6) Eu me sinto alegre: 0 ( ) A maior parte do tempo 1 ( ) Muitas vezes 2 ( ) Poucas vezes 3 ( ) Nunca	**A (13) De repente, tenho a sensação de entrar em pânico:** 3 ( ) A quase todo momento 2 ( ) Várias vezes 1 ( ) De vez em quando 0 ( ) Não sinto isso
A (7) Consigo ficar sentado a vontade e me sentir relaxado: 0 ( ) Sim, quase sempre 1 ( ) Muitas vezes 2 ( ) Poucas vezes 3 ( ) Nunca	**D (14) Consigo sentir prazer quando assisto a um bom programa de televisão, de rádio ou quando leio alguma coisa:** 0 ( ) Quase sempre 1 ( ) Várias vezes 2 ( ) Poucas vezes 3 ( ) Quase nunca