ANA CAROLINA VELASCO PONDÉ DE SENA

ESTUDO DA INFILTRAÇÃO DE TECIDOS ORAIS EM PACIENTES COM DOENÇAS HEMATOLÓGICAS MALIGNAS

Faculdade de Odontologia
Universidade Federal de Minas Gerais
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Orientadora: Profa. Dra. Tarcília Aparecida da Silva

Coorientadora: Profa. Dra. Denise Vieira Travassos

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ANA CAROLINA VELASCO PONDÉ DE SENA

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em ODONTOLOGIA, como requisito para obtenção do grau de Mestre em ODONTOLOGIA, área de concentração ESTOMATOLOGIA.

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“Grandes realizações não são feitas por impulso, mas por uma soma de pequenas realizações.”

Vincent van Gogh

RESUMO

Este trabalho realizou um estudo retrospectivo dos prontuários do Hospital das Clínicas (HC) da Universidade Federal de Minas Gerais (UFMG). Foram incluídos os indivíduos admitidos no período de 2010 a 2021 com diagnóstico de leucemia/linfoma e que foram avaliados pela equipe do Serviço de Odontologia do HC-UFMG. Foram coletados dados demográficos, características clínicas da doença de base e da cavidade bucal e presença de infiltração oral maligna. O teste t não pareado foi utilizado para avaliar os hemogramas e o teste McNemar para comparar indivíduos que desenvolveram infiltração oral maligna e aqueles que não desenvolveram. A significância estatística foi estabelecida como $p<0,05$. Adicionalmente, uma revisão da literatura de relatos de casos e séries de casos foi realizada em quatro bases de dados eletrônicas (PubMed, Web of Science, Scopus e Embase). Dos 781 prontuários analisados, a leucemia linfocítica aguda (30,1%) foi o diagnóstico mais frequente. Pacientes nas duas primeiras décadas de vida foram mais acometidos pela doença de base. Cárie (36,7%) e alterações periodontais (34,6%) foram as condições bucais mais observadas. Infiltração oral maligna ocorreu em 25 (3,2%) indivíduos, envolvendo principalmente a gengiva (80%) e indivíduos diagnosticados com leucemia mieloide aguda (64%). Comparando os dados de pacientes pediátricos que desenvolveram infiltração maligna e aqueles que não desenvolveram, a proporção de óbitos foi maior naqueles que tiveram infiltração ($p=0,002$), enquanto em adultos, aqueles que desenvolveram infiltração exibiram pior condição periodontal e maior proporção de óbitos ($p<0,001$). Dados da revisão da literatura demonstraram que a infiltração oral maligna foi mais frequente na gengiva (37%) e em pacientes com leucemia mieloide aguda (47%). As principais características clínicas e de imagem associadas à infiltração oral foram aumento de volume e lesões osteolíticas. Em conjunto, os dados sugerem a importância do monitoramento clínico odontológico de pacientes com leucemia/linfoma considerando os piores desfechos clínicos relacionados à infiltração dos tecidos orais.

Palavras-chave: Cavidade oral. Gengiva. Infiltração leucêmica. Leucemia. Linfoma. Neoplasias hematológicas.

ABSTRACT

Study of oral infiltration in patients with malignant haematological diseases

This work carried out a retrospective study of the medical records at the Hospital das Clínicas (HC), Universidade Federal de Minas Gerais (UFMG). Individuals admitted in the period from 2010 to 2021 with a diagnosis of leukaemia/lymphoma and who were evaluated by the team of the dental service of HC-UFMG were included. Demographic data, clinical characteristics of the underlying disease and oral cavity, and presence of malignant oral infiltration were collected. The unpaired t test was employed to assess the blood count and the McNemar test to compare individuals who developed malignant oral infiltration and those who did not. Statistical significance was set at $p<0.05$. Additionally, a literature review of case reports and case series was undertaken in four electronic databases (PubMed, Web of Science, Scopus, and Embase). Of the 781 medical records analysed, acute lymphocytic leukaemia (30.1%) was the most frequent diagnosis. Patients in the first two decades of life were more affected by the underlying disease. Caries (36.7%) and periodontal changes (34.6%) were the most frequently observed oral conditions. Oral malignant infiltration took place in 25 (3.2%) individuals, mainly involving the gingiva (80%) and individuals diagnosed with acute myeloid leukaemia (64%). Comparing data from paediatric patients who developed malignant infiltration and those who did not, the proportion of deaths was higher in those who had infiltration ($p=0.002$), while in adults, those who developed infiltration had worse periodontal status and a higher proportion of death ($p<0.001$). Data from the literature review showed that oral malignant infiltration was more frequent in the gingiva (37%) and in patients with acute myeloid leukaemia (47%). The main clinical and imaging features associated with oral infiltration were swelling and osteolytic lesions. Altogether, the data suggest the importance of clinical dental monitoring of patients with leukaemia/lymphoma considering the worst clinical outcomes related to oral tissue infiltration.

Keywords: Gingiva. Hematologic neoplasms. Leukaemia. Leukemic infiltration. Lymphoma. Oral cavity.

LISTA DE ABREVIATURAS E SIGLAS

HC Hospital das Clínicas

HIV *Human Immunodeficiency Virus*

INCA Instituto Nacional de Câncer José de Alencar Gomes da Silva

LMA Leucemia Mieloide Aguda

LLA Leucemia Linfoide Aguda

LMC Leucemia Mieloide Crônica

LLC Leucemia Linfoide Crônica

LNH Linfoma não Hodgkin

LH Linfoma de Hodgkin

NK *Natural Killers*

OMS Organização Mundial de Saúde

SNC Sistema Nervoso Central

STROBE *Strengthening the Reporting of Observational studies in Epidemiology*

SUMÁRIO

1 CONSIDERAÇÕES INICIAIS

A leucemia e o linfoma são doenças hematológicas malignas com características clínicas e biológicas diferentes, que ocorrem devido à proliferação de células malignas (ROSENQUIST, 2008). O acúmulo dessas células na medula óssea pode alterar os componentes sanguíneos ocasionando anemia, neutropenia e plaquetopenia, manifestando-se clinicamente como fadiga, febre, emagrecimento, sangramento espontâneo e até alterações na cavidade bucal (MALARD; MOHTY, 2020; MIRANDA-FILHO *et al.,* 2018; SHORT *et al.,* 2018). O desenvolvimento de alterações bucais relacionadas à leucemia/linfoma pode ser devido à presença do fator local (biofilme oral); secundária a alterações nos componentes sanguíneos ou decorrentes de efeitos diretos e indiretos das terapias antineoplásicas (FRANCISCONI *et al.,* 2016). As manifestações bucais mais comuns e relatadas são palidez da mucosa, aumento gengival, petéquias e sangramento espontâneo (ANGST *et al.,* 2011; ORBAK; ORBAK, 1997).

Clinicamente, a leucemia é denominada como aguda ou crônica e, histologicamente, como mieloide ou linfoide (ANGST *et al.,* 2011; LIM; KIM, 2014; MIRANDA-FILHO *et al.,* 2018; SHORT *et al.,* 2018). A leucemia aguda é caracterizada por um início abrupto e agressivo, enquanto a leucemia crônica tem um curso clínico mais lento (CAMMARATA-SCALISI *et al.,* 2020). Esses aspectos dão origem aos subtipos leucêmicos: leucemia mieloide aguda (LMA), leucemia linfoide aguda (LLA), leucemia mieloide crônica (LMC) e leucemia linfoide crônica (LLC) (SHORT *et al.,* 2018; SWERDLOW *et al.,* 2017). A LLA é mais comum em crianças e a LMA em adultos (CAMMARATA-SCALISI *et al.,* 2020; MALARD; MOHTY, 2020; REDAELLI *et al.,* 2005; SHORT *et al.,* 2018). As formas crônicas são mais comuns em adultos com mais de 60 anos (HOCHHAUS et al., 2017).

O linfoma pode ocorrer nodal ou extranodal, sendo classificado em dois grupos principais: Hodgkin (LH) e não-Hodgkin (LNH) com seus subtipos (SWERDLOW *et al.,* 2017). O LNH é classificado principalmente em três grupos correspondentes às células B, T e NK (*Natural Killers*) (DE LEVAL; JAFFE, 2020; SWERDLOW *et al.,* 2017). O LH é dividido principalmente em dois grupos, o clássico

(LHc) e linfoma nodular com predomínio linfocitário (LHNPL) (SWERDLOW *et al.,* 2017). Ambos podem ocorrer nodal ou extranodal, sendo o LH comumente associado à base nodal e o LNH nodal e/ou extranodal, acometendo diferentes sítios anatômicos, incluindo a região de cabeça e pescoço (DE ARRUDA *et al.,* 2021; KUSUKE; CUSTÓDIO; DE SOUSA, 2019). O LH ocorre mais frequentemente em adultos jovens e o LNH acomete indivíduos com idade entre a 6ª e a 7ª décadas de vida (ALEXANDER *et al*., 2007).

Em 2020, foram diagnosticados 544.352, 474.519 e 83.087 casos de LNH, leucemia e LH, respectivamente, ocupando a posição de 13º, 15º e 28º cânceres mais comuns no mundo (SUNG *et al*., 2021). No Brasil, segundo o Instituto Nacional de Câncer José de Alencar Gomes da Silva (INCA), a estimativa de leucemia para cada ano do triênio de 2020-2022 é de 10.810 casos, sendo 5.920 em homens e 4.890 em mulheres. A estimativa de linfomas é de 2.640, sendo 1.590 em homens e 1.050 em mulheres para LH e de 12.030, sendo 6.580 em homens e 5.450 em mulheres para LNH (INCA, 2019).

As manifestações bucais podem ser o primeiro sinal de doença hematológica maligna, podendo ocorrer pela infiltração de células malignas nas estruturas bucais (ORBAK; ORBAK, 1997). Esta infiltração pode se apresentar como aumento gengival ou lesão tumoral exofítica indolor (ORBAK; ORBAK, 1997). O diagnóstico da infiltração oral maligna é difícil devido à sobreposição de fatores e à variedade de manifestações clínicas, sendo a gengiva a localização mais frequente (CAMMARATA-SCALISI *et al*., 2020). Aumentos gengivais não induzidos por biofilme podem ser um sinal relevante para o diagnóstico precoce da doença de base, seja primária ou recorrente (CAMMARATA-SCALISI *et al*., 2020; LIM; KIM, 2014; LÓPEZ-VALVERDE *et al*., 2019). Por vezes, essas infiltrações podem ser confundidas com gengivite e periodontite, pois simulam clinicamente essas condições ou são sobrepostas (DREIZEN *et al*., 1983). Nesse contexto, o aumento gengival ocorre independentemente da presença de biofilme dental e da condição inflamatória do periodonto, servindo como reservatório de células malignas na cavidade bucal (CAMMARATA-SCALISI *et al*., 2020; DREIZEN *et al*., 1983). No entanto, a presença de biofilme pode exacerbar o quadro clínico dessa condição devido ao aumento da resposta inflamatória local e muitas vezes mascarar o diagnóstico de infiltração oral maligna (BEAUMONT *et al*., 2017; DREIZEN *et al*., 1983). Além disso, a infiltração

pode simular lesões inflamatórias periapicais, aparecendo como áreas osteolíticas nos exames de imagem (SILVA *et al*., 2016; ZIMMERMANN *et al*., 2015). Como esses recursos de imagem mimetizam várias possibilidades de doenças ósseas, estabelece-se a importância da biópsia para confirmação do diagnóstico (SILVA *et al*., 2016).

Indivíduos com leucemia/linfoma podem apresentar sinais sistêmicos como fadiga, perda de peso e febre devido a alterações nos componentes sanguíneos (HOCHHAUS et al., 2017). Anemia, plaquetopenia e neutropenia podem se manifestar na cavidade bucal por meio de palidez da mucosa, infeções fúngicas ou virais e lesões hemorrágicas (ex., sangramento espontâneo e petéquias/equimoses), sendo mais comum nas leucemias quando comparadas aos linfomas (ORBAK; ORBAK, 1997). A neutropenia está associada ao aparecimento de infecções como herpes simples e candidíase, e a má higiene bucal tende a acentuar o desenvolvimento dessas condições (PTASIEWICZ; MAKSYMIUK; CHALAS, 2022; THOMAZ *et al*., 2013). Indivíduos com lesões hemorrágicas geralmente apresentam baixa contagem de plaquetas, condição comum em pacientes com leucemias agudas (CAMMARATA-SCALISI *et al*., 2020; RAMÍREZ-AMADOR *et al*., 1996).

Os tratamentos indicados para leucemia/linfoma envolvem quimioterapia, radioterapia, transplante de células tronco, imunoterapia e uma combinação deles (SILVA *et al*., 2016). A escolha depende do tipo/subtipo da doença, idade do paciente e fatores de risco, sendo a quimioterapia a modalidade mais utilizada, podendo ser realizada com ou sem radiação (SILVA *et al*., 2016; ZIMMERMANN *et al*., 2015). Durante o período de tratamento antineoplásico, podem surgir toxicidades que acometem a cavidade bucal, como a mucosite. (ZADIK *et al*., 2019). A mucosite oral é caracterizada como uma condição inflamatória dolorosa da mucosa, geralmente apresentando-se como eritema, pseudomembrana e/ou úlcera (HONG *et al*., 2019). Sua apresentação clínica mais severa pode resultar na necessidade de nutrição parenteral, uso de analgésicos sistêmicos e vulnerabilidade a infecções por perda da barreira mucosa, podendo levar a internação prolongada ou mesmo interrupção do tratamento antineoplásico (HONG *et al*., 2019; ZADIK *et al*., 2019). Ademais, devido ao quadro doloroso ocasionado por essa sequela, esses indivíduos apresentam dificuldades em manter a higiene bucal, o que pode agravar outras condições inflamatórias (PTASIEWICZ; MAKSYMIUK; CHALAS, 2022). A mucosite é outro achado bucal esperado em indivíduos com leucemia/linfoma, podendo também se

sobrepor a outras condições (ALNUAIMI *et al*., 2018; THOMAZ *et al*., 2013). Após o início das terapias antineoplásicas, as infiltrações orais malignas tendem a regredir, o que pode servir como informação adicional para o diagnóstico clínico (CAMMARATA-SCALISI *et al*., 2020).

Alterações na cavidade bucal são frequentes em indivíduos com leucemia/linfoma devido à presença de diversos fatores, como biofilme, alterações hematológicas, sequelas da terapia antineoplásica e infiltração oral maligna. O infiltrado na cavidade bucal é de difícil diagnóstico, pois além de outros fatores preexistentes, existe uma diversidade de apresentação clínica. Assim, o presente estudo avaliou o perfil de saúde bucal destes indivíduos em um hospital de referência no período de 2010 a 2021, com o objetivo de coletar dados para a caracterização de infiltrações malignas na cavidade bucal, fornecendo subsídios para o diagnóstico clínico dessas condições.

1.1 Objetivos

1.1.1 Objetivos gerais

Identificar o perfil de saúde bucal e a ocorrência de infiltrações orais malignas em indivíduos com leucemia/linfoma em uma análise retrospectiva.

1.1.2 Objetivos específicos

a) Realizar revisão de literatura sobre infiltração leucêmica na região oral e maxilofacial;
b) Descrever os dados sociodemográficos e desfechos dos pacientes com leucemia/linfoma;
c) Relatar o estado de saúde bucal intragrupo (crianças e adolescentes e adultos);
d) Caracterizar a ocorrência de infiltração oral maligna nesses indivíduos intragrupo;
e) Identificar as possíveis variáveis associadas à infiltração oral maligna.

2 METODOLOGIA EXPANDIDA

2.1 Capítulo 1: Revisão da literatura

2.1.1 Critérios de elegibilidade

Os critérios de inclusão de trabalhos nesta revisão consistiram em relatos de casos ou séries de casos de indivíduos com infiltração leucêmica na cavidade bucal e maxilofacial publicado em inglês com descrição de dados suficientes para confirmação do diagnóstico. Os critérios de exclusão consistiram em pesquisa experimental, artigos de revisão, cartas ao editor (a menos que fornecessem dados suficientes) e artigos cujo texto completo não estava disponível. Síndromes associadas as neoplasias hematológicas (ex., mielodisplasia) também não foram incluídas.

2.1.2 Estratégias de busca

As buscas foram realizadas no PubMed, Web of Science, Scopus e Embase no dia 29 de outubro de 2020, utilizando as seguintes palavras-chave e entretermos: *leukaemic infiltrate OR leukemic infiltrate OR leukaemic infiltration OR leukemic infiltration AND extramedullary disease OR leukemia OR leukaemia OR myeloid sarcoma OR granulocytic sarcoma OR chloroma OR extramedullary myeloid tumor AND oral OR oral cavity OR mouth OR oral mucosa OR buccal mucosal OR floor of the mouth OR lip OR lips OR tongue OR alveolar process OR alveolar ridge OR gingiva OR palate OR hard palate OR soft palate OR jaw OR jaws OR mandible OR maxilla OR sinus OR maxillary sinus OR oropharynx OR oropharyngeal*. Foi realizada também uma busca manual nas listas de referências dos estudos selecionados. Quando necessário, os autores foram contatados para obter informações adicionais. As referências duplicadas em diferentes bancos de dados

foram identificadas e removidas usando o programa EndNote (EndNote®, Clarivate Analytics, Toronto, Canada).

2.1.3 Seleção dos trabalhos e extração de dados

Os títulos e resumos de todas as referências recuperadas das buscas eletrônicas foram lidas separadamente por dois revisores. Caso o título ou resumo cumprisse o conjunto de critérios de inclusão, o artigo era imediatamente incluído. Os textos completos dos títulos/resumos com informações incompletas foram obtidos e avaliados e se atendendo os critérios de elegibilidade, também foram incluídos. Em casos de divergência de opinião, um terceiro revisor foi consultado para confirmar a inclusão ou exclusão.

Os dados extraídos dos artigos corresponderam a: nome do autor(es), ano de publicação, país onde o(s) caso(s) foi(foram) reportado(s), número de casos reportados, idade dos pacientes e sexo, localização anatômica e diagnóstico da doença hematológica maligna (SWERDLOW *et al.,* 2017). Informações sobre apresentação clínica e sintomas, características radiográficas, dados histopatológicos da infiltração leucêmica, manejo e desfecho também foram extraídos.

2.1.4 Análise de dados

O software MedCalc (software MedCalc bvba, Ostend, Flanders, Bélgica) foi usado para análise estatística. O teste qui-quadrado foi utilizado para avaliar a associação do sexo dos indivíduos e localização anatômica das lesões com o diagnóstico de infiltração leucêmica. O teste de Kruskal-Wallis foi empregado para determinar a associação entre a idade dos indivíduos e o diagnóstico de infiltração leucêmica. A significância estatística foi estabelecida em $p<0,05$. A sobrevida global foi calculada pela análise de sobrevida com o teste de Kaplan-Meier.

2.2 Capítulo 2: Estudo retrospectivo

2.2.1 Aspectos éticos

O estudo foi submetido a avaliação no trâmite regulatório do HC (Unidade Funcional Pediatria e Oncohematologia), à Diretoria de Ensino, Pesquisa e Extensão (DEPE) do HC e ao Comitê de Ética em Pesquisa (COEP) da Universidade Federal de Minas Gerais (UFMG), e aprovado sob número de parecer: 4.849.734 e CAAE: 47136721.5.0000.5149 (**Anexo A**), conforme a Resolução 466, de 12 de dezembro de 2012.

2.2.2 Desenho do estudo

Este foi um estudo observacional retrospectivo. As diretrizes do *STROBE* foram seguidas (KNOTTNERUS & TUGWELL, 2008).

2.2.3 Pacientes e seleção da amostra

Foram selecionados os prontuários médicos dos indivíduos admitidos no ambulatório e internação do Hospital das Clínicas (HC-UFMG) com diagnóstico de leucemia/linfoma nos anos de 2010 a 2021.

2.2.4 Critérios de inclusão e exclusão

Indivíduos com leucemia/linfoma como diagnóstico de base, entre os anos 2010 e 2021, avaliados pela equipe da odontologia foram os critérios de inclusão para este estudo. Os critérios de exclusão consistiram em prontuários com informações incompletas acerca dos dados sociodemográficos e do diagnóstico de base e aqueles que não foram avaliados pelo serviço de odontologia do HC-UFMG.

2.2.5 Coleta de dados

A coleta de dados ocorreu no ano de 2021. Foram avaliados 781 prontuários médicos de indivíduos com diagnóstico de leucemia/linfoma, seguindo diagnóstico da OMS (SWERDLOW *et al.,* 2017). Os dados coletados dos prontuários foram sexo, idade, diagnóstico de leucemia/linfoma (e subtipo), manifestação da doença (primária ou recidiva), infiltração do sistema nervoso central (ausente ou presente), HIV status (positivo ou negativo) e o desfecho (vivo ou óbito). Para as condições orais, cárie, alterações periodontais, infecções virais (ex. herpes simples, citomegalovírus), doenças fúngicas (ex. candidíase), mucosite oral, outras manifestações (alterações na língua, condições reativas ou inflamatórias, hiperpigmentação da mucosa devido a terapia antineoplásica), lesões traumáticas, petéquia/equimose e saburra lingual foram avaliadas com desfechos dicotômicos (ausente ou presente).

As informações acerca da infiltração oral maligna foram características clínicas, controle da placa dentária, hemograma no dia do diagnóstico clínico da infiltração e o acompanhamento final foram coletadas. Clinicamente, manifestações orais, sem resolução após protocolos de higiene, como aumento gengival, ulceração, necrose, sangramento espontâneo e friabilidade do tecido foram consideradas para o diagnóstico da infiltração maligna (DE SENA *et al.,* 2021; DREIZEN *et al*., 1983). No serviço de odontologia do HC-UFMG, protocolos preventivos de higiene bucal adequada são estabelecidos a partir da admissão do paciente, como escovação diária dos dentes e, em alguns casos, bochechos com digluconato de clorexidina 0,12%.

2.2.6 Análise dos dados

A análise de dados foi realizada no software Statistical Package for the Social Sciences (SPSS), versão 25.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM

Corp.). A estatística descritiva foi realizada para caracterizar a amostra total e intragrupos para indivíduos ≤18 anos de idade e ≥19 anos.

Indivíduos que desenvolveram infiltração oral maligna foram pareados com aqueles que não desenvolveram para as variáveis idade, sexo, ambulatório ou internação e o ano de avaliação odontológica. O teste t não pareado foi utilizado para avaliar os hemogramas dos pacientes que tinham infiltração e os que não tinham. O teste McNemar foi utilizado para comparar indivíduos que desenvolveram infiltração oral maligna e os que não desenvolveram nos dados óbito, alterações periodontais, manifestação da doença e infiltração em SNC. Significância estatística foi estabelecida em $p<0,05$.

3 ARTIGOS

3.1 Capítulo 1: Revisão da literatura

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ORIGINAL ARTICLE

Leukaemic infiltration in the oral and maxillofacial region: An update

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Abstract

Background: The purpose of this study was to integrate the available data published on leukaemic infiltration in the oral and maxillofacial region into a comprehensive analysis of its clinical manifestations, imaginological characteristics, management and survival.

Materials and methods: An electronic search with no publication date restriction was undertaken in October 2020 in the following databases: PubMed, Web of Science, Scopus and Embase. Overall survival was calculated by survival analysis with the Kaplan-Meier test. A critical appraisal of included articles was performed using the Joanna Briggs Institute tool.

Results: A total of 63 studies including 68 patients were selected for data extraction. The most common haematologic diagnosis was acute myeloid leukaemia (47%). The most affected individuals were 40 to 49 years old (20.9%). The male-to-female ratio was 1.2:1. The gingiva was the most affected site (37%). Swelling/mass/oedema (33.7%) and enlargement/hyperplasia/hypertrophy (25.5%) were the main clinical findings. Osteolytic lesions with bone destruction were the main imaginological characteristics among the reported cases. Follow-up was available for 36 patients. Overall, within the 21-month follow-up, the survival probability dropped to 14.3%.

Conclusion: A considerable number of studies reported oral manifestations mainly in individuals with the acute form of leukaemia. Children and adults were affected, but the fifth decade of life was the most common. Dentists should be vigilant since these manifestations may be important for a diagnosis and for the monitoring of the treatment response and recurrence of haematological neoplasia.

KEYWORDS
haematologic neoplasms, leukaemia, myeloid sarcoma, oral cavity, survival

Special issue "Lymphomas and lymphoid lesions of the oral cavity".

1 | INTRODUCTION

Leukaemia is a general designation for a broad spectrum of malignant neoplasms that affect the haematopoietic components of the bone marrow, increasing the number of immature and abnormal leukocytes.[1,2] In 2018, there were 437 033 individuals living with leukaemia and this condition represented the fifteenth most common cause of cancer worldwide.[3] Leukaemia can be classified as acute or chronic. The acute form has a bimodal distribution occurring during childhood (peak age between one and four years) and adulthood (peak age between 40 and 49 years).[4,5] The chronic form of leukaemia predominantly affects older adults, particularly those in the sixth and seventh decades of life.[6,7] Moreover, leukaemia can be categorized as myelocytic or lymphocytic according to the predominant type of cell involved.[1] The four major types of leukaemia are acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML).[4-7]

In addition to nonspecific findings, including bleeding, bone pain, bruising, fatigue, fever or weight loss,[1,4-7] oral and maxillofacial manifestations may also occur in leukaemic individuals.[8] Manifestations in the oral and maxillofacial region may be a result of the direct infiltration of leukaemic cells (primary) or any outcome secondary to anaemia, thrombocytopenia, neutropenia or altered granulocyte function, which are common features in these individuals.[1,8,9] These findings provide evidence about the onset or recurrence of leukaemia.[9,10]

Although clinical manifestations are usually associated with symptoms related to systemic complications of pancytopenia (eg anaemia, neutropenia and thrombocytopenia), oral and maxillofacial signs or symptoms have not been fully described in initial diagnoses.[8,11] A study found that about 31% of patients with a recent diagnosis of acute leukaemia showed oral signs, the most common being oral bleeding (12.9%), followed by gingival enlargement (5.7%).[12] Due to the varied clinical manifestations in the oral and maxillofacial region, the diagnosis of leukaemic infiltration is not quite straightforward.[8,10] In this respect, dentists may play an important role in the diagnosis of these oral alterations by excluding other pathological processes.[12]

Herein, we aimed to integrate the available data into a comprehensive analysis of leukaemic infiltration in the oral and maxillofacial region, emphasizing the clinical manifestations, imaginological characteristics and management of the condition, as well as survival. This study forms a part of a special issue published by the Journal of Oral Pathology and Medicine covering the most important aspects of haematolymphoid lesions and neoplasms affecting the oral cavity and neighbouring structures.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

The inclusion criteria for this review were case reports or cases series of individuals with leukaemic infiltration in the oral and maxillofacial region published in English. Description of sufficient data to confirm the diagnosis of the condition was also a prerequisite for inclusion. No restriction concerning the geographic region or date of publication of the article was imposed. Exclusion criteria were experimental research, review articles, letters to the editor (unless the articles provided enough data) and articles whose full text was unavailable. Syndromes associated with haematological neoplasms (eg myelodysplasia and myelofibrosis) were not included.

2.2 | Databases and search strategies

Searches were conducted in PubMed, Web of Science, Scopus and Embase from the date of database inception to 29 October 2020. File S1 depicts the search strategies employed in each electronic database. A hand search of the reference lists of the selected studies was also performed. If necessary, authors were contacted in order to obtain additional information. Duplicate references across the different databases were identified and removed using the EndNote program (EndNote®, Clarivate Analytics, Toronto, Canada).

2.3 | Selection of studies

Titles/abstracts of all references retrieved through the electronic searches were read independently by two review authors (A.C.V.P.S. and J.A.A.A.). If the title/abstract fulfilled the set of inclusion criteria, the article was included straight away. Full texts of the articles with titles/abstracts providing incomplete information for a clear decision were obtained and assessed as well. The references whose full text fulfilled the same eligibility criteria were also included. In cases of divergence of opinion, a third review author (T.A.S.) was consulted to confirm inclusion or to exclude.

2.4 | Data extraction

The following data were extracted on a standardized form: authors' name, publication year, country where the case(s) was(were) reported, number of case(s) reported, patients' age and sex, anatomical location and diagnosis of the haematological malignant neoplasm.[2] Information on clinical presentation and symptoms, radiographic characteristics, histopathological data of the leukaemic infiltration, management and outcome was also extracted.

2.5 | Quality assessment

File S1 provides the critical appraisal[13] performed in the included studies.

2.6 | Data aggregation

The MedCalc software (MedCalc software bvba, Ostend, Flanders, Belgium) was used for statistical analysis. The chi-square test was used to evaluate the association of individuals' sex and lesions' anatomical location with the diagnosis of leukaemic infiltration. The Kruskal-Wallis test was employed to determine the association between individuals' age and diagnosis of leukaemic infiltration. Statistical significance was set at $p < 0.05$. Overall survival was calculated by survival analysis with the Kaplan-Meier test.

3 | RESULTS

3.1 | Literature search

A total of 636 studies were retrieved from the electronic databases searched. However, only 47 references met the eligibility criteria. The full text of 41 was available and the references were included. Efforts were made to contact the authors of six studies; however, their articles could not be retrieved. The hand search found 22 suitable articles. Thus, the final sample consisted of 63 articles reporting 68 cases. File S1 reports the full references of the included studies and general information about the cases of leukaemic infiltration in the oral and maxillofacial region.

3.2 | Demographic data

The most common diagnoses were AML (*n* = 32/47.0%), ALL (*n* = 10/14.7%) and CLL (*n* = 10/14.7%) (Figure 1A). With respect to origin, 28 (41.1%) cases were reported as *de novo*, whereas 39 (57.3%) involved pre-existing haematological disease. One case did not provide this information. The age of the affected individuals ranged from eight months to 84 years and the mean age at diagnosis was 40.7 ± 21.4 years. The most represented age group was the fifth decade of life (*n* = 14/20.9%) (Figure 1B). Thirty-six (53.7%) patients were males and 31 (46.3%) were females (Figure 1C). The male-to-female ratio was 1.2:1. The age and sex of an individual were not reported in one article. The gingiva was the most affected site (37%), but some cases were found concurrently in different locations (Figure 1D). To better illustrate the gingival involvement, we provided clinical images of one unpublished case of generalized gingival enlargement (Figure 2).

The chi-square test demonstrated no statistically significant difference between individuals with different types of leukaemic infiltration regarding sex ($p = 0.877$) (File S1) or anatomical location of the lesions ($p = 0.269$). The Kruskal-Wallis test showed that individuals with ALL were significantly younger than individuals with CLL ($p < 0.001$), AML + myeloid sarcoma (MS) ($p = 0.011$) and CML + MS ($p = 0.040$) (File S1).

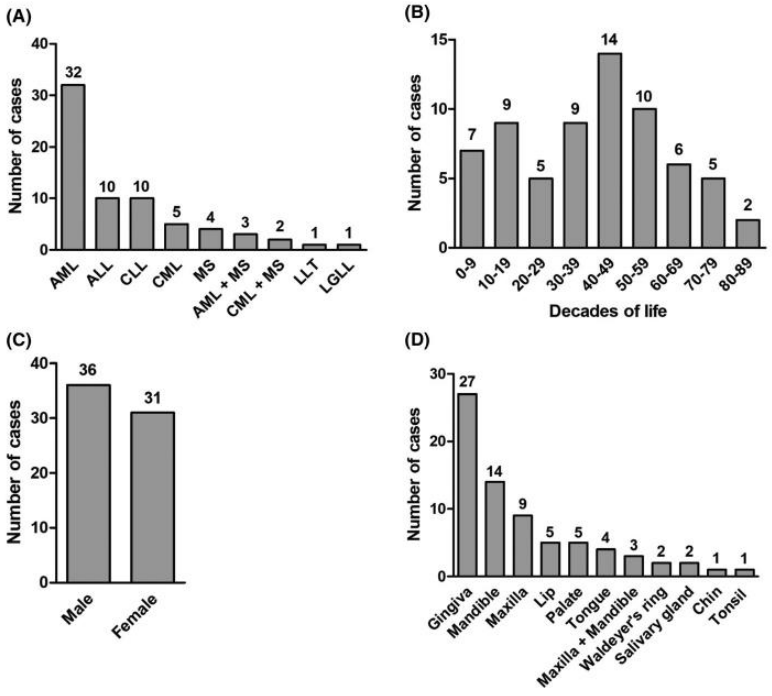

FIGURE 1 Frequency of reported cases of leukaemic infiltration in the oral and maxillofacial region by (A) haematological diagnosis (*n* = 68), (B) decade of life (*n* = 67), (C) sex (*n* = 67) and (D) anatomical location (*n* = 73). Data on the anatomical location were not analysed by number of individuals and data on oral manifestation were not analysed by number of anatomical locations, but rather by number of manifestations (ie the same individual may have been affected at more than one anatomical site, and the same anatomical site may have shown more than one manifestation). ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MS, myeloid sarcoma; LGLL, large granular lymphocyte leukaemia; and LLT, lymphoma with leukaemic transformation

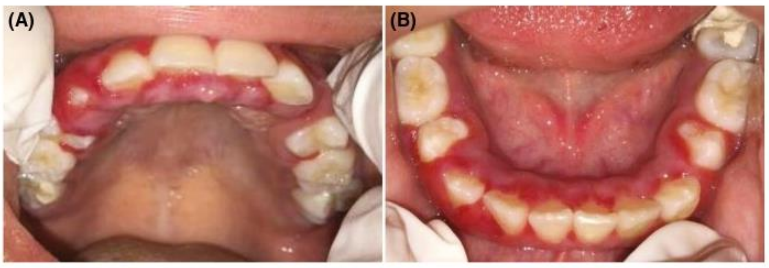

FIGURE 2 (A,B) An 11-year-old female patient with acute myeloid leukaemia presenting generalized and erythematosus gingival enlargement

3.3 | Clinical data, management and imaginological findings

Swelling/mass/oedema (*n* = 29/33.7%) and enlargement/hyperplasia/hypertrophy (*n* = 22/25.5%) were the main clinical findings. Other oral manifestations associated or not with those features were also described: ulcer (*n* = 8/9.3%), bleeding (*n* = 7/8.1%), tooth mobility (*n* = 6/6.9%), ulcer surface (*n* = 4/4.6%), erythema (*n* = 2/2.3%), erythematous nodules (*n* = 1/1.1%), necrotizing papules (*n* = 1/1.1%) and trismus (*n* = 1/1.1%). Pain (*n* = 4/4.6%) and paraesthesia (*n* = 1/1.1%) were reported as well. In six cases, there were no clinical details about oral manifestations.

In 54 (79.4%) cases, an oral biopsy was performed to better investigate leukaemic infiltration. In 28 (41.1%) cases, immunohistochemistry analysis was performed to confirm the diagnosis. The main markers used were myeloperoxidase (*n* = 13), lysozyme (*n* = 7) and CD68 (*n* = 7). Other markers such as CD3, CD5, CD7, CD10, CD14, CD19, CD20, CD22, CD24, CD34, CD43, CD45, CD66, CD79, CD117, CD45RO, CD45RB, HLA-DR, TdT, MB1, MB2, PAX5 and neutrophil esterase were also employed.

Image exams were available for 26 cases. The most common imaginological exams were those involving plain films, particularly panoramic radiographs (*n* = 12), periapical/bitewing radiographs (*n* = 7), computed tomography (*n* = 7) and magnetic resonance imaging (*n* = 2). The most common characteristic was the presence of a radiolucent area involving the tooth region (*n* = 9). Other features such as bone loss (*n* = 6), hyperintensity area (*n* = 3), widening of periodontal ligament (*n* = 2), loss of lamina dura (*n* = 1), loss of canal line (*n* = 1) and absence of cortical line (*n* = 1) were also described. In six cases, no imaginological features were identified.

3.4 | Outcome data

Regarding the resolution of oral signs after neoplastic therapy, 31 (45.5%) cases were resolved, seven cases (10.2%) were not resolved, and in 30 (44.1%) cases, this information was not provided. Fifty-two cases provided details about the outcome of the affected individuals. The mean duration of surveillance ranged from 0.1 to 25 months, with a mean of 7.2 ± 6.8 months. Thirty-one (59.6%) patients died, and the mean duration of patient follow-up ranged from 0.1 to 21 months, with a mean of 5.5 ± 5.2 months.

Survival analysis was conducted, providing data for 36 cases. Among these 36 individuals, 26 had died and 10 were alive during the follow-up period. The mean time of follow-up was 9.7 ± 1.4 months. The survival probability at one month of follow-up was 86.1%. Within the 21-month follow-up, the survival probability plummeted to 14.3%. Figure 3A shows the survival curve for all individuals with leukaemic infiltration. Survival analysis providing data for 20 individuals with AML was also conducted. Among these 20 individuals, 16 had died and four were alive during follow-up. The mean time of follow-up was 8.2 ± 1.7 months. The survival probability at one month of follow-up was 85.0%. Within the 21-month follow-up, the survival probability plummeted to 00.0%. Figure 3B displays the survival curve for AML individuals. File S1 displays the entire information about the calculation of the survival probability.

4 | DISCUSSION

The first signs of leukaemia may usually manifest in the oral cavity due to the infiltration of leukaemic cells or the association with a reduction in normal marrow elements, especially in the acute phase of the disease.[14] Thus, manifestations of this haematological illness can be screened and diagnosed by oral healthcare providers.[12]

In this review, we noticed that individuals in their fifties were the most affected by oral manifestations of leukaemic infiltration; however, there were differences regarding the leukaemia subtypes. The reported cases described 40–49-year-old individuals as the most affected, and 51.4% of the sample was diagnosed with AML. The acute form is abrupt and aggressive with primitive blasts cells in the peripheral blood and activation of mechanisms of tissue infiltration, while the chronic form is linked to a prolonged course and the presence of more mature cells.[11,15] Nevertheless, both may occur in the myeloid and lymphoid lineage and demographic differences among affected individuals have been observed.[15] Acute leukaemia usually affects children or young adults,[15] as also observed in this study. By contrast, a study found that the median age of individuals with acute leukaemia was 61 years.[12] Although ALL affected mainly the paediatric population (mean age of 11.7 years),[5] the occurrence of AML among individuals in this age group was very rare. We identified six cases of AML in children and adolescents. On the other hand, chronic leukaemia is frequently diagnosed in individuals in the sixth decade of life.[11]

Although there was a slight male preference of oral leukaemic infiltration, this occurrence was not marked when the illnesses were

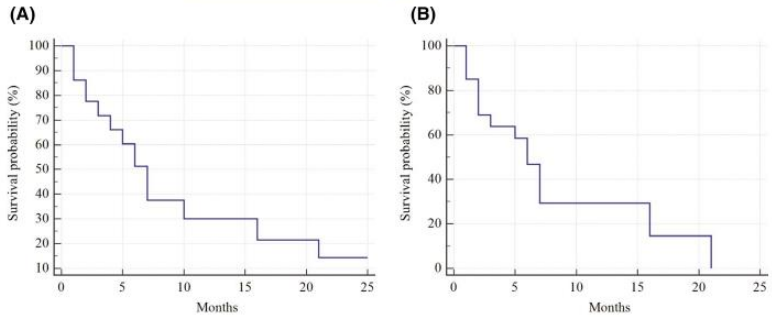

FIGURE 3 (A) Survival curve analysis of individuals with oral and maxillofacial leukaemic infiltration. (B) Survival curve analysis of individuals with acute myeloid leukaemia and infiltration in the oral and maxillofacial region

analysed individually. This finding is in line with two large series of individuals with leukaemia reported by Dreizen et al[16] and Hou et al,[17] who demonstrated a slight male predominance of 1.4:1 and 1.5:1, respectively. Another interesting finding is that the acute leukaemia group is reported more frequently. Hou et al[17] documented 209 of 230 patients diagnosed with the acute form, 60% of whom were males. Likewise, a recent study by Watson et al[12] demonstrated that among 263 individuals with leukaemia evaluated, 188 had received a diagnosis of AML and 39 a diagnosis of ALL. Herein, of the 45 cases of acute leukaemia, 35 were of myeloid lineage and 10 were lymphoid.

Individuals with swelling/mass/oedema in the oral and maxillofacial region represented 33.7% of cases of leukaemia, followed by enlargement/hyperplasia/hypertrophy (25.5%). In a large study, gingival bleeding was the most common clinical manifestation in all leukaemic groups, affecting in particular 27.8% of individuals with CML and 43.2% of individuals with AML.[17] Other series, however, found petechiae (59.7%) and ulcerations (36.3%) in the oral cavity of individuals with acute leukaemia.[18] Moreover, pain and tooth mobility may also occur regardless of the presence of the acute or chronic form, as documented elsewhere.[18] Importantly, secondary oral infections such as candidiasis, herpes simplex virus, bacterial infections and other conditions such as oral mucositis can occur in parallel to leukaemic infiltration as a consequence of treatment.[11,18]

In the current study, 37% of the reports described leukaemic infiltration in the gingiva. According to Watson et al,[12] the most common oral manifestation was bleeding, observed in 34 (12.9%) of the 263 documented patients. Gingival enlargement was also observed in 15 (5.7%) patients and was more associated with AML.[12] Another study reported that, in 16 of 22 patients with gingival enlargement, the condition was due to leukaemic infiltration (72.7%).[19] Gingiva is most often associated with leukaemic infiltration possibly because of its own microanatomy.[15] However, the mechanisms explaining gingival involvement are poorly defined. It is well known that poor hygiene can exacerbate gingival growth due to endotoxins released by pathogenic bacteria that elevate the levels of inflammatory cytokines.[15] Shankarapillai et al[20] reported that gingival growth was observed in three quarters of AML patients, probably associated with poor hygiene. Similarly, oral bleeding associated with poor hygiene that frequently occurs in the gingiva has been previously described in 15 patients with AML and ALL.[18] The gingival tissue affected by pre-existing inflammatory conditions can favour an influx of leukaemic cells to the periodontal sites.[15] Therefore, trauma and local irritants may be modifiers of leukaemic infiltrations in the oral and maxillofacial region, regardless of whether the patient is edentulous or not.[16,19] Conversely, leukaemias can be present in the course of periodontitis, associating with or even simulating this condition regardless of the inflammation induced by the biofilm of the dental plaque.[21] In these cases, even when conventional periodontal therapy was established, the tissue did not respond or maintain its clinical features, a fact that can be an additional tool for the final diagnosis.[21] Other conditions may be similar to the leukaemic manifestation in the gingival tissue, including those induced by oral medications (anticonvulsants), hereditary conditions (gingival fibromatosis), and neoplastic or reactive conditions.[15] Of note, leukaemic infiltration of bone generating osteolytic lesions was the main reported radiological finding. According to Michaud et al,[18] widening of the periodontal ligament space and loss of the trabecular pattern are also observed.

Some of the reported cases of oral leukaemic infiltration were related to MS, an extramedullary lesion that can be related to leukaemia and can occur separately or in association with other myeloproliferative disorders.[22] MS can precede or be associated with the diagnosis of AML without bone marrow involvement.[22] A former study documented nine cases without any history of bone marrow disease. The symptoms reported by these patients included skin lesions or oral rash, sore/painful throat, bleeding of the tongue or gingiva, bulging of the eye, painless mass and jaw pain.[22] Furthermore, the prognosis for cases of MS is reserved. Of the nine individuals with MS whose cases have been documented herein, five died. A fact that draws attention is that 50% of patients who had been diagnosed with isolated MS died prematurely.

Since leukaemic cells have the ability to infiltrate tissues, including those of the oral cavity,[14] an oral biopsy is an important tool for diagnosing challenging cases. Although the majority of documented cases (79.4%) had an oral biopsy, there still is no consensus about this approach. According to Watson et al,[12] it is not prudent to perform biopsies to confirm the presence of a leukaemic infiltrate or to determine whether there is an increase in the number or size of gingival cells in patients who have already had a diagnosis of acute leukaemia. It is important to consider that leukaemic patients may develop bleedings and infections due to pancytopenia, so that biopsies should be performed with

caution.[19] Notably, some studies have documented the presence of leukaemic infiltration in the gingival tissue by means of biopsies in patients who did not have clinically detectable gingival enlargement.[14,19] Microscopically, myeloid cells such as myeloblasts, monoblasts or megakaryoblasts are present.[4] In some cases, immunohistochemistry analysis was carried out to confirm the diagnosis and the markers most commonly used were myeloperoxidase, lysozyme and CD68.

Chemotherapy is the main therapeutic modality or, in some cases, allogeneic bone marrow transplantation.[15] Yet, gingival enlargement can be completely resolved in three to four weeks after the onset of antineoplastic treatment.[15] In this review, 45.5% of cases were completely resolved orally after the initiation of antineoplastic therapy. Unfortunately, death may be an event for individuals with leukaemic infiltration in the oral and maxillofacial region. Survival analysis demonstrated that 72.2% of the individuals died over a mean period of 21 months. The mean follow-up time of those individuals was 9.7 months.

Although this review has been performed with a comprehensive approach in order to incorporate the broadest literature possible, shortcomings should be addressed. First, we only included studies published in English. The vast majority of articles included herein were case reports or case series that could have influenced demographic characteristics such as sex and age. Also, some studies failed to provide radiographic exams and follow-up data. Thus, data aggregation and quantitative analyses were limited.

In summary, the oral and maxillofacial region may be affected by leukaemic infiltration and oral manifestations may be pivotal for the diagnosis of primary manifestation and relapse of haematological neoplasias. The acute form of leukaemia is more associated with the development of oral manifestations and individuals in their 40s are the most affected, with a slight preference for men. Dentists should be aware of swelling, enlargement and/or bleeding, especially in the gingiva, as predictors of this disease.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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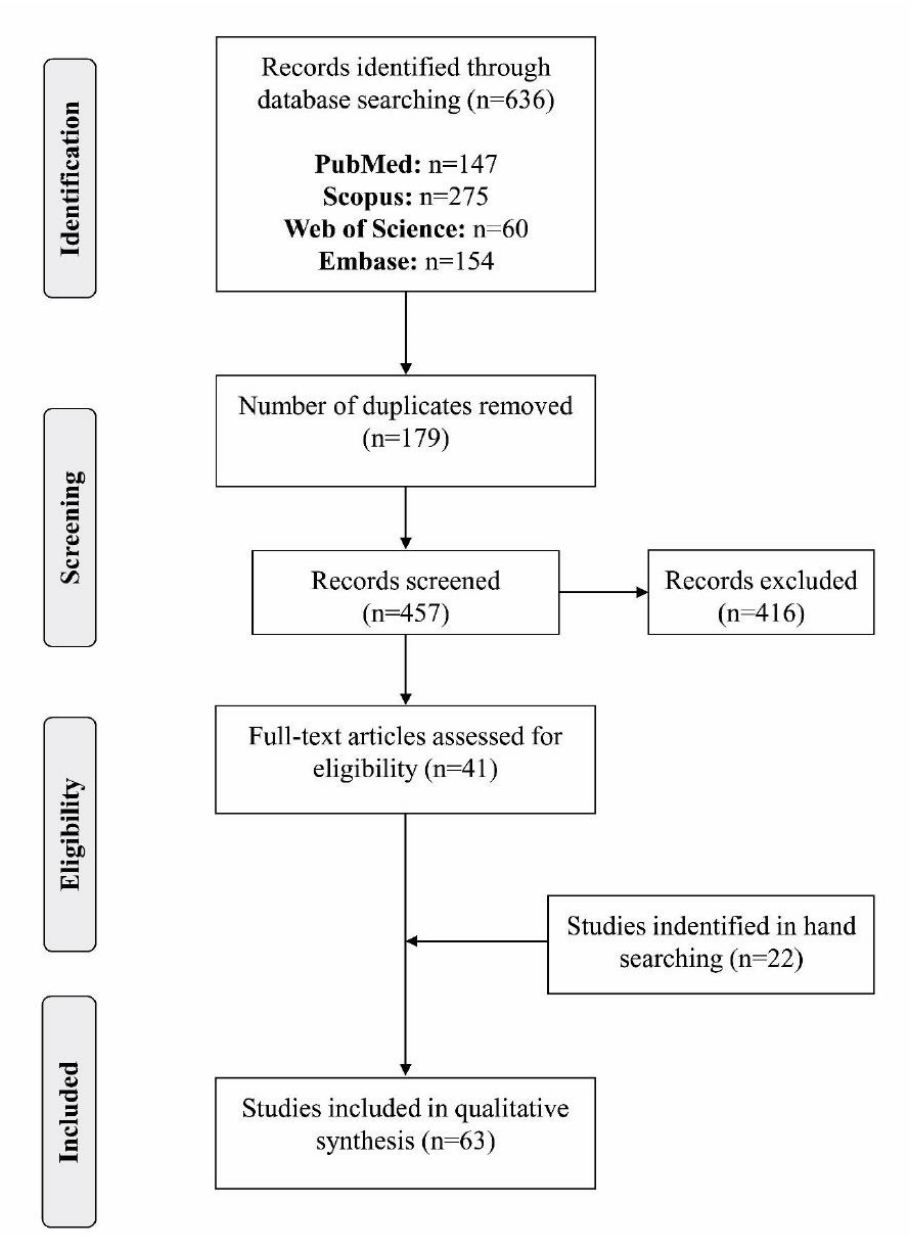
Supplementary file A. Search strategy for each searched electronic database

Database	Search strategy
PubMed	leukaemic infiltrate OR leukemic infiltrate OR leukaemic infiltration OR leukemic infiltration AND extramedullary disease OR leukemia OR leukaemia OR myeloid sarcoma OR granulocytic sarcoma OR chloroma OR extramedullary myeloid tumor AND oral OR oral cavity OR mouth OR oral mucosa OR buccal mucosal OR floor of the mouth OR lip OR lips OR tongue OR alveolar process OR alveolar ridge OR gingiva OR palate OR hard palate OR soft palate OR jaw OR jaws OR mandible OR maxilla OR sinus OR maxillary sinus OR oropharynx OR oropharyngeal
Web of Science	Same as PubMed
Scopus	"leukaemic infiltrate" OR "leukemic infiltrate" OR "leukaemic infiltration" OR "leukemic infiltration" AND "extramedullary disease" OR leukemia OR leukaemia OR "myeloid sarcoma" OR "granulocytic sarcoma" OR chloroma OR "extramedullary myeloid tumor" AND oral OR "oral cavity" OR mouth OR "oral mucosa" OR "buccal mucosal" OR "floor of the mouth" OR lip OR lips OR tongue OR "alveolar process" OR "alveolar ridge" OR gingiva OR palate OR "hard palate" OR "soft palate" OR jaw OR jaws OR mandible OR maxilla OR sinus OR "maxillary sinus" OR oropharynx OR oropharyngeal
Embase	Same as Scopus

Supplementary file B. Flow chart showing the results of the search process.



Supplementary file C. Quality assessment of included studies

Critical appraisal of the included articles was performed by means of the Joanna Briggs Institute, University of Adelaide tool for case reports or case series.[13] The included articles were evaluated according to the following parameters: clear description of individual's demographic characteristics, clear description of individual's medical history and presentation as a timeline, clear description of the individual's current clinical condition, clear description of the diagnostic test or any other evaluation method, clear description of treatment provided, clear description of post-intervention clinical condition, adequate identification of adverse events, and lessons provided by the case report; i.e., histopathological analysis with representative images. For each parameter, the included article was rated as "yes" (low risk of bias), "no" (high risk of bias), "unclear" (unclear risk of bias) or "not applicable".

All but eight cases provided a clear description of the demographic characteristics and the current clinical condition of the patients. Fifty-one (58%) cases provided the history of the patient as a timeline. Most cases (n=45/66.1%) provided take away lessons. A total of 19 articles reporting 23 cases (33.8%) did not provide histopathological analysis. Most articles provided intervention data (n=56/82.3%), and the post-intervention (n=53; 77.9%) clinical condition of the affected individuals.

Supplementary file D. Critical appraisal of the reported and included cases of leukemic infiltration of the oral and maxillofacial region

Author(s) (year of publication)	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Were the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Presant et al., 1973	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Stern & Cole, 1973	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Goepp, 1976	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Lorson et al., 1978	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Peterson et al., 1983	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Reichart et al., 1984	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Barrett, 1986	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Barrett, 1987	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Ficarra et al., 1987	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Saleh et al., 1987	Yes	Unclear	Yes	Yes	Yes	Yes	NA	Yes
Barker & Sloan, 1988	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Bergmann et al., 1988	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Hou & Tsai, 1988	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
de Vicente Rodriguez et al., 1990	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Eisenberg et al., 1991	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Hirota et al., 1992	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Smith et al., 1993	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Asada et al., 1994	Yes	Unclear	Yes	Yes	No	Unclear	NA	Yes
Porter et al., 1994	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Stack & Ridley, 1994	Yes	Unclear	Yes	Unclear	Unclear	Unclear	NA	Yes
Haznedaroğlu et al., 1995	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Morgan, 1995	Yes	Yes	Yes	Yes	Yes	Yes	NA	No

Anil et al., 1996	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Açikgöz et al., 1999	Yes	Yes	Yes	Unclear	Yes	Yes	NA	No
Bassichis et al., 2000	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Baughman et al., 2000	Yes	Unclear	No	Yes	Yes	Yes	NA	No
Tong & Lam, 2000	Yes	Yes	Yes	Yes	Yes	Unclear	NA	Yes
Tomás Carmona et al., 2000	Yes	Unclear	Yes	Yes	Unclear	Unclear	NA	Yes
Amin et al., 2002	Yes	Unclear	Yes	Yes	Yes	Yes	NA	Yes
Rhee et al., 2002	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Katz & Peretz, 2002	Yes	Unclear	Unclear	Yes	Unclear	Unclear	NA	No
Antmen et al., 2003	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Haytac et al., 2003	Yes	Yes	Yes	Yes	Yes	Unclear	NA	No
Sollecito et al., 2003	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Gomez et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Stoopler et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Vural et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Goteri et al., 2006	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Benson et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Gallipoli & Leach, 2007	Yes	Unclear	Unclear	Yes	Unclear	Unclear	NA	No
Matsushita et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Matsushita et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Xie et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Au et al., 2008	Yes	Yes	Yes	Yes	Unclear	Unclear	NA	Yes
Mohamedbhai et al., 2008	Yes	Yes	Yes	Yes	Unclear	Unclear	NA	Yes
Srinivasan et al., 2008	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Bakathir & Al-Hamdani, 2009	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
da Silva Santos et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes

da Silva-Santos et al., 2010	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Pau et al., 2010	Unclear	Yes	Yes	Yes	Yes	Yes	NA	Yes
Brito et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Güzeldemir et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Obi et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Sonoi et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Kolli et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Abdolkarimi et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Hasan et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Melton & Pearlman, 2015	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	No
Melton & Pearlman, 2015	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	No
Melton & Pearlman, 2015	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	No
Melton & Pearlman, 2015	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	No
Melton & Pearlman, 2015	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	NA	No
Jin et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Yacoub & Mahalwar, 2016	Yes	Unclear	Yes	Yes	Yes	Yes	NA	No
Yoshida et al., 2016	Yes	Unclear	Yes	Yes	Yes	Yes	NA	No
Kuswandani et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	NA	No
Kacem et al., 2019	Yes	Unclear	Yes	Yes	Yes	Unclear	NA	Yes
Benites et al., 2020	Yes	Unclear	Yes	Yes	Yes	Yes	NA	Yes

NA, not applicable.

Supplementary file E. Summary of cases retrieved in the review of leukemic infiltration of the oral and maxillofacial region

Author(s)/year of publication	Country	Diagnosis	Age (years)	Sex	Clinical features	Anatomical location	Imaging findings	Intraoral biopsy to investigate leukemic infiltration	Origin of the disease	Oral resolution after antineoplastic therapy
Presant et al., 1973	US	CLL	45	M	Hyperplasia	Gingiva	NR	Yes	Recurrence	Yes
Stern & Cole, 1973	US	AML	19	M	Enlargement and tooth mobility	Gingiva	Bone loss	Yes	Recurrence	No
Goepp, 1976	US	ALL	3	M	Mass with ulceration surface and tooth mobility	Mandible	Bone loss	Yes	Recurrence	NA
Lorson et al., 1978	US	AML*	29	F	Swelling	Mandible	Radiolucent area	NR	*De novo*	No
Peterson et al., 1983	US	AML	33	M	Pain	Mandible	Widening of periodontal ligament	Yes	Recurrence	Yes
Reichart et al., 1984	Germany	AML*	35	F	Swelling	Mandible	Radiolucent area	Yes	*De novo*	No
Barrett, 1986	Australia	AML*	40	M	Enlargement	Gingiva	NR	NR	Recurrence	Yes
Barrett, 1987	Australia	AML*	29	F	Neutropenic ulceration	Tongue and lip	NR	NR	Recurrence	Yes
Ficarra et al., 1987	US	AML	67	F	Swelling	Hard Palate	None	Yes	*De novo*	Yes
Saleh et al., 1987	US	MS + AML	62	F	Mass	Mandible	NR	Yes	Recurrence	Yes
Barker & Sloan, 1988	England	AML	4	F	Swelling	Maxilla	Bone loss	Yes	Recurrence	NA
Bergmann et al., 1988	Denmark	AML	47	M	Swelling	Gingiva	NR	Yes	Recurrence	Yes
Hou & Tsai, 1988	Taiwan	AML*	25	F	Swelling, bleeding, and pain	Gingiva	NR	NR	*De novo*	Yes

de Vicente Rodriguez et al., 1990	Spain	MS	56	M	Swelling	Mandible	Bone loss	Yes	*De novo*	NA
Eisenberg et al., 1991	US	AML	33	M	Erythematous nodules	Gingiva	NR	Yes	*De novo*	Yes
Hirota et al., 1992	Japan	LLT	44	F	Necrotic ulcer	Hard palate	NR	Yes	*De novo*	NA
Smith et al., 1993	US	AML	13	F	Mass and hyperplasia	Mandible and maxilla	NR	Yes	Recurrence	Yes
Asada et al., 1994	Japan	LGLL	36	M	Necrotizing papules and nodules	NR	NR	NR	NA	NA
Stack & Ridley, 1994	US	CML + MS	70	M	Mass	Mandible	Bone loss	Yes	*De novo*	NA
Porter et al., 1994	England	CLL	71	M	Enlargement with ulceration	Gingiva	NR	Yes	Recurrence	No
Haznedaroğlu et al., 1995	Turkey	AML*	19	M	Swelling	Gingiva	NR	Yes	Recurrence	NA
Morgan, 1995	US	CLL	77	F	Mass	Mandible	Radiolucent area	Yes	Recurrence	Yes
Anil et al., 1996	India	AML*	34	F	Enlargement	Gingiva	NR	Yes	*De novo*	NA
Açikgöz et al., 1999	Turkey	AML	28	M	Hyperplasia	Maxilla	None	NR	*De novo*	Yes
Bassichis et al., 2000	US	AML	8 months	M	Mass	Mandible	Hyperintensity area	Yes	Recurrence	Yes
Baughman et al., 2000	US	AML	44	M	NR	Mandible	Radiolucent area	Yes	Recurrence	NA
Tomás Carmona et al., 2000	Spain	CML + MS	60	F	Mass	Mandible	NR	Yes	Recurrence	NA
Tong & Lam, 2000	China	AML + MS	76	F	Ulcerative lesion	Maxilla	None	Yes	*De novo*	Yes
Amin et al., 2002	US	AML	58	M	Mass	Hard palate	NR	Yes	*De novo*	NA
Rhee et al., 2002	US	ALL	11	M	Enlargement	Salivary gland	Hyperintensity area	Yes	Recurrence	Yes

Katz & Peretz, 2002	Israel	ALL	6	M	Trismus	Maxilla and mandible	None	NR	*De novo*	NA
Antmen et al., 2003	Turkey	MS	12	F	Mass	Gingiva	Radiolucent area	Yes	*De novo*	Yes
Haytac et al., 2003	Turkey	ALL	14	M	Enlargement and teeth mobility	Gingiva	Bone loss, loss of lamina dura, and radiolucent area	NR	*De novo*	NA
Sollecito et al., 2003	US	AML	32	M	Oedema and erythema with bleeding	Gingiva	NR	Yes	Recurrence	No
Gomez et al., 2004	Brazil	CLL	62	F	Swelling	Hard palate	NR	Yes	Recurrence	NA
Stoopler et al., 2004	US	AML	50	M	Ulcer and erythema	Lip and tongue	NR	Yes	*De novo*	Yes
Vural et al., 2004	Turkey	CML*	38	F	Hypertrophy with bleeding	Gingiva	NR	Yes	Recurrence	Yes
Goteri et al., 2006	Italy	MS	84	F	Mass	Hard palate	NR	Yes	*De novo*	Yes
Benson et al., 2007	England	ALL	10	F	Pain, tenderness, and loss of sensation	Mandible, lip, and chin	Absence of cortical line	Yes	Recurrence	Yes
Gallipoli & Leach, 2007	Scotland	AML*	45	F	Enlargement	Gingiva	NR	NR	*De novo*	Yes
Matsushita et al., 2007	Japan	AML + MS	50	M	Swelling	Maxilla	NR	Yes	*De novo*	Yes
Matsushita et al., 2007	Japan	CML*	59	M	Ulcer	Mandible	NR	Yes	Recurrence	No
Xie et al., 2007	China	CML	32	F	Swelling	Maxilla and mandible	NR	Yes	Recurrence	Yes
Au et al., 2008	China	ALL	22	F	Swelling	Gingiva	NR	Yes	Recurrence	NA
Mohamedbhai et al., 2008	England	AML	45	M	Ulcer	Tongue	NR	Yes	*De novo*	Yes
Srinivasan et al., 2008	England	AML	77	M	Ulcer	Lip	NR	Yes	Recurrence	NA

Bakathir & Al-Hamdani, 2009	Oman	ALL	19	F	Swelling and teeth mobility	Maxilla and mandible	Radiolucent area and loss of canal line	Yes	Recurrence	NA
da Silva Santos et al., 2010	Brazil	CML	47	F	Hyperplasia and bleeding	Gingiva	None	Yes	*De novo*	Yes
da Silva-Santos et al., 2010	Brazil	AML	43	M	Enlargement and bleeding	Gingiva	NR	Yes	Recurrence	NA
Pau et al., 2010	Austria	CML	NR	NR	Swelling and tooth mobility	Maxilla	Radiolucent area	Yes	Recurrence	Yes
Brito et al., 2012	Brazil	ALL	4	M	Swelling, pain and tooth mobility	Maxilla	Radiolucent area	Yes	Recurrence	Yes
Güzeldemir et al., 2012	Turkey	AML*	47	M	Enlargement	Gingiva	NR	Yes	Recurrence	No
Obi et al., 2012	US	AML	52	F	Enlargement with haemorrhagic ulceration	Lip	NR	Yes	Recurrence	NA
Sonoi et al., 2012	Japan	AML	39	F	Enlargement	Gingiva	NR	Yes	Recurrence	Yes
Kolli et al., 2014	India	ALL	19	F	Enlargement	Gingiva	NR	NR	Recurrence	NA
Abdolkarimi et al., 2015	Iran	ALL	9	M	Swelling	Maxilla	Hyperintensity area	Yes	*De novo*	Yes
Hasan et al., 2015	India	AML	18	F	Swelling	Gingiva	None	NR	*De novo*	NA
Melton & Pearlman, 2015	US	CLL	44	M	NR	Waldeyer's ring	NR	Yes	*De novo*	NA
Melton & Pearlman, 2015	US	CLL	81	F	NR	Waldeyer's ring	NR	Yes	*De novo*	NA
Melton & Pearlman, 2015	US	CLL	47	M	NR	Palatine tonsil	NR	Yes	Recurrence	NA
Melton & Pearlman, 2015	US	CLL	57	M	NR	Maxilla (maxillary sinus)	NR	Yes	Recurrence	NA
Melton & Pearlman, 2015	US	CLL	58	F	NR	Salivary gland	NR	Yes	Recurrence	NA

Jin et al., 2016	South Korea	MS	52	M	Swelling	Gingiva	Widening of periodontal ligament	Yes	Recurrence	NA
Yacoub & Mahalwar, 2016	US	AML*	57	M	Enlargement	Gingiva	NR	NR	*De novo*	NA
Yoshida et al., 2016	Japan	AML	69	M	Hyperplasia with ulceration and necrosis	Maxilla	NR	NR	*De novo*	Yes
Kuswandani et al., 2017	Indonesia	AML	46	F	Enlargement and bleeding	Gingiva	NR	NR	Recurrence	NA
Kacem et al., 2019	Tunisia	CLL	66	F	Enlargement	Gingiva	NR	Yes	Recurrence	NA
Benites et al., 2020	Brazil	AML	48	M	Hyperplasia, bleeding, and ulcer	Gingiva and tongue	NR	Yes	*De novo*	Yes

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; F, female; MS, myeloid sarcoma; LGLL, large granular lymphocyte leukaemia; LLT, lymphoma with leukemic transformation; M, male; NA, not applicable; NR, not reported; US, United States.
*Some cases were categorized in the major haematological group.

Supplementary file F. Comparison of sex between individuals with different types of leukemic infiltration of the oral and maxillofacial region

Diagnosis	Males – number (%)	Females – number (%)
AML	19 (52.8)	13 (41.9)
CML	1 (2.8)	3 (9.7)
ALL	6 (16.7)	4 (12.9)
CLL	5 (13.9)	5 (16.1)
MS	2 (5.6)	2 (6.5)
AML + MS	1 (2.8)	2 (6.5)
CML + MS	1 (2.8)	1 (3.2)
LLT	0 (00.0)	1 (3.2)
LGLL	1 (2.8)	0 (00.0)

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MS, myeloid sarcoma; LGLL, large granular lymphocyte leukaemia; LLT, lymphoma with leukemic transformation.

For the sex variable, the chi-square test demonstrated no significant difference between individuals with different types of leukemic infiltration of the oral and maxillofacial region (p=0.877).

Supplementary file G. Comparison of age between individuals with different types of leukemic infiltration of the oral and maxillofacial region

	Number of individuals	Mean	Standard deviation	Median	Min - Max
AML	32	38.30	17.73	39.50	0.66 – 77.00
CML	4	44.00	11.74	42.50	32.00 – 59.00
ALL	10	11.70	6.63	10.50	3.00 – 22.00
CLL	10	60.80	13.11	60.00	44.00 – 81.00
MS	4	51.00	29.64	54.00	12.00 – 84.00
AML + MS	3	62.66	13.01	62.00	50.00 – 76.00
CML + MS	2	65.00	7.07	65.00	60.00 – 70.00
LLT	1	44.00	-	-	-
LGLL	1	36.00	-	-	-

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MS, myeloid sarcoma; LGLL, large granular lymphocyte leukaemia; LLT, lymphoma with leukemic transformation.

For the age variable, the Kruskal Wallis test demonstrated a statistically significant difference between ALL and CLL ($p<0.001$), between ALL and AML + MS ($p=0.011$), and between ALL and CML + MS ($p=0.040$).

Supplementary file H. Survival analysis of individuals with leukemic infiltration and individuals with acute myeloid leukaemia (analysed individually) in the oral and maxillofacial region

	Time (months)	Number of cases	Status of the individual		Cumulative events	Remaining cases	Survival probability
			Dead	Alive			
All cases	1	6	5	1	5	30	86.1%
	2	3	3	0	8	27	77.5%
	3	2	2	0	10	25	71.8%
	4	2	2	0	12	23	66.0%
	5	3	2	1	14	20	60.3%
	6	5	3	2	17	15	51.2%
	7	5	4	1	21	10	37.6%
	10	2	2	0	23	8	30.1%
	12	1	0	1	23	7	-
	16	2	2	0	25	5	21.5%
	18	2	0	2	25	3	-
	21	1	1	0	26	2	14.3%
	23	1	0	1	26	1	-
	25	1	0	1	26	1	-
AML	1	4	3	1	3	16	85.0%
	2	3	3	0	6	13	69.1%
	3	1	1	0	7	12	63.8%
	5	2	1	1	8	10	58.4%
	6	2	2	0	10	8	46.8%
	7	3	3	0	13	5	29.2%
	12	1	0	1	13	4	-
	16	2	2	0	15	2	14.6%
	18	1	0	1	15	1	-
	21	1	1	0	16	0	00.0%

Supplementary file I. Full references of the included studies

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3.2 Capítulo 2: Estudo retrospectivo

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Leukaemia/lymphoma oral infiltration and its impact on disease outcomes: a Brazilian study

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Abstract

Objective: Oral malignant infiltrations (OMI) are relevant for the diagnosis and prognosis of leukaemia/lymphoma. This study analysed the oral health status and OMI of individuals with leukaemia/lymphoma.

Materials and Methods: A retrospective analysis (2010-2021) of data from individuals seen at a specialized hospital-based dental service in Brazil.

Results: A total of 781 cases of leukaemia/lymphoma were surveyed. Acute lymphoblastic leukaemia (30.1%), acute myeloid leukaemia (AML; 26.0%), and non-Hodgkin lymphoma (22.2%) were the most common diagnoses. The first (21.3%) and second (19.3%) decades of life were the most affected. Overall, dental caries (36.7%) and periodontal changes (34.6%) were the most frequent oral conditions. OMI occurred in 25 (3.2%) individuals. Lesions mainly involved the gingiva (80%) and patients diagnosed with AML (64%). Death (p<0.001) and worse periodontal condition (p=0.036) were more frequent among adults with OMI than among those without OMI. Death (p=0.002) was more frequent among paediatric individuals with OMI than among those without OMI. When controlling for underlying disease, no association was observed between OMI and these outcomes.

Conclusion: Oral status of individuals with leukaemia, particularly those with acute leukaemia or lymphoma, should be closely monitored since one or multiple conditions may occur, including OMI, which may influence disease outcomes.

Keywords: hospital dental service; leukaemia; leukemic infiltration; lymphoma; oral manifestations

1. Introduction

Leukaemia and lymphoma are malignant diseases that affect the haematolymphoid system, resulting in the proliferation of neoplastic cells (de Leval & Jaffe, 2020; Miranda-Filho et al., 2018; Swerdlow et al., 2017). In 2017, there were approximately 2.43 million cases of leukaemia around the world, with an age-standardized prevalence rate of 32.26 per 100,000 (Lin et al., 2021). Additionally, in 2020, 544,352 and 83,087 individuals were diagnosed with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), respectively (Sung et al., 2021). Leukaemias, NHL and HL are the 15th, 13th, and 28th most common cancers (Sung et al., 2021).

Leukaemia manifests in either immature (precursor) or mature cells, giving rise to its acute or chronic form and a distinct age prognosis. The condition is commonly divided into four major subtypes: acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphoblastic leukaemia (CLL), and chronic myeloid leukaemia (CML) (Miranda-Filho et al., 2018; Short, Rytting, & Cortes, 2018; Swerdlow et al., 2017). Traditionally, lymphomas are classified as NHL or HL. The former shows a myriad of entities that are subcategorized into mature B-cell neoplasms and mature T- and NK-cell neoplasms (Swerdlow et al., 2017). In the latter, two major types are recognized, i.e., nodular lymphocyte predominant HL (NLPHL) and classic HL (CHL) (de Leval & Jaffe, 2020; Swerdlow et al., 2017).

In both diseases, the affected individual exhibits systemic findings such as weight loss, fever, and fatigue which are usually due to anaemia, neutropenia, and thrombocytopenia (Burke & Startzell, 2008; Hochhaus et al., 2017; Malard & Mohty, 2020; Miranda-Filho et al., 2018; Short, Rytting, & Cortes, 2018). Lymphoma can affect virtually any location, including the oral and oropharyngeal regions (de Arruda et al., 2021; de Leval & Jaffe, 2020). Previous studies have reported oral manifestations mainly in individuals with acute forms of leukaemia (de Sena et al., 2021). Importantly, more than 30% of patients with newly diagnosed leukaemia had some

oral manifestations (Watson, Wood, Maxymiw, & Schimmer, 2018). The first signs of leukaemia can usually manifest in the oral cavity due to the infiltration of leukaemic cells or the decline of normal marrow elements, especially in the acute phase of the disease (Francisconi, Caldas, Oliveira Martins, Fischer Rubira, & da Silva Santos, 2016). Gingival enlargement and bleeding, petechiae, and oral pallor are the main common findings (de Sena et al., 2021). Recent literature has revealed a paradox, with the rate of individuals with leukaemia seeking dental consultations being very low (Owlia, Ansarinia, & Vahedian Ardakani, 2021). Moreover, dental hospital-based services are limited, especially in Brazil, where public policy was implemented only in 2004 prioritizing primary care (Pucca, Gabriel, de Araujo, & de Almeida, 2015).

Epidemiological data on diseases of haematopoietic and lymphoid tissues affecting the oral cavity have been published, but most of them are single reports or case series (de Sena et al., 2021), including patients with leukaemic infiltration (Angst, Maier, Dos Santos Nogueira, Manso, & Tedesco, 2020; Watson, Wood, Maxymiw, & Schimmer, 2018), and few have evaluated the oral status of individuals with lymphoma (Kusuke, Custódio, & de Sousa, 2019). In Brazil, reports regarding the oral health status of patients with leukaemia are apparently restricted to small case series (Angst, Maier, Dos Santos Nogueira, Manso, & Tedesco, 2020). Thus, the purpose of the present study was to report the oral health status of individuals with leukaemia/lymphoma and associated factors from a Brazilian referral service in an 11-year retrospective analysis. Moreover, it is of clinical relevance to identify the most vulnerable groups with oral malignant infiltrations (OMI) and to provide scientific evidence of their impact on disease outcomes, improving health care and the prognosis for these individuals.

2. Materials and Methods

2.1 Study design and ethical clearance

This was a retrospective and cross-sectional study based on the medical records of Hospital das Clínicas, Belo Horizonte – a public referral service supported by the Brazilian Public Health System. The sample of this study consisted of inpatients or outpatients diagnosed with leukaemia/lymphoma who were registered at the onco-haematology service and attended the dental service between January 2010 and December 2021. The guidelines for Strengthening the Reporting of Observational studies in Epidemiology (Knottnerus & Tugwell, 2008) were followed. The study was approved by the Institutional Ethics Committee (No. 47136721.5.0000.5149) and the patient's identity remained anonymous according to the Declaration of Helsinki.

2.2 Patients and data collection

Data collection took place in 2021. A total of 781 records of patients diagnosed with leukaemia/lymphoma were retrieved. Individuals were classified according to the 2017 WHO classification of tumours of haematopoietic and lymphoid tissues (Swerdlow et al., 2017). The exclusion criteria were incomplete clinicodemographic information, cases with borderline diagnoses, and cases who had not been evaluated by a dentist at the oral health service of the hospital.

Two authors (A.C.V.P.S. and J.A.A.A.) reviewed all records. Affected individuals were analysed regarding sex, age, diagnosis of leukaemia/lymphoma (subtype), status of manifestation (primary or relapse), infiltration of the central nervous system (CNS) (absent or present), HIV status (positive or negative), and outcome (alive or dead). For oral health status assessment, dental caries, periodontal changes, viral infections (e.g., herpes simplex, cytomegalovirus), fungal diseases (e.g., candidiasis), oral mucositis, other manifestations (e.g., tongue alterations, inflammatory and/or reactive conditions, oral mucosa hyperpigmentation

due to antineoplastic drugs), physical injuries, petechiae/ecchymosis, and tongue coating were evaluated as dichotomous outcomes (absent or present).

Malignant infiltration-related oral information such as clinical features, control of dental plaque, blood count on the day of OMI diagnosis, and follow-up of the patients was collected from the records. The diagnosis of OMI was presumed, considering that the biopsy was performed in three cases. Biopsy was allowed only in cases in which patients were haemodynamically stabilized and had neutrophil counts $\geq 1.0\times10^3$ cells/mm^3 and platelet counts $\geq 50{,}000\times10^3$ cells/mm^3. Clinically, oral manifestations such as gingival enlargement/swelling, ulceration, necrosis, pain, friability, and bleeding were considered (de Sena et al., 2021; Dreizen, McCredie, Keating, & Luna, 1983). During the patient's hospitalisation, preventive protocols of adequate oral hygiene such as daily tooth brushing and mouthwash with 0.12% chlorhexidine digluconate are recommended by the service.

2.3 Data 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 statistics were performed for the whole sample and in intra-group assessments for individuals aged ≤18 years and individuals aged ≥19 years. To better examine the outcomes of individuals who developed OMI (exposure), we matched these patients to those without OMI for the variables age, sex, inpatients/outpatients, and year in which the individual had attended the oral health service. The unpaired t-test was used to examine the blood count of patients who developed OMI and those who did not. McNemar's test was used to compare individuals who developed OMI and those without OMI, focusing on data about the following outcomes: death, periodontal changes, status of manifestation, and CNS infiltration. In a second analysis, we matched individuals who developed OMI to those who did not develop OMI for the following

variables: underlying disease (type, status of manifestation and CNS infiltration), age and sex of the individual, inpatients/outpatients, and year in which the individual had attended the oral health service. The McNemar's test was used for exploring data on the outcomes death and periodontal changes. For all analyses, the level of significance was set at <0.05.

3. Results

3.1 General information and population characteristics

A total of 8,371 individuals were evaluated during the 11-year timeframe. Of these, 2,539 were evaluated in hospital wards and 5,832 in outpatient clinics and a total of 781 records (220 from outpatient clinics, 542 from hospital wards, and 19 from both) fulfilled the inclusion criteria. A flowchart of the study is depicted in **Figure 1**.

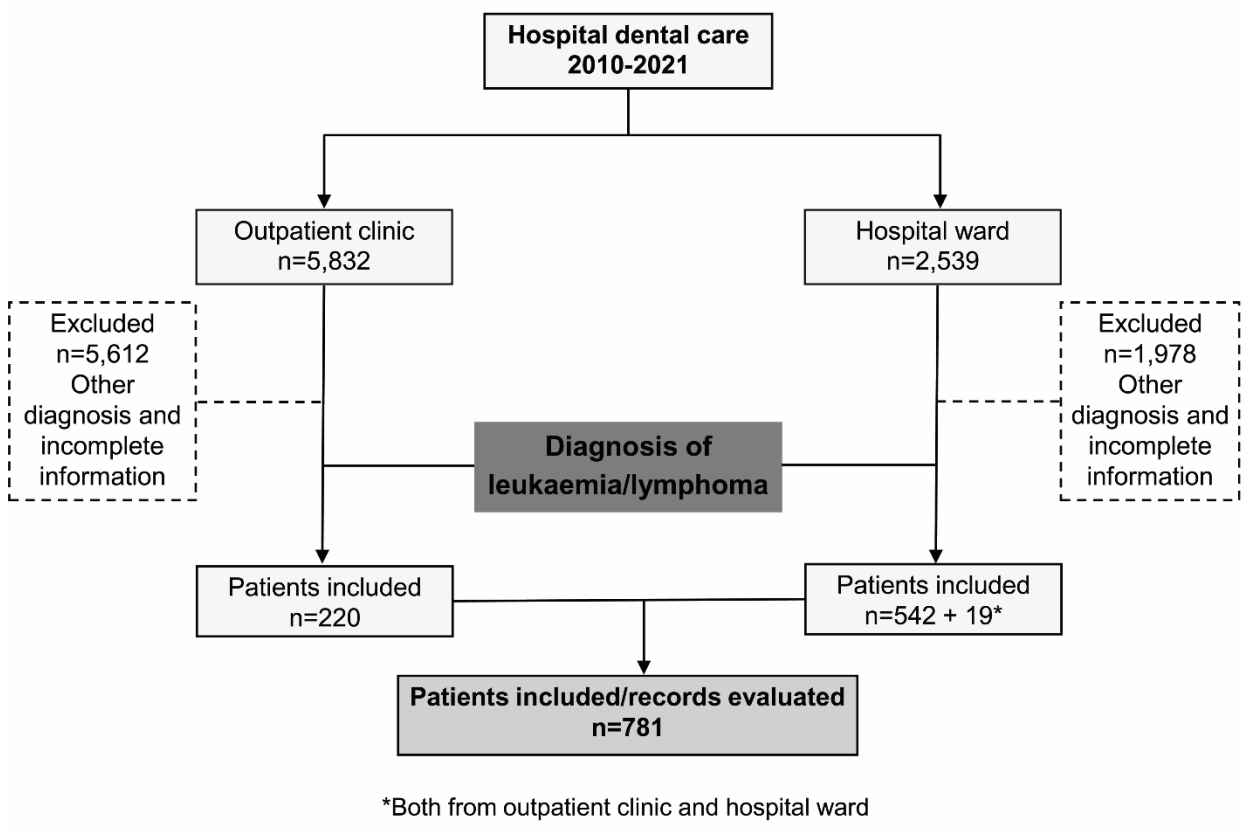

Figure 1. Study flow diagram.

Data on the clinicodemographic aspects and outcomes of the patients are provided in **Table 1**. Males (n=449/57.2%) were more affected than females (n=332/42.5%), with a male-to-female ratio of 1.3:1. The mean age of affected individuals was 31.4 (±21.9) years (range: 5 months to 85 years). The mean age of males was 29.9 (±21.1) years and the mean age of females was 32.9 (±23.0) years. Individuals in the first (n=166/21.3%) and second (n=151/19.3%) decades of life were more affected. The three most common diagnoses were ALL (n=235/30.1%), AML (n=203/26.0%), and NHL (n=173/22.2%) (**Supplementary Table 1** and **Supplementary Table 2**). Regarding the status of manifestation, in 88.1% (n=688) of the records, the baseline diseases were presented as primary, while 11.9% (n=93) presented as relapses. Most individuals were HIV negative (n=762/97.6%). A total of 701 (89.8%) patients remained alive, while 80 (10.2%) died.

Table 1. Clinicopathological data and outcomes of 781 records of individuals with malignant haematological neoplasms seen at a hospital-based dental service from 2010 to 2021

Variable	*n (%)*
Sex	
Male	449 (57.5)
Female	332 (42.5)
Ratio	1.3:1
Age (year)	mean: 31.4±21.9 (male: 29.9±21.1 and female: 32.9±23.0) Range: 5 months-85 years
0-9	166 (21.3)
10-19	151 (19.3)
20-29	93 (11.9)
30-39	77 (9.9)
40-49	87 (11.1)
50-59	98 (12.5)
60-69	80 (10.3)
70-79	23 (2.9)
80-89	6 (0.8)
Diagnosis	
ALL	235 (30.1)
AML	203 (26.0)
NHL	173 (22.2)
CML	109 (14.0)
HL	52 (6.7)
BAL	3 (0.4)
PCL	2 (0.3)
MS	2 (0.3)
CEL, NOS	1 (0.1)
JMML	1 (0.1)
Manifestation	
Primary	688 (88.1)
Relapse	93 (11.9)
HIV status	
Negative	762 (97.6)
Positive	19 (2.4)
Outcome	
Alive	701 (89.8)
Died	80 (10.2)

Note: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BAL, biphenotypic acute leukaemia; CEL, NOS, chronic eosinophilic leukaemia, not otherwise specified; CLL, chronic lymphocytic

leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; JMML, juvenile myelomonocytic leukaemia; MS, myeloid sarcoma; NHL, non-Hodgkin lymphoma; PCL, plasma cell leukaemia.

3.2 Oral status of patients with leukaemia/lymphoma

Table 2 describes the clinical oral aspects of the individuals, with the sample stratified into children and adolescents (0-18 years) (n=302/38.7%) and adults (≥19 years) (n=479/61.3%). Both paediatric and adult populations exhibited the same three most frequent oral findings, i.e., dental caries (n=104/34.4% and n=183/38.2%), periodontal changes (n=80/26.5% and n=190/39.7%), and oral mucositis (n=171/56.6% and n=142/29.6%).

Table 2. Oral health status of children and adolescents (0-18 years) and adults (≥19 years) with malignant haematological neoplasms (n=781) seen at a hospital-based dental service from 2010 to 2021

Variables	*0-18 years (n=302/38.7%)*	*≥19 years (n=479/61.3%)*
	n (%)	*n (%)*
Dental caries		
Absent	198 (75.6)	296 (61.8)
Present	104 (34.4)	183 (38.2)
Periodontal changes		
Absent	222 (73.5)	289 (60.3)
Present	80 (26.5)	190 (39.7)
Viral infections		
Absent	226 (74.8)	405 (84.6)
Present	76 (25.2)	74 (15.4)
Fungal diseases		
Absent	226 (74.8)	404 (84.3)
Present	76 (25.2)	75 (15.7)
Oral mucositis		
Absent	131 (43.4)	337 (70.4)
Present	171 (56.6)	142 (29.6)
Other manifestations		
Absent	222 (73.5)	368 (76.8)
Present	80 (26.5)	111 (23.2)
Physical injuries		
Absent	214 (70.9)	388 (81.0)
Present	88 (29.1)	91 (19.0)
Petechia/ecchymosis		
Absent	272 (90.1)	419 (87.5)
Present	30 (9.9)	60 (12.5)
Tongue coating		
Absent	252 (83.4)	411 (85.8)
Present	50 (16.6)	68 (14.2)

3.3 Leukaemia/lymphoma oral infiltration: clinical presentation and outcomes

OMI occurred in 25 (3.2%) individuals, 14 (56.0%) of them adults and 11 (44.0%) children and adolescents (**Table 3**). Females (n=14/56.0%) were more affected than males

(n=11/44.0%). The mean age of affected individuals was 29.8 (±21.3) years (range: 1 to 73 years). The most frequent diagnosis was AML (n=16/64%), followed by NHL (n=5/20%) and ALL (n=4/16%). In 84% (n=21) of the cases, the manifestation of disease was primary. In three (12%) patients, there was CNS infiltration. One (4.0%) individual was HIV positive. The gingiva (n=20/80%) was the anatomical location most affected by malignant infiltration. Overall, the diagnosis of OMI was presumed, and the lesions appeared as swelling, gingival enlargement, ulcer, and bleeding, as illustrated in **Figure 2**. Three (12%) patients underwent an incisional oral biopsy to confirm the diagnosis. Regression after antineoplastic therapy was observed in 10 (40.0%) patients. In 15 (60.0%) records, information on regression was unavailable due to death or hospital discharge. In parallel to OMI, periodontal changes (n=12/48.0%) and oral mucositis (n=12/48.0%) were the most frequent oral findings.

Table 3. Clinicodemographic data and outcomes of individuals with malignant haematological neoplasms with oral infiltration (n=25) seen at a hospital-based dental service from 2010 to 2021

Variable	*0-18 years (n=11/44.0%)* *n (%)*	*≥19 years (n=14/56.0%)* *n (%)*
Sex		
Male	4 (36.4)	4 (28.6)
Female	7 (63.6)	10 (71.4)
Mean; range	9.9±5.6; 1-18 years	45.5±15.8; 19-73 years
Diagnosis/subtype		
ALL	4 (36.4)	-
B	1 (9.1)	-
T	1 (9.1)	-
NI	1 (9.1)	-
AML	5 (45.5)	11 (78.6)
M2	-	1 (7.1)
M3	2 (18.2)	4 (28.6)
M4	1 (9.1)	1 (7.1)
M5	1 (9.1)	1 (7.1)
NI	1 (9.1)	3 (21.4)
NHL	2 (18.2)	3 (21.4)
Burkitt lymphoma	3 (27.3)	-
Mantle	-	1 (7.1)

Small cell lymphocytic	-	1 (7.1)
NI	-	1 (7.1)
Manifestation		
Primary	10 (90.9)	11 (78.6)
Relapse	1 (9.1)	3 (21.4)
Dental caries		
Absent	9 (81.8)	10 (71.4)
Present	2 (18.2)	4 (28.6)
Periodontal changes		
Absent	7 (63.6)	6 (42.9)
Present	4 (36.4)	8 (57.1)
Viral infections		
Absent	6 (54.5)	11 (78.6)
Present	5 (45.5)	3 (21.4)
Fungal diseases		
Absent	8 (72.7)	13 (92.9)
Present	3 (27.3)	1 (7.1)
Oral mucositis		
Absent	4 (36.4)	9 (64.3)
Present	7 (63.6)	5 (35.7)
Other manifestations		
Absent	6 (54.5)	10 (71.4)
Present	5 (45.5)	4 (28.6)
Physical injuries		
Absent	5 (45.5)	10 (71.4)
Present	6 (54.5)	4 (28.6)
Petechia/ecchymosis		
Absent	7 (63.6)	12 (85.7)
Present	4 (36.4)	2 (14.3)
Tongue coating		
Absent	7 (63.6)	13 (92.9)
Present	4 (36.4)	1 (7.1)
Anatomical location of oral infiltration		
Gingiva	9 (81.8)	11 (78.6)
Palate	-	1 (7.1)
Gingiva + palate	1 (9.1)	1 (7.1)
Lips	1 (9.1)	-
Buccal mucosa	-	1 (7.1)
Oral biopsy		
Absent	11 (100)	11 (78.6)
Present	-	3 (21.4)
CNS infiltration		

Absent	9 (81.8)	13 (92.9)
Present	2 (18.2)	1 (7.1)
HIV status		
Negative	11 (100)	13 (92.9)
Positive	-	1 (7.1)
Outcome during the hospital period		
Alive	8 (72.7)	7 (50)
Died	3 (27.3)	7 (50)

Note: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CNS, central nervous system; NHL, non-Hodgkin lymphoma; NI, not informed.

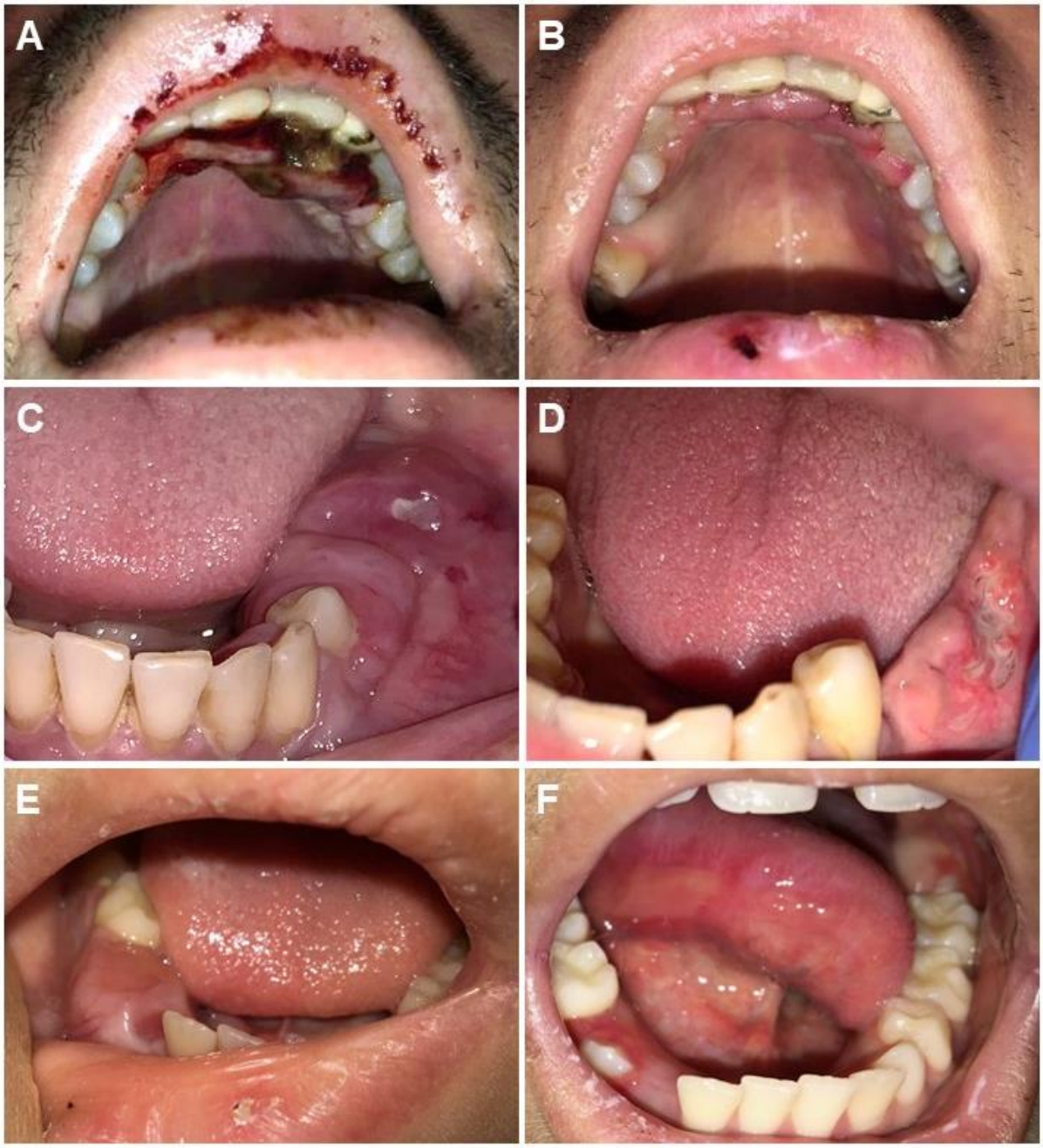

Figure 2. (A) Leukaemic infiltration. A 38-year-old man diagnosed with acute myeloid leukaemia exhibiting swelling lasting for two months. The lesion has a reddish-brown colour with a necrotic appearance of approximately 3.0 cm, accompanied by bleeding and pain on palpation in the palatal gingiva of the maxillary incisors and canines. **(B)** On the 18th day of the chemotherapy regimen, a significant regression of the lesion was observed. **(C) Lymphoid infiltration.** A 43-year-old man, with a previous history of bone marrow aplasia and haematopoietic stem cell transplantation. A firm, asymptomatic, irregular mass, with a colour

similar to the mucosa and erythematous regions measuring approximately 4.0 cm. Note expansive lesion with effacement of the mandibular vestibule. The patient was diagnosed with high-grade lymphoma. **(D)** One month after the oral biopsy, already in the hospital bed, the patient was asymptomatic, but with ulceration surface in the mandible. **(E) Lymphoid infiltration.** A 9-year-old boy was referred due to otalgia, sore throat, epistaxis, accompanied by malaise, vomiting, and weight loss. The evolution time of the lesion was 30 days, after the extraction of the deciduous mandibular molar. The diagnosis of Burkitt lymphoma was made. Swelling with erythematous and irregular areas was observed. **(F)** Under chemotherapy regimen, remission of the lesion was observed with a discrete erythematous area on the gingiva close to the erupting mandibular premolar. Note the presence of oral mucositis on the right lateral border of the tongue.

The blood results of individuals with OMI were outside the reference values for leukocytes (n=19/76%), neutrophils (n=17/74%), red blood cells (n=21/84%), and platelets (n=20/80%). However, significantly lower platelet counts (p=0.03) were observed in these individuals compared to individuals without OMI (**Figure 3**).

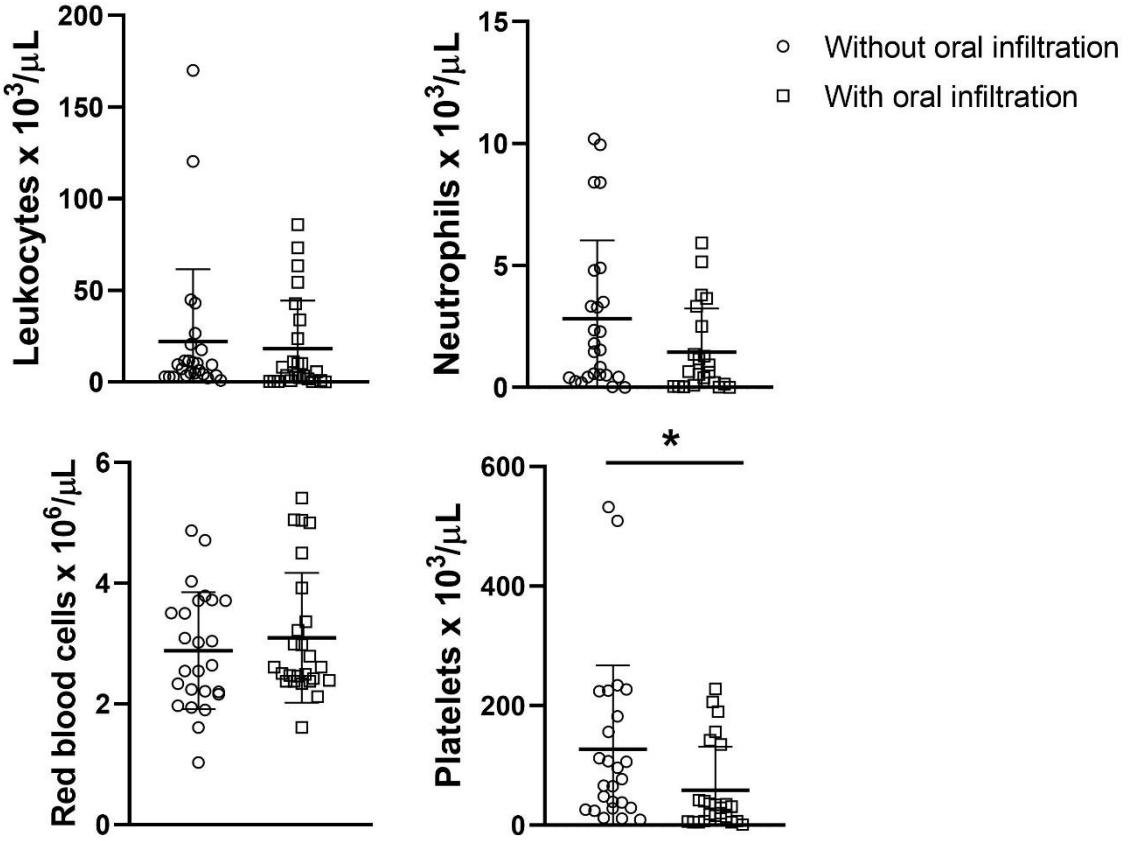

Figure 3. Blood counts of individuals with and without oral malignant infiltrations.

Of the patients with OMI, 15 (60%) survived and 10 (40%) died. Regarding the associations of OMI with death in paediatric individuals (0-18 years), the proportion of individuals who died among individuals who exhibited OMI was significantly higher than among individuals who did not exhibit OMI (p=0.002). For the associations of OMI with periodontal changes, status of manifestation, and CNS infiltration, no significant differences were observed between paediatric individuals who exhibited OMI and paediatric individuals who did not exhibit OMI (p>0.05) (**Supplementary Figure 1**). For adults (>19 years), the proportion of individuals who died (p<0.001) and those who had worse periodontal changes among individuals who exhibited OMI were significantly higher than among individuals who did not exhibit OMI. For status of manifestation and CNS infiltration, no significant differences

were observed between adult individuals who exhibited OMI and adult individuals who did not exhibit OMI (p>0.05) (**Supplementary Figure 2**). In the analyses in which individuals with OMI were matched to individuals without OMI for underlying disease as well, in both the paediatric and adult populations, there was no association of OMI with the variables death and periodontal changes (p>0.05) (**Supplementary Figure 3**).

4. Discussion

The present study reports clinicopathological data from 25 cases of oral leukaemia/lymphoma infiltrates in a large cohort seen at a hospital-based dental service. The results reinforce that OMI were relatively rare manifestations of leukaemia/lymphoma. Furthermore, dental caries, periodontal changes, oral mucositis, and haemorrhagic lesions were the main oral findings in these individuals.

OMI occurred in 3.2% of the patients. In line with previous studies, OMI was observed in patients with acute leukaemias, predominantly AML (64.0%), followed by NHL (20.0%), and ALL (16.0%) (Cammarata-Scalisi et al., 2020; de Sena et al., 2021; Dreizen, McCredie, Keating, & Luna, 1983). Worldwide, the incidence of ALL is highest in Ecuador and the incidence of AML is high in Australia (Miranda-Filho et al., 2018). Oceania also reported high NHL incidence rates, followed by North America and some European countries (Bispo, Pinheiro, & Kobetz, 2020). In Brazil, for instance, individuals aged 40 to 59 years are more affected by NHL, which represents 47.5% of all haematological malignancies that affect people in this age group (Grando et al., 2015). Epidemiological data have revealed that ALL is predominantly a childhood disease, accounting for 80% of all leukaemia cases (Cammarata-Scalisi et al., 2020; Malard & Mohty, 2020; Redaelli, Laskin, Stephens, Botteman, & Pashos, 2005). On the other hand, AML is more common among adults, with incidence peaking in the seventh decade of life (De Kouchkovsky & Abdul-Hay, 2016; Heuser et al., 2020; Short,

Rytting, & Cortes, 2018). Likewise, NHL primarily affects the sixth and seventh decades of life (Alexander et al., 2007) and its occurrence increases with age (i.e., ≤65 years: 9.3 per 100,000 and ≥65 years: 91.5 per 100,000 inhabitants) (Chiu & Hou, 2015). In the present study, except for AML cases that showed a predilection for females (Busjan et al., 2018), the other conditions revealed a slight predilection for males (Dreizen, McCredie, Keating, & Luna, 1983; Grando et al., 2015; Watson, Wood, Maxymiw, & Schimmer, 2018).

Although the literature has shown that OMI is predominant among men (Dreizen, McCredie, Keating, & Luna, 1983), herein we observed that oral infiltrations occurred more in women. In part, this discrepancy may be due to the rarity of these conditions, as reported in single case reports (de Sena et al., 2021). Moreover, diagnosing OMI is difficult, often leading to misdiagnosis or underdiagnosis. The gingiva is the anatomical location most affected by OMI (Cammarata-Scalisi et al., 2020; de Sena et al., 2021). Accordingly, many of the patients evaluated also had periodontal disease. It has been suggested that the gingiva may be affected by previous inflammatory conditions associated with poor hygiene, which in turn may exacerbate malignant infiltration (Cammarata-Scalisi et al., 2020; Dreizen, McCredie, Keating, & Luna, 1983). Nevertheless, OMI may also occur in patients with good oral health (Dreizen, McCredie, Keating, & Luna, 1983). Patients with periodontal conditions may be more susceptible to infiltration due to the flow of malignant cells into the gingival tissues (Cammarata-Scalisi et al., 2020). On this basis, involvement of gingival lymphoid foci (Dutzan, Konkel, Greenwell-Wild, & Moutsopoulos, 2016) and continuous bacterial antigen-driving inflammation may be postulated for these conditions.

The gingiva may suffer with blood count alterations (e.g., bleeding secondary to thrombocytopenia) and this finding may represent additional information for dental practitioners when diagnosing OMI (Cammarata-Scalisi et al., 2020; Dreizen, McCredie, Keating, & Luna, 1983). In our sample, an elevated number of patients with OMI also had

concomitant periodontal disease. In addition, more than half of these patients had changes in their red blood cell, platelet, and neutrophil counts. However, when comparing patients with and without OMI, the only difference was found in platelets, with lower values in individuals with OMI. In fact, in patients with leukaemia/lymphoma, oral findings related to changes in blood count have been described, but relating the latter to OMI has been poorly reported (de Sena et al., 2021). A former study detected that 66.7% of patients with leukaemia-related malignant gingival infiltration had leucocyte counts higher than the expected (Dreizen, McCredie, Keating, & Luna, 1983). In the present study, 32% of patients with OMI exhibited elevated leucocyte counts. Of clinical relevance, our results suggest an association of OMI with endpoints such as worse periodontal condition and death. However, when underlying disease was controlled in paired OMI versus non-OMI patients, no association between OMI and these outcomes was detected. This suggests that there is a substantial influence of underlying disease on patient's prognosis. The literature regarding associations of OMI with prognosis is scarce (de Sena et al., 2021). Therefore, to confirm the hypothesis, more robust samples must be analysed.

For an accurate diagnosis, an oral biopsy can be an important diagnostic tool, especially when OMI is the first sign of haematologic disease (Cammarata-Scalisi et al., 2020). Conversely, some authors state that it is not prudent to perform any biopsy to confirm the presence of an infiltrate in individuals with a previous haematological diagnosis of malignancy (Watson, Wood, Maxymiw, & Schimmer, 2018). In the current study, an oral biopsy was performed in 12% of patients. Of note, a recent review reported that a biopsy was performed in 54 of 68 patients with OMI to confirm the diagnosis (de Sena et al., 2021). Additional clinical information of help for diagnosis is that OMI tends to regress after the initiation of antineoplastic therapy (Cammarata-Scalisi et al., 2020; de Sena et al., 2021). In our sample,

however, OMI regression was observed for some cases, but this information was not available in others due to early death or hospital discharge.

As expected, oral mucositis was the most frequent finding recorded in hospitalized patients since the condition affects more than 75% of patients undergoing chemotherapy regimens (Mazhari, Shirazi, & Shabzendehdar, 2019). Previous studies have reported a high frequency of oral mucositis in individuals with ALL (Alnuaimi, Al Halabi, Khamis, & Kowash, 2018; Nasim, Shetty, & Hegde, 2007; Thomaz et al., 2013). Furthermore, dental caries and periodontal changes were also frequent in our sample, observed mainly in individuals with acute leukaemias. Accordingly, the latter oral condition was expressively higher in individuals with acute leukaemias when compared to a healthy group (Busjan et al., 2018; Wang et al., 2021). Patients undergoing chemotherapy are susceptible to salivary changes (e.g., acidic pH and low buffering capacity) that directly impact the risk of developing dental caries, in addition to being related to poor oral hygiene (Wang et al., 2021). Indeed, hospitalized patients undergoing antineoplastic therapy may have difficulty in maintaining oral hygiene due to weakness and especially pain related to oral mucositis (Ptasiewicz, Maksymiuk, & Chałas, 2022). Oral findings are frequently detected and coexist in the same individual during hospitalization (Carrilho Neto, De Paula Ramos, Sant'ana, & Passanezi, 2011). It is well known that the presence of bacterial plaque associated with poor oral hygiene is a source of microorganisms that lead to gingivitis or periodontitis (Ptasiewicz, Maksymiuk, & Chałas, 2022). In the case of hospitalized patients, the assessment of oral hygiene quality was moderate to poor in 46% of cases (Ramírez-Amador et al., 1996). According to Thomaz et al. (2013), patients developed gingivitis in the first six months of chemotherapy with an increased plaque index during this period, despite having received oral hygiene instructions. Herein, periodontal changes were a marked finding in affected individuals. Watson, Wood, Maxymiw, & Schimmer (2018) documented that, of 169 patients who had reported having regular oral health care, 33.7% had

clinical evidence of oral diseases. In addition, oral infections, including fungal diseases (candidiasis) and viral infections (HSV-1) may be present due to the neutropenic condition (Ramírez-Amador et al., 1996). In line with some studies reporting that hospitalized leukaemic individuals frequently exhibited candidiasis (Alnuaimi, Al Halabi, Khamis, & Kowash, 2018; Gazi, Ashri, & Lambourne, 1991), our study showed that viral infections and fungal diseases were expressively observed in inpatients (25.8%; 26.0%) in relation to outpatients (2.3%; 3.2%). These discrepancies have also been documented elsewhere (Ramírez-Amador et al., 1996).

In individuals with haematological diseases, changes in blood count (e.g., anaemia, thrombocytopenia, and neutropenia) result in repercussions in the oral cavity (Quispe, Aguiar, de Oliveira, Neves, & Santos, 2021; Watson, Wood, Maxymiw, & Schimmer, 2018). Neutropenia is associated with infection and thrombocytopenia may result in spontaneous bleeding, petechiae, and ecchymosis, known as haemorrhagic lesions (Thomaz et al., 2013; Watson, Wood, Maxymiw, & Schimmer, 2018). A neutropenic patient with poor oral hygiene is more vulnerable to the development of infections (Ptasiewicz, Maksymiuk, & Chałas, 2022). Indeed, low platelet counts ($<40 \times 10^3/mm^3$) have been observed in patients with haemorrhagic lesions (Ramírez-Amador et al., 1996). Nearly 80% of patients had low platelet counts ($<60 \times 10^3/mm^3$) associated with gingival bleeding (Hou, Huang, & Tsai, 1997). In our study, however, haemorrhagic lesions (petechiae/ecchymosis) corresponded to 11.5% of the oral findings. In contrast, haemorrhagic lesions, including petechiae and oral bleeding, appeared to be some of the most common oral manifestations reported elsewhere (Hou, Huang, & Tsai, 1997; Michaud, Baehner, Bixler, & Kafrawy, 1977; Owlia, Ansarinia, & Vahedian Ardakani, 2021; Ramírez-Amador et al., 1996; Watson, Wood, Maxymiw, & Schimmer, 2018). Thus, for dental practitioners, haematological values such as neutrophil and platelet counts are particularly important for decision making about any procedures for these individuals. Nonetheless, when

neutrophil levels are low (≤1 × 10^3 cells/mm^3), prophylactic antibiotics should be considered, while for low platelet levels (≤40–60 ×10^3 cells/mm^3), the possibility of transfusion should be evaluated (Zimmermann et al., 2015).

The present study has strengths and shortcomings. The primary limitation regards its retrospective nature and the impossibility to perform a biopsy to confirm OMI. However, compared to previous reports (Angst, Maier, Dos Santos Nogueira, Manso, & Tedesco, 2020), we performed a large survey over an 11-year period at a referral hospital. Moreover, the representativeness of the sample of our research is of great value also due to the rarity of OMI. The alignment of the dental team with onco-haematology permitted the evaluation of the patient at admission and close monitoring of the diagnosis of those who developed OMI.

5. Conclusion

In summary, data regarding the clinicopathological aspects of the patients reported herein agree with findings from other retrospective studies. Dental caries, periodontal changes, and oral mucositis were the main oral findings. Overall, OMI occurred more in women with acute leukaemias, especially AML. It is important to systematize the diagnosis of OMI with prospects for better health care.

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Supplementary files

Supplementary Table 1. Clinicodemographic data, outcomes, and oral health status of individuals with malignant haematological neoplasms distributed by settings (n=771)

Variables	*Hospital ward (n=542; 69.4%)*	*Outpatient clinic (n=220; 28.2%)*	*Both (n=19; 2.4%)*
	n (%)	*n (%)*	*n (%)*
Sex			
Male	309 (57.0)	126 (57.3)	14 (73.7)
Female	233 (43.0)	94 (42.7)	5 (26.3)
Ratio	1:1.3	1:1.3	1:2.8
Age (year)	mean: 27.1±21.0 (male: 26.1 ±20.1 and female: 28.3±22.2) Range: 0.4-81	mean: 42.1±20.7 (male: 40.1 ±20.1 and female: 44.8±21.1) Range: 2-85	mean: 23.6±18.2 (male: 23.0±19.8 and female: 25.4±12.7) Range: 1-68
0-9	144 (26.6)	16 (7.3)	6 (31.6)
10-19	122 (22.5)	27 (12.3)	2 (10.5)
20-29	66 (12.2)	22 (10.0)	5 (26.3)
30-39	45 (8.3)	30 (13.6)	2 (10.5)
40-49	57 (10.5)	28 (12.7)	2 (10.5)
50-59	52 (9.6)	45 (20.5)	1 (5.3)
60-69	45 (8.3)	34 (15.4)	1 (5.3)
70-79	9 (1.6)	14 (6.4)	0 (0.0)
80-89	2 (0.4)	4 (1.8)	0 (0.0)
Manifestation			
Primary	462 (85.2)	210 (95.5)	16 (84.2)
Relapse	80 (14.8)	10 (4.5)	3 (15.8)
HIV status			
Negative	526 (97.0)	217 (98.6)	19 (100.0)
Positive	16 (3.0)	3 (1.4)	0 (0.0)
Outcome			
Alive	467 (86.2)	216 (98.2)	18 (94.7)
Died	75 (13.8)	4 (1.8)	1 (5.3)
Dental caries			
Absent	377 (69.6)	106 (48.2)	11 (57.9)
Present	165 (30.4)	114 (51.8)	8 (42.1)
Periodontal changes			
Absent	385 (71.0)	113 (51.4)	13 (68.4)
Present	157 (29.0)	107 (48.6)	6 (31.6)
Viral infections			

Absent	402 (74.2)	215 (97.7)	14 (73.7)
Present	140 (25.8)	5 (2.3)	5 (26.3)
Fungal diseases			
Absent	401 (74.0)	213 (96.8)	16 (84.2)
Present	141 (26.0)	7 (3.2)	3 (15.8)
Oral mucositis			
Absent	256 (47.2)	206 (93.6)	6 (31.6)
Present	286 (52.8)	14 (6.4)	13 (68.4)
Other manifestations			
Absent	399 (73.6)	177 (80.4)	14 (73.7)
Present	143 (26.4)	43 (19.6)	5 (26.3)
Physical injuries			
Absent	390 (72.0)	200 (90.9)	12 (63.2)
Present	152 (28.0)	20 (9.1)	7 (36.8)
Petechia/ecchymosis			
Absent	464 (85.6)	216 (98.2)	18 (94.7)
Present	78 (14.4)	4 (1.8)	1 (5.3)
Tongue coating			
Absent	435 (80.3)	212 (96.4)	16 (84.2)
Present	107 (19.7)	8 (3.6)	3 (15.8)

Supplementary Table 2. Clinicodemographic data, outcomes, and oral health status of individuals distributed according to the five main malignant haematological diagnosis (n=772)

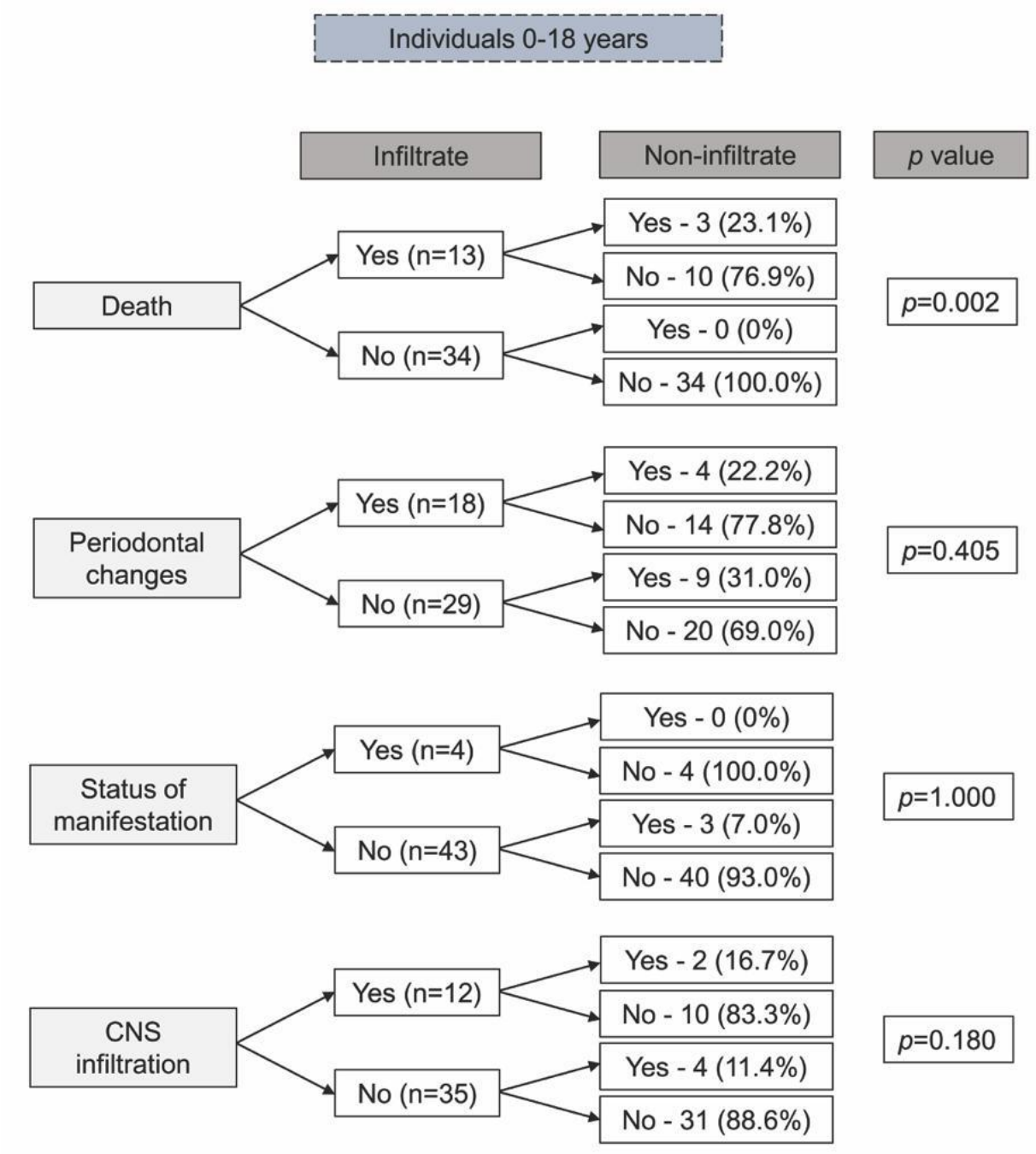
Variables	*ALL (n=235; 30.1%)*	*AML (n=203; 26.0%)*	*NHL (n=173; 22.2%)*	*CML (n=109; 14.0%)*	*HL (n=52; 6.7%)*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Sex					
Male	139 (59.1)	92 (45.3)	113 (65.3)	66 (60.6)	34 (65.4)
Female	96 (40.9)	111 (54.7)	60 (34.7)	43 (39.4)	18 (34.6)
Ratio	1:1.4	1:0.8	1:1.9	1:1.5	1:1.9
Age (year)	mean: 15.7±15.2 (male: 15.8±15.0 and female: 15.4±15.5) Range: 0.4-74	mean: 32.6±20.4 (male: 32.4±20.6 and female: 32.8±20.2) Range: 0.5-81	mean: 40.1±21.7 (male: 36.9±20.6 and female: 46.2±22.4) Range: 2-85	mean: 47.2±16.4 (male: 43.2±16.4 and female: 53.4±14.4) Range: 6-83	mean: 30.6±18.9 (male: 29.1±19.4 and female: 33.3±17.5) Range: 5-71
0-9	108 (46.0)	30 (14.8)	20 (11.6)	3 (2.8)	2 (3.8)
10-19	70 (29.8)	35 (17.2)	22 (12.7)	5 (4.6)	19 (36.5)
20-29	23 (9.8)	33 (16.3)	17 (9.8)	9 (8.3)	11 (21.2)
30-39	11 (4.7)	29 (14.3)	17 (9.8)	14 (12.8)	6 (11.5)
40-49	10 (4.3)	25 (12.3)	24 (13.9)	25 (22.9)	3 (5.8)
50-59	6 (2.5)	26 (12.8)	34 (19.7)	27 (24.8)	3 (5.8)
60-69	6 (2.5)	21 (10.3)	26 (15.0)	17 (15.6)	7 (13.5)
70-79	1 (0.4)	3 (1.5)	10 (5.8)	8 (7.3)	1 (1.9)
80-89	0 (0.0)	1 (0.5)	3 (1.7)	1 (0.9)	0 (0.0)
Manifestation					
Primary	208 (88.5)	169 (83.3)	155 (89.6)	107 (98.2)	41 (78.8)
Relapse	27 (11.5)	34 (16.7)	18 (10.4)	2 (1.8)	11 (21.2)
HIV status					
Negative	234 (99.6)	201 (99.0)	159 (91.9)	108 (99.1)	51 (98.1)

Positive	1 (0.4)	2 (1.0)	14 (8.1)	1 (0.9)	1 (1.9)
Outcome					
Alive	219 (93.2)	169 (83.3)	148 (85.5)	105 (96.3)	51 (98.1)
Died	16 (6.8)	34 (16.7)	25 (14.5)	4 (3.7)	1 (1.9)
Local of evaluation					
Hospital ward	199 (84.7)	171 (84.2)	118 (68.2)	23 (21.1)	24 (46.2)
Outpatient	25 (10.6)	27 (13.3)	52 (30.1)	86 (78.9)	28 (53.8)
Both	11 (4.7)	5 (2.5)	3 (1.7)	0 (0.0)	0 (0.0)
Dental caries					
Absent	157 (66.8)	140 (69.0)	100 (57.8)	60 (55.0)	29 (55.8)
Present	78 (33.2)	63 (31.0)	73 (42.2)	49 (45.0)	23 (44.2)
Periodontal changes					
Absent	167 (71.1)	120 (59.1)	118 (68.2)	69 (63.3)	29 (55.8)
Present	68 (28.9)	83 (40.9)	55 (31.8)	40 (36.7)	23 (44.2)
Viral infections					
Absent	173 (73.6)	154 (75.9)	142 (82.1)	105 (96.3)	49 (94.2)
Present	62 (26.4)	49 (24.1)	31 (17.9)	4 (3.7)	3 (5.8)
Fungal diseases					
Absent	179 (76.2)	163 (80.3)	133 (76.9)	101 (92.7)	46 (88.5)
Present	56 (23.8)	40 (19.7)	40 (23.1)	8 (7.3)	6 (11.5)
Oral mucositis					
Absent	104 (44.3)	121 (59.6)	105 (60.7)	98 (89.9)	33 (63.5)
Present	131 (55.7)	82 (40.4)	68 (39.3)	11 (10.1)	19 (36.5)
Other manifestations					
Absent	173 (73.6)	152 (74.9)	136 (78.6)	76 (69.7)	45 (86.5)
Present	62 (26.4)	51 (25.1)	37 (21.4)	33 (30.3)	7 (13.5)
Physical injuries					
Absent	156 (66.4)	151 (74.4)	141 (81.5)	102 (96.3)	45 (86.5)

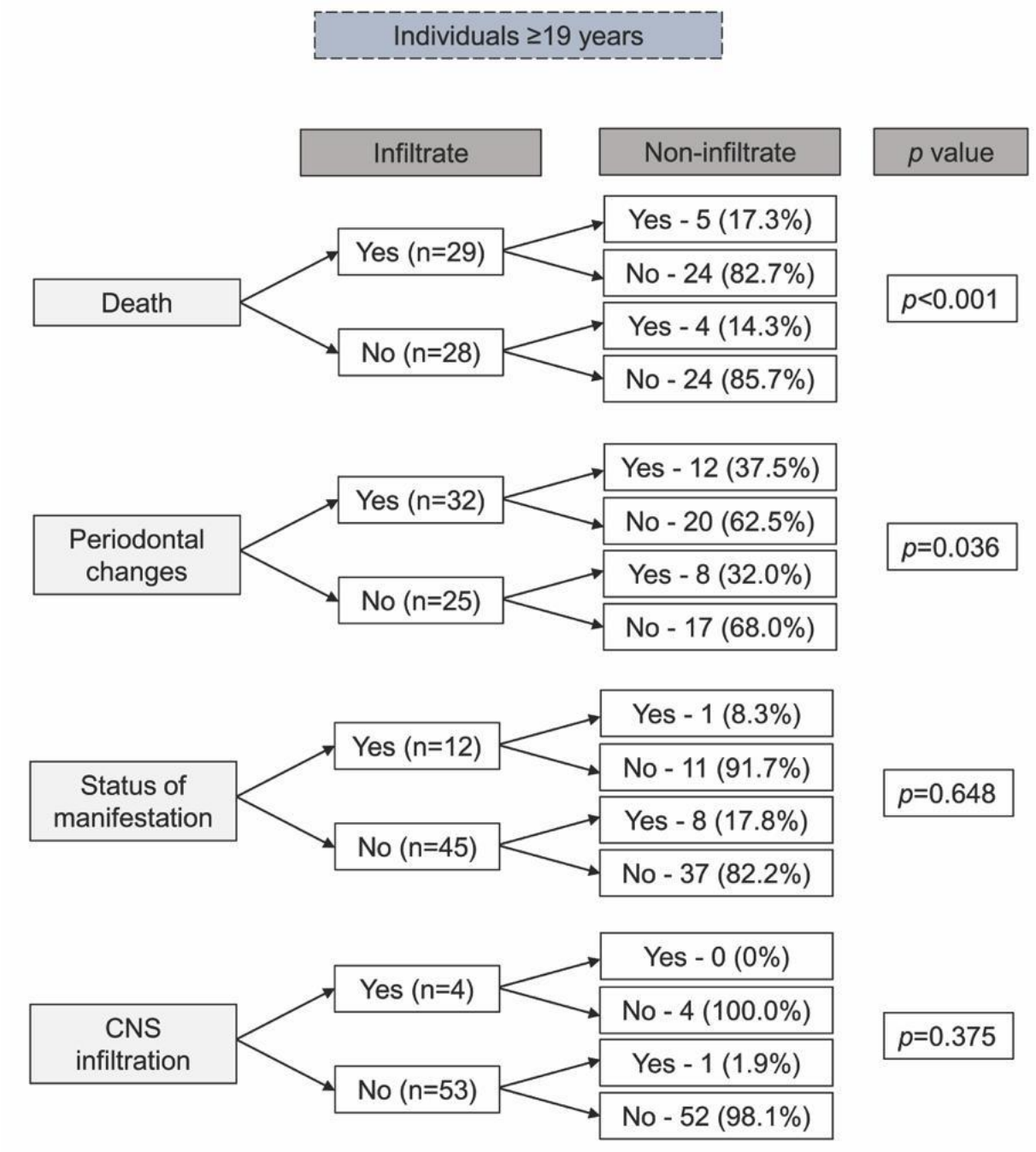
Present	79 (33.6)	52 (25.6)	32 (18.5)	7 (6.4)	7 (13.5)
Petechia/ecchymosis					
Absent	210 (89.4)	164 (80.8)	165 (95.4)	105 (96.3)	47 (90.4)
Present	25 (10.6)	39 (19.2)	8 (4.6)	4 (3.7)	5 (9.6)
Tongue coating					
Absent	192 (81.7)	169 (83.3)	149 (86.1)	105 (96.3)	41 (78.8)
Present	43 (18.3)	34 (16.7)	24 (13.9)	4 (3.7)	11 (21.2)

Note: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

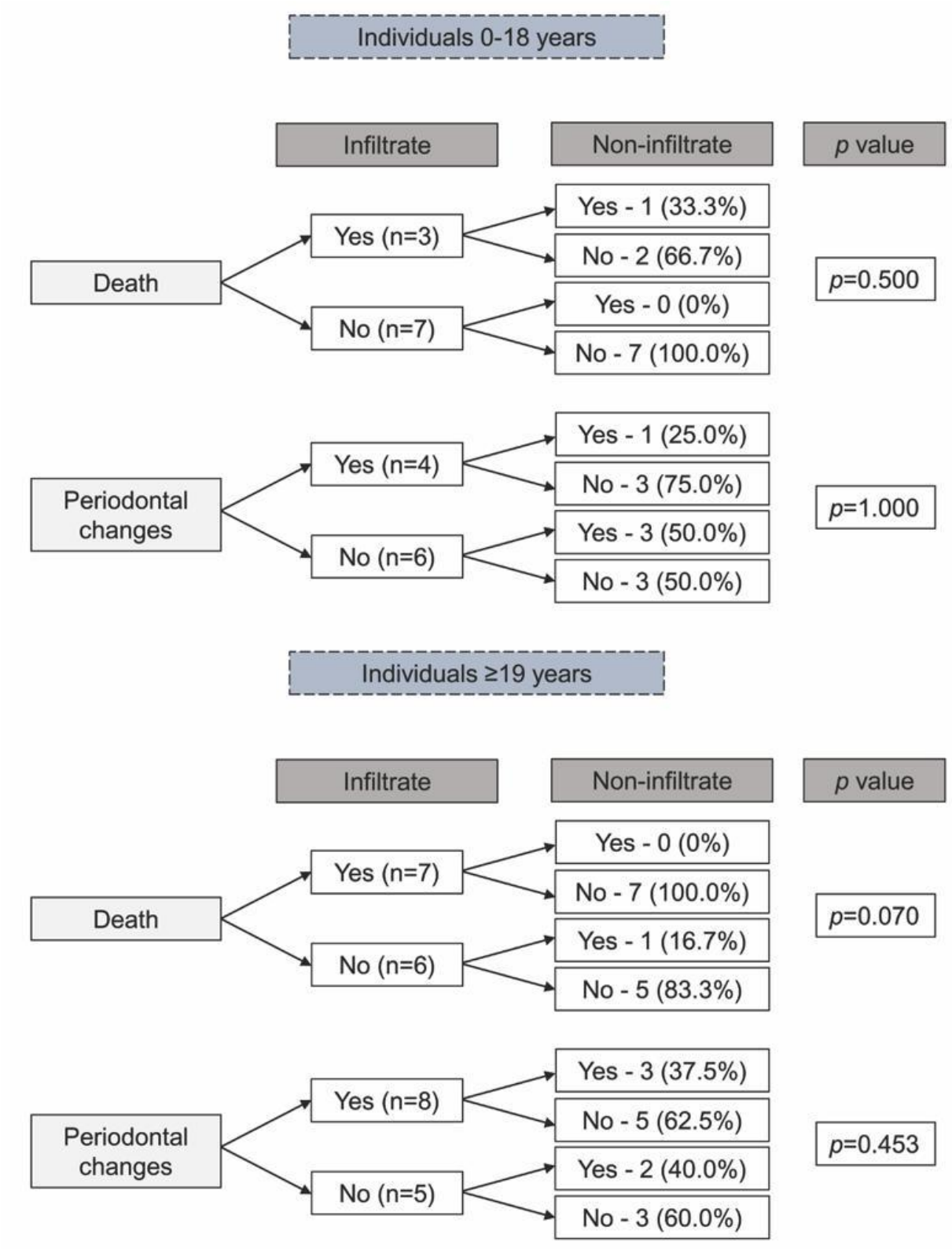
Supplementary Figure 1. Comparisons of outcomes between patients with infiltration and non-infiltration in individuals aged ≤18 years with haematolymphoid malignancies.



Supplementary Figure 2. Comparisons of outcomes between patients with infiltration and non-infiltration in individuals aged ≥19 years with haematolymphoid malignancies.



Supplementary Figure 3. Comparisons of outcomes between patients with infiltration and non-infiltration in individuals aged ≤18 years and ≥19 years, controlled for underlying haematolymphoid malignancies.



4 CONSIDERAÇÕES FINAIS

Neste estudo, as principais doenças de base foram as leucemias agudas e LNH, acometendo as primeiras décadas de vida, sendo o sexo masculino o mais comum. As principais condições bucais foram cárie e alterações periodontais. A infiltração oral maligna acometeu principalmente indivíduos do sexo feminino que foram diagnosticadas com leucemias agudas, sendo a gengiva o local mais frequente. As alterações periodontais foram muito presentes nesses indivíduos com infiltração oral. Além disso, a revisão da literatura revelou que a infiltração leucêmica oral e maxilofacial ocorreu principalmente em indivíduos do sexo masculino com leucemia mieloide aguda na quinta década de vida, sendo a gengiva a localização mais frequente. O conhecimento da infiltração maligna na cavidade oral por leucemia/linfoma é de suma importância, pois pode ser um sinal primário da doença ou sua recidiva, e o diagnóstico precoce pode favorecer o prognóstico da doença.

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ANEXO A – Aprovação do comitê de ética em pesquisa

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ESTUDO DA INFILTRAÇÃO DE TECIDOS ORAIS EM PACIENTES COM DOENÇAS HEMATOLÓGICAS MALIGNAS

Pesquisador: Tarcília Aparecida da Silva

Área Temática:

Versão: 3

CAAE: 47136721.5.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.849.734

Apresentação do Projeto:

Trata-se de segunda análise de respostas de diligências apresentadas no parecer de número 4.839.086, do projeto intitulado "ESTUDO DA INFILTRAÇÃO DE TECIDOS ORAIS EM PACIENTES COM DOENÇAS HEMATOLÓGICAS MALIGNAS" registrado na Plataforma Brasil sob o número de CAAE: 47136721.5.0000.5149.

As diligências apresentadas foram:

1) TALE: Como orientado no primeiro parecer, o TALE para os menores de 18 anos por faixa etária com linguagem acessível para acompanhar o TCLE do responsável (vide: https://www.ufmg.br /bioetica/coep/tale/). Considerando que a pesquisa irá trabalhar com participantes menores de 17 anos 11 meses e 29 dias de idade é importante que sejam confeccionados um modelo de TALE por idade (6 a 8 anos – 9 a 12 anos – 12 a 17 anos, por exemplo, pois a compreensão é diferente por faixas etárias) apresentado como carta convite com linguagem acessível. Sendo informado aos participantes o objetivo, o procedimento, os riscos e desconforto e os benefícios. Foi assegurado o sigilo e o direito à recusa. Campos de assinatura presente. Consentimento para registro de áudio, vídeo, imagens. Inserir dados do pesquisador e dos CEP relatados.

2) Inserir nos TALEs as medidas propostas pelos pesquisadores para a minimização dos riscos. 3) Projeto e em Informações Básicas do projeto: modificar o termo "paciente" por "participante".

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
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Objetivo da Pesquisa:

Objetivo Geral: Avaliar a ocorrência de infiltração dos tecidos orais e a contribuição da micro biopsia nos diagnósticos destas condições em pacientes com doenças hematológicas malignas.

Objetivos Específicos

• Identificar e caracterizar clinicamente a presença de manifestações na região oral nestes pacientes e relacionar a presença destas lesões com fatores clínicos da doença de base e dados demográficos;

• Realizar a análise microscópica dos aumentos gengivais utilizando micro biópsia por punch do tecido gengival, avaliando potencial contribuição deste exame complementar para o diagnóstico;

• Relacionar a evolução das manifestações orais com resposta ao tratamento da doença de base.

Avaliação dos Riscos e Benefícios:

Riscos: Existe risco de sangramento no sítio de biópsia, entretanto estes riscos serão minimizados pelas seguintes medidas:

1) transfusão de plaquetas previamente ao procedimento caso o valor seja menor que 50.000;

2) medidas hemostáticas locais: os sítios de biópsia serão recobertos com cimento cirúrgico ou ácido tranexâmico e, suturas bem posicionadas serão realizadas quando necessário;

3) emprego de micropunchs para minimizar a ferida cirúrgica.

Benefícios: os dados podem contribuir para o manejo precoce e seguro de manifestações orais em pacientes com leucemia e linfoma, estabelecimento do diagnóstico correto e monitoramento de recidivas das doenças.

Comentários e Considerações sobre a Pesquisa:

Projeto relevante para a área da saúde, conforme parecer do Departamento de Clínica, Patologia e Cirurgia Odontológicas Faculdade de Odontologia.

Considerações sobre os Termos de apresentação obrigatória:

1) Os pesquisadores formularam um TALE para as idades de 6 a 12 anos e um TALE para 12 a 17 anos na atual versão submetida, incluindo a minimização de riscos

2) Em relação a solicitação de modificar o termo “paciente” por “participante” em Projeto e em Informações Básicas do projeto os pesquisadores responderam que quando possível, conforme solicitado, foram alterados e sinalizados na cor vermelha no decorrer do texto da metodologia e

no cronograma do projeto.

Recomendações:

- Necessidade de trocar o termo “cópia” por “via”, nos TALEs: Termo "cópia" foi utilizado ao invés de "via", conforme recomenda a Resolução CNS 466/12, para assegurar legitimidade legal do documento;

Conclusões ou Pendências e Lista de Inadequações:

Na condição de se atender as recomendações solicitadas, somos, S.M.J. favoráveis à aprovação do projeto.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1713476.pdf	13/07/2021 09:29:42		Aceito
Outros	respostapareceristaversao3.pdf	13/07/2021 09:28:38	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	taleversao3.pdf	13/07/2021 09:27:55	Tarcília Aparecida da Silva	Aceito
Projeto Detalhado / Brochura Investigador	projetoversao3.pdf	13/07/2021 09:27:39	Tarcília Aparecida da Silva	Aceito
Outros	respostaparcer.pdf	30/06/2021 15:00:25	Tarcília Aparecida da Silva	Aceito
Outros	tcudassinado.pdf	30/06/2021 15:00:01	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de	talesversao2.pdf	30/06/2021 14:58:55	Tarcília Aparecida da Silva	Aceito

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Continuação do Parecer: 4.849.734

Ausência	talesversao2.pdf	30/06/2021 14:58:55	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	tcleversao2.pdf	30/06/2021 14:58:31	Tarcília Aparecida da Silva	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	temobiorepositorio.pdf	30/06/2021 14:55:10	Tarcília Aparecida da Silva	Aceito
Projeto Detalhado / Brochura Investigador	projetoversao2.pdf	30/06/2021 14:53:49	Tarcília Aparecida da Silva	Aceito
Outros	parecergep.pdf	21/05/2021 17:59:24	Tarcília Aparecida da Silva	Aceito
Outros	TCUD.pdf	21/05/2021 17:58:28	Tarcília Aparecida da Silva	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	21/05/2021 17:58:11	Tarcília Aparecida da Silva	Aceito
Folha de Rosto	folhaDeRosto_assinado.pdf	30/03/2021 20:42:57	Tarcília Aparecida da Silva	Aceito
Outros	Parecerdepartamento.pdf	06/03/2021 18:50:36	Tarcília Aparecida da Silva	Aceito
Declaração de concordância	CartaSEDTO.pdf	06/03/2021 18:49:29	Tarcília Aparecida da Silva	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BELO HORIZONTE, 15 de Julho de 2021

Assinado por:
Críssia Carem Paiva Fontainha
(Coordenador(a))

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
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