Epidemiological Association between Oral Diseases and COVID-19: Pulpitis as a Key Risk Factor in a Primary Care Setting

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ABSTRACT

Aims: To establish a possible association between pulpitis and COVID-19.
Study design: A descriptive, cross-sectional and retrospective study with an analytical approach was designed.
Place and Duration of Study: Ambulatory Care Medical Unit. The study was conducted from January 1st to July 31st, 2024, with Mexican patients attending outpatient consultations in the Dentistry, and the Family Medicine Specialty and General Medicine departments at the "División del Norte" Family Medicine Clinic, ISSSTE, in Mexico City, Mexico. The data collection was since January to December, 2022.
Methodology: Data on health and sociodemographic variables were collected through a retrospective design, using medical records from the Medical Financial Information System "SIMEF system".
Results: We included 13,359 adult patients, mainly females (n=8,510; 63.7%) and people in their sixties (n=3,637; 27.3%). The average age was 61.76 years old (SD=12.65, median age=61 [IQR=52-71]). The most prevalent diseases were: hypertension (4,682; 35.0%), type 2 diabetes (3,502; 26.2%), COVID-19 virus identified (1,970; 14.7%), hyperlipidaemia (1,255; 9.4%), and obesity due to excess calories (1,222; 9.1%). The average age of the 48 patients with irreversible pulpitis was 57.33 years (SD=9.99 years, median age= 57 [IQR=49.25-62]). The majority of patients were females (n=29, 60.4%) and older adults between 50 and 59 years old (n=15, 31%). The logistic regression models showed associations with: sex (female) OR=1.196 (1.080-1.323), p=0.001; age (years) OR=0.920 (0.915-0.925), p<0.001; anomalies in the relationship between dental arches OR=0.399 (0.185-0.859), p=0.019; dentofacial functional anomalies OR=0.486 (0.262-0.902), p=0.022; temporomandibular joint disorder OR=0.620 (0.386-0.998), p=0.049; retained dental root OR=0.273 (0.111-0.672), p=0.005; disorders of the teeth and their supporting structures OR=0.407 (0.189-0.877), p=0.022; maxillary alveolitis OR=11.573 (1.049-127.692), p=0.046; and pulpitis OR=2.198 (1.047-4.614), p=0.037.
Conclusion: These findings shown epidemiological associations between oral conditions and COVID-19, and indicated that pulpitis is an associated risk factor. This supports the notion that oral conditions may play a significant role in modulating the risk of SARS-CoV-2 infection and the development of COVID-19, potentially through genetic and epigenetic mechanisms related to inflammatory and immunological processes.

Keywords: COVID-19; pulpitis; periodontal diseases; primary care; risk factors.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a proinflammatory condition caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), affecting multiple organ systems (López-Hernández 2022). This virus has infected over six million individuals globally (Galicia et al. 2020). The majority of cases (81%) present with mild respiratory or gastrointestinal symptoms or remain asymptomatic, while 15% develop severe illness requiring hospitalisation (Galicia et al. 2020, López-Hernández 2022, Anguiano-Velazquez et 2024, López-Hernández et al. 2024a). Recent studies have reported that patients with COVID-19 also exhibit oral manifestations with diverse clinical presentations. The most

frequently documented manifestations include ulcers, blisters, necrotising gingivitis, opportunistic co-infections, salivary gland dysfunction, white and erythematous plaques, and gustatory impairment, which often coincide with anosmia and ageusia (Brandini et al. 2021).

SARS-CoV-2 demonstrates endothelial cell tropism (Brandini et al. 2021). COVID-19-mediated endotheliitis promotes inflammation within oral tissues and facilitates viral dissemination (Brandini et al. 2021). SARS-CoV-2 is a positive-sense, single-stranded RNA virus with an icosahedral morphology and spike proteins (Brandini et al. 2021, Haque et al. 2020). These spike proteins mediate high-affinity binding to human angiotensin-converting enzyme 2 (ACE2) receptors, which are highly expressed not only in pulmonary tissue but also in the salivary glands of the oral cavity (Brandini et al. 2021, Haque et al. 2020). This interaction enables viral replication and contributes to inflammation and tissue destruction (Brandini et al. 2021, Hu et al. 2021, Herrera et al. 2020)

SARS-CoV-2 has been reported to induce a significant inflammatory response, potentially altering gene expression profiles across various tissues. In patients with irreversible pulpitis and a history of COVID-19, genes associated with inflammation, angiogenesis, and wound healing—such as LINGO3 (Leucine Rich Repeat and Ig Domain Containing 3), UTS2R (Urotensin 2 Receptor), and HSFX1 (Heat Shock Transcription Factor Family, X-Linked 1), respectively—were found to be upregulated in the COVID-19 group (Cho et al. 2023). Conversely, genes with well-established proinflammatory roles, such as IL8 (Interleukin-8) and CCL15 (C-C Motif Chemokine Ligand 15), were downregulated (Cho et al. 2023). These findings suggest that COVID-19 may induce immune and inflammatory gene dysregulation within pulpal tissues, potentially impacting dental health.

Furthermore, Galicia et al. provide evidence suggesting that dental pulp may be susceptible to SARS-CoV-2 infection (Galicia et al. 2020), potentially due to increased genetic susceptibility. In light of findings indicating a potential impact of SARS-CoV-2 infection on immune and inflammatory responses within dental pulp tissues, it is imperative to establish a possible association between pulpitis and COVID-19.

1.1 The Aims of the Study.

To establish a possible association between pulpitis and COVID-19.

2. MATERIAL AND METHODS

2.1 Study design and data collection

A descriptive, cross-sectional and retrospective study with an analytical approach was designed and conducted with Mexican adult patients who attended outpatient consultations in the Dentistry, and the Family Medicine Specialty and General Medicine departments at the "División del Norte" Family Medicine Clinic (FMC), ISSSTE, in Mexico City, Mexico. The study was conducted from January 1st to July 31st, 2024. The data collection was sourced from secondary data, using medical records from the Medical Financial Information System, SIMEF, from January to December 2022. This system captures information on outpatient consultations by health personnel. A database, previously published, was analysed (López-Hernández et al. 2024b). This database contains a total of 73,974 records, with a total of 17,918 patients of all ages (López-Hernández et al. 2024b). The records were analysed and those that met the inclusion criteria were included.

2.2 Patient Selection and study population

The inclusion criteria were: patients, of both sexes, mature adults aged 40 years and over who had at least one consultation registered in the system during the study period. Patients with complete records, including identification data such as name, file number, sex, type of beneficiary, International Classification of Diseases version 10 (ICD-10) diagnosis code and

consultation dates. The exclusion criteria were: patients under 40 years of age, of both sexes; patients with incomplete records in the "SIMEF" system, any record identified as duplicate or containing inconsistencies.

All this ensured that only patients with complete and consistent records were included in the study. The data collection procedure included the following steps:

1. The information was downloaded by month (from January to December), using work tools Excel files generated by the "SIMEF" system.
2. The “SIMEF” database was initially analysed to select records that met the inclusion criteria.
3. A single database was then generated and all individual patient records were cross-referenced, excluding records that did not meet the inclusion criteria.
4. A final review of the new combined database was performed to ensure the integrity and consistency of the information.
5. The information collected was stored in an Excel workbook, which served as a statistical database for subsequent analysis.

To minimize potential bias in the selection process, we ensured that the inclusion and exclusion criteria were strictly adhered to. Records were cross-referenced between the “SIMEF” databases by month to ensure their accuracy. Finally, a total of 13,359 adults aged 40 and over were included. This procedure ensured the accuracy, quality, and reliability of the extracted data, supporting the integrity of our study’s findings.

2.3 Variables and Statistical analysis.

We included all complete records, ensuring a comprehensive dataset. The variables included were: age (in years), sex (male and female), and comorbidities (coded using the International Classification of Diseases revision 10th, ICD-10). A total of 2,491 ICD-10 codes were coded. The categorical variables are described as absolute frequency and percentage, and quantitative variables as mean, standard deviation (SD), and interquartile range (IQR). Confidence Interval 95% (CI95%) was included. Categorical variables were compared using Yates' corrected chi-square (X_Y^2) test and likelihood ratio, as appropriate. Quantitative variables were compared using the Mann-Whitney U test or Student's T test as appropriate. To assess the association between COVID-19 and potential associated factors, data were analysed as numerical (age) and dichotomous (sex, morbidities) variables, using univariate and multivariate logistic regression models. Univariate analysis was performed to examine the relationship between individual variables (age, sex, morbidities of code K00–K14 corresponding to diseases of the oral cavity, salivary glands, and jaws) and the presence of COVID-19. Univariate analysis indicated which variables were significantly associated with COVID-19 and provided initial information on potential risk or protective factors, but did not account for confounding variables. Multivariate logistic regression analysis was performed to identify factors independent of COVID-19. Variables significant in the univariate analysis were included in the multivariate model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to quantify the strength of the associations. This method allows adjustment for confounding variables and identification of independent predictors. An OR greater than 1 indicated a higher likelihood of COVID-19, while an OR less than 1 indicated a lower likelihood. The 95% CI provided an estimate of the accuracy of the ORs. A P value < 0.05 (two-tailed test) was considered significant.

2.4 Ethical Considerations.

The study was conducted in accordance with the Good Clinical Practice Guidelines of our laws and the Declaration of Helsinki for human experiments. The protocol was approved by two committees: The Research Committee and the Ethics Committee in Research of the FMC "División del Norte". The Data was treated confidentially. To guarantee confidentiality,

only the principal investigators had access to the complete dataset, including identifiable patient information (e.g., names). The patient names were replaced with unique identification numbers. The assigned number allows the data to be linked to a specific individual without revealing the individual's identity. This approach ensured that all patient data were handled under ethical standards and maintained the highest level of confidentiality throughout the study. This anonymization was conducted before sharing the dataset for statistical analysis with some researchers. After the statistical analysis, only the processed statistical data were made available to the rest of the research team.

3. RESULTS AND DISCUSSION.

3.1 Characteristics of the study population

We included 13,359 adult patients. The majority of the participants are females (n=8,510; 63.7%) and people in their sixties (n=3,637; 27.3%). The average age was 61.76 years old (SD=12.65, range=68, minimum age=40, maximum age=108 years old, median age=61 [IQR=52-71]).

The 20 most prevalent diseases were: hypertension (I10.X=4,682; 35.0%), followed by type 2 diabetes (E11.9=3,502; 26.2%), COVID-19 virus identified (U07.1=1,970; 14.7%), unspecified hyperlipidaemia (E78.5=1,255; 9.4%), obesity due to excess calories (E66.0=1,222; 9.1%), hypothyroidism (E03.9=891, 6.7%), acute pharyngitis (J02.9=880, 6.6%), obesity, unspecified (E66.9=863, 6.5%), other specified disorders of metabolism (E88.8=826, 6.2%), chronic venous insufficiency (peripheral) (I87.2=814, 6.1%), low back pain (M54.5=744, 5.6%), urinary tract infection (N39.0=665, 5.0%), prostatic hyperplasia (N40.X=625, 4.7%), mixed hyperlipidaemia (E78.2=612, 4.6%), chronic obstructive pulmonary disease (J44.9=553, 4.1%), gonarthrosis (M17.9=477, 3.6%), irritable bowel syndrome without diarrhea (K58.9=462, 3.5%), depressive episode (F32.9=445, 3.3%), gastroenteritis and colitis of unspecified origin (A099=44.2, 3.3%) and anxiety disorder (F41.9=416, 3.1%).

Regarding the differences between males and females, the total number average of outpatient consultations, is significantly higher in females (females=14.23 consultations per year; SD=13.59 vs., males=12.89 consultations per year; SD=12.18, $p < 0.001$), while the average age was higher in males (females=61.12 years, SD=12.61 vs., males=62.88 years, SD=12.65, $p < 0.001$).

In relation to diseases of the oral cavity, salivary glands and jaws, the 30 most prevalent diseases diagnosed by the Dental Service staff are: caries limited to enamel (K02.0=204, 1.53%), other specified conditions of teeth and their supporting structures (K08.8=197, 1.47%), temporomandibular joint disorders (K07.6=195, 1.46%), functional dentofacial anomalies (K07.5=141, 1.05%), retained tooth root (K08.3=110, 0.8%), anomalies of the relationship between dental arches (K07.2=108, 0.8%), disorder of teeth and their supporting structures, unspecified (K08.9=106, 0.79%), periapical abscess without fistula (K04.7=101, 0.76%), other dentofacial anomalies (K07.8=81, 0.61%), leucoplakia and other oral epithelial abnormalities including tongue (K13.2=54, 0.4%), dentin caries (K02.1=51, 0.38%), acute periodontitis (K05.2=49, 0.37), pulpitis (K04.0=48, 0.36), acute gingivitis (K05.0=43, 0.32), chronic periodontitis (K05.3=38, 0.28%), impacted teeth (K01.0=35, 0.26%), deposits [accretions] on teeth (K03.6=33, 0.25%); tooth loss due to accident, extraction or local periodontal disease (K08.1=29, 0.22%), other and unspecified lesions of oral mucosa (K13.7=29, 0.22%), abrasion of teeth (K03.1=25, 0.19%), periapical abscess with fistula (K04.6=19, 0.14%), impacted teeth (K01.1=18, 0.13%), other specified disorders of gingiva and edentulous area (K06.8=18, 0.13%), other forms of stomatitis (K12.1=18, 0.13%), excessive attrition of teeth (K03.0=15, 0.11), lesions of gingiva and edentulous area associated with trauma (K06.2=13, 0.1%), other and unspecified diseases of the gums and

edentulous area pulp and periapical tissue (K04.9=11, 0.08%), alterations in salivary secretion (K11.7=11, 0.08%), other tongue diseases (K14.8=11, 0.08%), and cellulitis and mouth abscess (K12.2=10, 0.07%).

3.2 General characteristics of the pulpitis population

The average age of the 48 patients with irreversible pulpitis was 57.33 years (SD=9.99 years) and the median age was 57 years (IQR=49.25-62 years). The youngest person was 40 years old, while the oldest was 80 years old (range=40 years). The majority of patients were females (n=29, 60.4%) and older adults between 50 and 59 years old (n=15, 31%). The top 10 conditions and diseases of the oral cavity, salivary glands and jaws (K00–K14) were: specified disorders and conditions of teeth and their supporting structures (K08.8 and K08.9=29, 60.4%), caries limited to enamel (K02.0=28, 58.3%), other dentofacial and functional anomalies (K07.5 and K07.8=12, 25.0%), periapical abscess without fistula (K04.7=10, 20.8%), retained tooth root (K08.3=10, 20.8%), temporomandibular joint disorders (K07.6=9, 18.8%), dentine caries (K02.1=7, 14.6%), leucoplakia and other changes in oral epithelium including tongue (K13.2=7, 14.6%), and oral mucosa (K13.3=7, 14.6%). 14.6%), acute gingivitis (K05.0=6, 12.5%), and abnormalities in the relationship between the dental arches (K07.2=5, 10.4%). In turn, the 5 most prevalent communicable diseases were: COVID-19 (n=13, 27.1%), acute pharyngitis (n=7, 14.6%), gastroenteritis and colitis of unspecified origin (n=6, 12.5%), acute upper respiratory tract infection (n=3, 6.3%), and otitis media (n=2, 4.2%). In addition, we observed cases of acute rhinopharyngitis [common cold] (n=2, 4.2%), acute tonsillitis (n=2, 4.2%), urinary tract infection (n=3, 6.3%), conjunctivitis (n=1, 2.1%), acute cystitis (n=1, 2.1%), postmenopausal atrophic vaginitis (n=1, 2.1%), nail tinea (n=1, 2.1%), vulvar and vaginal candidiasis (n=1, 2.1%), and mycosis (n=1, 2.1%). Similarly, the 5 most prevalent chronic non-communicable diseases were: obesity (n=12, 25.0%), chronic peripheral venous insufficiency (n=9, 18.8%), type 2 diabetes (n=8, 16.7%), essential (primary) hypertension (n=7, 14.6%), and irritable bowel syndrome without diarrhea (n=6, 12.5%).

3.3 Analysis of the association among sociodemographic and oral cavity, salivary gland and jaw diseases (K00–K14) and COVID-19

A univariate analysis was performed to examine the association between individual variables (K00–K14) and the presence of COVID-19. This analysis showed that the risk of developing COVID-19 is higher in females (15.5%) compared to males (13.3%) (Table 1). Likewise, the probability of developing COVID-19 in patients with anomalies of the relationship between dental arches (K07.2 = 6.5%), functional dentofacial anomalies (K07.5 = 7.8%), temporomandibular joint disorders (K07.6 = 9.7%), retained tooth root (K08.3 = 4.5%) and disorder of teeth and their supporting structures, unspecified (K08.9 = 6.6%) is lower compared to patients without the same anomalies or disorders (14.8%) (Table 1). Alveolitis of the maxilla (K10.3) increases the COVID-19 risk 11 times more compared to people without alveolitis of the maxilla. In turn, age showed an inversely proportional association, indicating that the older the person, the lower the probability of presenting COVID-19 (Table 1). A multivariate logistic regression analysis was performed to identify the independent factors of COVID-19 in relation to diseases of the oral cavity, salivary glands and jaws. All codes (K00–K14) were included in the multivariate model. This first model showed that pathological tooth resorption (K03.3) and pulpitis (K04.0) increase the risk of COVID-19 by 30 and 2 times more (Table 1). While the retained tooth root continues to show an inversely proportional relationship (Table 1).

Table 1. First model of association among COVID-19, sociodemographic variables and those related to diseases of the oral cavity, salivary glands and jaws in people aged 40 years and over

Variables	Crude OR (95% CI)	P^a	OR Adjusted (95% CI)	P^b

Females (1)	1.196 (1.080-1.323)	0.001	0.937 (0.842-1.044)	0.240
Age (years)	0.920 (0.915-0.925)	<0.001	0.919 (0.915-0.924)	<0.001
K000(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K001(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K002(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K010(1)	0.963 (0.373-2.486)	0.939	0.916 (0.307-2.73)	0.875
K011(1)	0.340 (0.045-2.554)	0.294	0.22 (0.027-1.768)	0.154
K012(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K020(1)	0.997 (0.675-1.473)	0.987	1.134 (0.684-1.878)	0.626
K021(1)	0.627 (0.249-1.581)	0.323	0.669 (0.22-2.035)	0.478
K022(1)	5.784 (0.362-92.504)	0.215	$4.674E^{+25}$ (0-ND)	0.998
K023(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K029(1)	0 (0-ND)	0.999	0 (0-ND)	0.998
K030(1)	0.413 (0.054-3.140)	0.393	0 (0-ND)	0.998
K031(1)	0.788 (0.236-2.635)	0.699	0.58 (0.098-3.422)	0.547
K032(1)	1.928 (0.200-18.540)	0.570	2.381 (0.242-23.407)	0.457
K033(1)	2.892 (0.262-31.904)	0.386	30.488 (1.004-925.821)	0.050
K036(1)	0.372 (0.089-1.557)	0.176	0.156 (0.02-1.245)	0.080
K038(1)	2.892 (0.262-31.904)	0.386	3.854 (0.181-82.226)	0.388
K039(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K040(1)	1.723 (0.877-3.383)	0.114	2.446 (1.026-5.829)	0.044
K041(1)	0.964 (0.116-8.008)	0.973	4.146 (0.287-59.832)	0.296
K042(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K043(1)	2.892 (0.262-31.904)	0.386	2.975 (0.186-47.588)	0.441
K044(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K045(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K046(1)	0.321 (0.043-2.405)	0.269	0.387 (0.036-4.132)	0.432
K047(1)	0.930 (0.528-1.638)	0.801	0.793 (0.391-1.609)	0.520
K048(1)	0.723 (0.090-5.780)	0.759	0 (0-ND)	0.999
K049(1)	0.578 (0.074-4.517)	0.601	2.698 (0.254-28.645)	0.410
K050(1)	1.323 (0.613-2.856)	0.476	1.58 (0.632-3.954)	0.328
K051(1)	0.964 (0.116-8.008)	0.973	2.775 (0.213-36.101)	0.435
K052(1)	0.513 (0.184-1.428)	0.201	0.492 (0.138-1.751)	0.273
K053(1)	0.679 (0.241-1.917)	0.465	0.904 (0.236-3.469)	0.883
K054(1)	2.892 (0.262-31.904)	0.386	104.29 (0.413-26305.105)	0.100
K055(1)	9344156043.04 (0-ND)	1.000	4038131931.007 (0-ND)	1.000
K056(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K060(1)	9344156043.04(0-ND)	1.000	$6,160E^{+27}$ (0-)	0.999
K062(1)	0.482 (0.063-3.705)	0.483	0.558 (0.051-6.085)	0.632
K063(1)	0 (0-ND)	1.000	4.021 (0-)	1.000
K068(1)	0.722 (0.166-3.144)	0.665	0 (0-ND)	0.998
K069(1)	0 (0-ND)	0.999	13.629 (0-)	1.000
K070(1)	0 (0-ND)	0.999	0 (0-ND)	1.000
K072(1)	0.399 (0.185-0.859)	0.019	0.409 (0.118-1.419)	0.159
K074(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K075(1)	0.486 (0.262-0.902)	0.022	1.109 (0.376-3.276)	0.851
K076(1)	0.620 (0.386-0.998)	0.049	0.933 (0.489-1.782)	0.834
K078(1)	0.461 (0.200-1.060)	0.068	0.953 (0.293-3.096)	0.936
K079(1)	0 (0-ND)	0.999	0 (0-ND)	1.000
K080(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K081(1)	0.428 (0.102-1.800)	0.247	0.66 (0.145-2.993)	0.590
K083(1)	0.273 (0.111-0.672)	0.005	0.277 (0.083-0.916)	0.035
K088(1)	0.650 (0.408-1.034)	0.069	0.808 (0.452-1.443)	0.471
K089(1)	0.407 (0.189-0.877)	0.022	0.573 (0.23-1.427)	0.232
K090(1)	0 (0-ND)	1.000	0.523 (0-)	1.000
K092(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K098(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K099(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K100(1)	0 (0-ND)	0.999	0 (0-ND)	0.999

K101(1)	0 (0-ND)	1.000	1,016E^{+16} (0-ND)	0.999
K103(1)	11.573 (1.049-127.692)	0.046	5039717125.38 (0-ND)	0.999
K108(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K109(1)	9344156043.04 (0-ND)	1.000	6.837E^{+32} (0-ND)	0.999
K112(1)	2.892 (0.262-31.904)	0.386	0 (0-ND)	0.999
K113(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K117(1)	0.578 (0.074-4.517)	0.601	0 (0-ND)	0.999
K118(1)	2.892 (0.262-31.904)	0.386	0 (0-ND)	1.000
K120(1)	5.786 (0.815-41.100)	0.079	11.952 (0.993-143.798)	0.051
K121(1)	0 (0-ND)	0.998	0 (0-ND)	0.998
K122(1)	1.446 (0.307-6.813)	0.641	1.64 (0.149-18.026)	0.686
K130(1)	0 (0-ND)	0.999	16.398 (0-ND)	1.000
K131(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K132(1)	1.005 (0.474-2.133)	0.989	1.626 (0.618-4.282)	0.325
K134(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K137(1)	0 (0-ND)	0.998	0 (0-ND)	0.998
K148(1)	1.285 (0.277-5.952)	0.748	3.849 (0.506-29.279)	0.193
K149(1)	0 (0-ND)	1.000	0.735 (0-ND)	1.000
Constant			22.890	0.000

OR: odds ratio. P values were calculated using the chi-square Wald test. a P value of the crude OR from the univariate logistic regression models. b P value of the OR adjusted for the variables included in the multivariate logistic regression model. Variables included in the multivariate logistic regression model: Sex: male = 0, female = 1. Age: years (numerical variable). ICD-10 codes: K000: presence=1, absence=0, K001: presence=1, absence=0, K002: presence=1, absence=0, K010: presence=1, absence=0, K011: presence=1, absence=0, K012: presence=1, absence=0, K020: presence=1, absence=0, K021: presence=1, absence=0, K022: presence=1, absence=0, K023: presence=1, absence=0, K029: presence=1, absence=0, K030: presence=1, absence=0, K031: presence=1, absence=0, K032: presence=1, absence=0, K033: presence=1, absence=0, K036: presence=1, absence=0, K038: presence=1, absence=0, K039: presence=1, absence=0, K040: presence=1, absence=0, K041: presence=1, absence=0, K042: presence=1, absence=0, K043: presence=1, absence=0, K044: presence=1, absence=0, K045: presence=1, absence=0, K046: presence=1, absence=0, K047: presence=1, absence=0, K048: presence=1, absence=0, K049: presence=1, absence=0, K050: presence=1, absence=0, K051: presence=1, absence=0, K052: presence=1, absence=0, K053: presence=1, absence=0, K054: presence=1, absence=0, K055: presence=1, absence=0, K056: presence=1, absence=0, K060: presence=1, absence=0, K062: presence=1, absence=0, K063: presence=1, absence=0, K068: presence=1, absence=0, K069: presence=1, absence=0, K070: presence=1, absence=0, K072: presence=1, absence=0, K074: presence=1, absence=0, K075: presence=1, absence=0, K076: presence=1, absence=0, K078: presence=1, absence=0, K079: presence=1, absence=0, K080: presence=1, absence=0, K081: presence=1, absence=0, K083: presence=1, absence=0, K088: presence=1, absence=0, K089: presence=1, absence=0, K090: presence=1, absence=0, K092: presence=1, absence=0, K098: presence=1, absence=0, K099: presence=1, absence=0, K100: presence=1, absence=0, K101: presence=1, absence=0, K103: presence=1, absence=0, K108: presence=1, absence=0, K109: presence=1, absence=0, K112: presence=1, absence=0, K113: presence=1, absence=0, K117: presence=1, absence=0, K118: presence=1, absence=0, K120: presence=1, absence=0, K121: presence=1, absence=0, K122: presence=1, absence=0, K130: presence=1, absence=0, K131: presence=1, absence=0, K132: presence=1, absence=0, K134: presence=1, absence=0, K137: presence=1, absence=0, K148: presence=1, absence=0, K149: presence=1, absence=0, Source: Prepared by the authors using the results of the SIMEF database, January-December, 2022.

The second multivariate model showed that age, retained tooth root, and disorder of teeth and their supporting structures (unspecified) have an inversely proportional relationship and a lower probability of presenting COVID-19 compared to people who do not have such a history (Table 2). While, pulpitis increases the risk at least 2 times more (Table 2). Finally, the third model shows that the probability of presenting COVID-19 in a 40-year-old person with pulpitis is 62.5%; in a 40-year-old person with retained tooth root, the probability is 21.2%, and in a person of the same age with a disorder of the teeth and their supporting structures, the probability is 18.6%, compared to a 40-year-old person who does not have the same history indicated above (43.2%). Retained tooth root and disorders of the teeth and their supporting structures continue to show an inversely proportional relationship (Table 2).

Table 2. Second and third models of association among COVID-19, sociodemographic variables and those related to diseases of the oral cavity, salivary glands and jaws in people aged 40 years and over

Variables	2nd OR adjusted (95% CI)	P^a	3rd OR adjusted (95% CI)	P^b
Females (1)	1.071 (0.962-1.192)	0.211		
Age (years)	0.920 (0.915-0.925)	<0.001	0.920 (0.915-0.925)	<0.001
K033(1)	7.820 (0.509-120.162)	0.140		
K040(1)	2.319 (1.100-4.891)	0.027	2.198 (1.047-4.614)	0.037
K072(1)	0.416 (0.136-1.272)	0.124		
K075(1)	1.163 (0.444-3.044)	0.758		
K076(1)	0.809 (0.466-1.404)	0.451		
K083(1)	0.373 (0.145-0.959)	0.041	0.353 (0.139-0.900)	0.029
K089(1)	0.337 (0.147-0.776)	0.011	0.300 (0.132-0.679)	0.004
K103(1)	8.934 (0.726-109.980)	0.087		
Constante	20.548	<0.001	21.528	<0.001

OR: odds ratio. P values were calculated using the chi-square Wald test.

[a] P value of OR adjusted for variables included in the 2nd multivariate logistic regression model.

[b] P value of OR adjusted for variables included in the 3rd multivariate logistic regression model.

Variables included in the 2nd multivariate logistic regression model: Sex: male = 0, female = 1. Age (numerical variable). ICD-10 codes; K033: presence = 1, absence = 0, K040: presence = 1, absence = 0, K072: presence = 1, absence = 0, K075: presence = 1, absence = 0, K076: presence = 1, absence = 0, K083: presence = 1, absence = 0, K089: presence = 1, absence = 0, K103: presence = 1, absence = 0.

Variables included in the 3rd multivariate logistic regression model: Age (numerical variable). ICD-10 codes; K040: presence=1, absence=0, K083: presence=1, absence=0, K089: presence=1, absence=0.

Source: Prepared by the authors using the results from the SIMEF database, January-December, 2022.

3.4 Discussion.

Data show that the risk of COVID-19 is higher in females compared to males, similar to other studies in Mexico (López-Hernández 2022, Anguiano-Velazquez et al. 2024). At the beginning of the pandemic, several risk factors for the development of COVID-19 were established: cardiovascular disease, cerebrovascular disease, type 2 diabetes, obesity, cancer, chronic obstructive pulmonary disease, advanced age, hypertension, chronic kidney disease, smoking and recently, it is proposed that patients with periodontal diseases (PD) could make up another risk group (López-Hernández 2022, Baltazar-Díaz & Zamora-Pérez 2021). Some authors suggest that the association between PD and COVID-19 is due to the presence of comorbidities that increase the risk of COVID-19 and that are also risk factors common to PD. Other hypotheses suggest that this association is due to the overexpression

of proinflammatory cytokines (Baltazar-Díaz & Zamora-Pérez 2021, Coureaux-Rojas & Cuevas-Gandaria 2021) and the expression of a differential inflammatory genetic profile in dental pulp tissues (Cho et al 2023). In these tissues, from people with a history of COVID-19 and pulpitis (COVID-19 group), transcriptome profiling by ribonucleic acid (RNA) sequencing identified a total of 1,461 differentially expressed messenger RNAs (mRNAs) compared to dental pulp tissues from people with pulpitis without a history of COVID-19 (controls) (Cho et al 2023). Approximately 21% (311 of 1461) of the identified mRNA transcripts were in protein-coding genes (Cho et al 2023). Of these genes, 252 (81%) were upregulated and 59 (19%) were downregulated in the COVID-19 group compared to controls (Cho et al 2023). Also, differential gene expression was observed in genes that have diverse functions ranging from a role in growth and development, ATP generation, neuropeptide signaling, transcriptional regulation, G protein-mediated transduction, cytoskeletal structure, innate immune response, antibacterial activity, inflammatory response, and wound healing (Cho et al 2023). Likewise, both the SARS-CoV2 receptor and its associated cellular serine protease (TPMRSS2, Transmembrane Serine Protease 2) (SARS-CoV2/human interactome) have been shown to be expressed in the dental pulp of people under physiological and inflammatory (pulpitis) conditions, in a similar manner (Galicia et al. 2020). These data suggest that the dental pulp is vulnerable to SARS-CoV-2 infection and that SARS-CoV-2 infection of the Dental pulp may contribute to worse outcomes in patients with pulpitis (Galicia et al. 2020). Furthermore, the ACE2 gene is characterized by a series of polymorphisms associated with higher levels of tissue expression of the ACE2 receptor in East Asian populations compared to European populations (Bourgonje et al. 2020). This implies differential susceptibility to SARS-CoV-2 infection in different populations (Bourgonje et al. 2020). In turn, these results suggest differential expressions of genetic and epigenetic profiles associated with greater or lesser susceptibility to SARS-CoV-2 infection and COVID-19. Understanding this relationship (inflammatory and immunological profile) could reveal critical information about the transmission routes (including: contact with nasal, ocular, and oral mucous membranes) and the pathophysiology between PD (diseases of the oral cavity, salivary glands, and jaws) and COVID-19 (Baltazar-Díaz & Zamora-Pérez 2021). Our data show epidemiological associations between COVID-19 and certain dental and maxillofacial conditions, such as abnormalities of the relationship between dental arches, functional dentofacial abnormalities, and temporomandibular joint disorders, which were associated with a lower risk of COVID-19. These findings reflect the multifactorial nature of the disease; however, we cannot rule out the influence of confounding variables not included in the logistic regression analyses. On the other hand, maxillary alveolitis stood out as a significant risk factor, considerably increasing the likelihood of COVID-19. Differential expression of genes associated with innate immune response, antibacterial activity and inflammatory response in patients with COVID-19 could partly explain this association. Multivariate analysis (adjusting for multiple factors) shows that pulpitis and pathological tooth resorption significantly increase the risk of COVID-19. These findings might be related to the discovery of increased expression of the heat shock transcription factor family, X-linked 1 (HSFX1), in patients with COVID-19 and pulpitis (Cho et al 2023). HSFX1 (located in the nucleus) is thought to enable the activity of deoxyribonucleic acid (DNA)-binding transcription factors, the DNA-binding activity of RNA polymerase II and the cis-regulatory region of RNA polymerase II, and to be involved in the regulation of transcription by RNA polymerase II. Heat shock transcription factors (HSFs) have broad functions in stress resistance that encompass protection against protein misfolding, inflammation, and environmental insults (Gomez-Pastor et al. 2018). On the other hand, retained tooth root and disorders of the teeth and their supporting structures (unspecified) continued to show an inverse relationship, suggesting that patients with these conditions might be less exposed or have other characteristics that protect them from the virus, which requires further analysis. Finally, in the third model, it was observed that the probability of COVID-19 varies significantly according to the combination of specific oral conditions and age. These findings reinforce the idea that

oral conditions could have a relevant role in modulating the risk of SARS-CoV-2 infection and COVID-19, possibly through genetic and epigenetic mechanisms related to inflammatory and immunological processes, without forgetting that biological or behavioural differences, or external factors such as access to health services, could also be related.

3.5 Limitations and applications.

This study has several limitations that should be considered when interpreting the findings. Firstly, as a retrospective, cross-sectional study, it can only establish an epidemiological association between PD and the risk of COVID-19. However, the observed associations may be influenced by unmeasured confounding variables, such as socioeconomic status, underlying health conditions, or differences in healthcare access. Secondly, the study relied on data from outpatient consultations at a single healthcare facility. Consequently, the findings may not be generalisable to individuals receiving care in different healthcare settings. Additionally, diagnostic criteria and data collection methods may have introduced biases. The identification of oral conditions was based on clinical records, which could be subject to variations in diagnostic accuracy and completeness. To minimise this potential bias, only medical records that met the inclusion criteria were selected. Moreover, the study did not account for potential differences in the severity of oral conditions, which may influence their relationship with COVID-19 risk. Finally, behavioural factors such as oral hygiene practices, diet, and lifestyle were not assessed. These variables could play a crucial role in influencing both oral health and susceptibility to COVID-19. Future studies employing longitudinal designs and comprehensive data collection are needed to confirm these findings and investigate the underlying biological and environmental interactions. Further research incorporating genetic, epigenetic, and immunological profiling is also required to elucidate these mechanisms more precisely. Although the results of this study offer valuable insights into the association between oral diseases and COVID-19 risk, it is critical to note that the analysis did not consider all potential confounding variables. Other factors such as systemic comorbidities, lifestyle, or genetic predisposition could also influence the results. Therefore, future studies that include a more detailed analysis of these variables will be essential to better understand the interactions between oral health and susceptibility to infectious diseases such as COVID-19.

4. CONCLUSION.

The findings of this study suggest that certain oral conditions may influence the risk of contracting covid-19. The second multivariate model revealed an inverse relationship between age, retained tooth roots, and disorders of the teeth and their supporting structures (unspecified), with a lower probability of COVID-19 compared to individuals without these conditions. In contrast, pulpitis was associated with at least a twofold increase in risk. Notably, retained tooth root and disorders of the teeth and their supporting structures consistently exhibited an inverse association with COVID-19 risk. These results highlight the complexity of the relationship between oral health and covid-19 susceptibility. While the mechanisms underlying these associations remain unclear, potential explanations may include immunological, inflammatory, genetic, or behavioural factors. Further research is needed to elucidate these interactions and to explore their implications for clinical and public health strategies.

DISCLAIMER.

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT.

The study was conducted using medical records, and no informed consent was obtained. The handling of the information was approved by the ethics committee, ensuring compliance with the appropriate ethical standards.

ETHICAL APPROVAL.

The study was conducted in accordance with the Good Clinical Practice Guidelines of our laws and the Declaration of Helsinki for human experiments. The protocol was approved by two committees: The Research Committee and the Ethics Committee in Research of the FMC "División del Norte", ISSSTE. The Data was treated confidentially to ensure the privacy and protection of participants' information.

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