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

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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 was collected from 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 of calories (1,222; 9.1%). The average age of the 48 patients with irreversible pulpitis was 57.33 years old (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 of dental arch relationship 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 disorders 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 teeth and supporting structures OR=0.407 (0.189-0.877), p=0.022; jaws' 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 have 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), which affects 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 irregular ulcers, small blisters, petechiae, necrotising and desquamative gingivitis, opportunistic co-infections, salivary gland dysfunction, white and erythematous plaques, and gustatory impairment, which often coincide with anosmia and ageusia (Amorim Dos Santos et al. 2021, Brandini et al. 2021). Additionally, the fact that the most common risk factors for severe COVID-19 correlate with poor oral health, tooth loss, and periodontitis suggests a possible association between oral diseases and COVID-19 (Herrera et al. 2020, Sahni & Gupta 2020, Patel & Woolley 2021, Costa et al. 2022, Herrera et al. 2023). Moreover, although periodontal symptoms were not associated with COVID-19 disease (OR = 1.1; 95% confidence intervals [CI], 0.73–1.65) or COVID-19 mortality (OR = 2.71; 95% CI, 0.64–11.51), were associated with COVID-19 severity (OR = 3.18; 95% CI, 1.81–5.58) (Qi et al. 2022).

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). In addition, 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 COVID-19 history, 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— they 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, which potentially impact dental health.

Furthermore, Galicia et al. provide evidence suggest 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 old 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 revision 10th (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 such as 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.

In order 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 per month, ensuring their accuracy. Finally, a total of 13,359 adults aged 40 years old 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 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). It was included a Confidence Interval 95% (CI95%). 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. In order to assess the association between COVID-19 and potential associated factors, the data was analysed as numerical (age) and dichotomous (sex, morbidities) variables, using univariate and multivariate logistic regression models. An Univariate analysis was performed to examine the relationship between individual variables (age, sex, morbidities of code K00–K14 corresponding to “diseases of 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, however they did not account for confounding variables. A multivariate logistic regression analysis was performed to identify factors independent from COVID-19. Significant variables 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. Therefore, this method allows adjustment for confounding variables and the 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) which was considered significant.

2.3.1 Diseases codes of oral cavity, salivary glands and jaws (K00–K14) utilised during the calculations of logistic regression models

K00 Disorders of tooth development and eruption:
- K00.0 Anodontia
- K00.1 Supernumerary teeth
- K00.2 Abnormalities of teeth size and form

K01 Embedded and impacted teeth
- K01.0 Embedded teeth
- K01.1 Impacted teeth

K02 Dental caries
- K02.0 Caries limited to enamel
- K02.1 Caries of dentine
- K02.2 Caries of cementum
- K02.3 Arrested dental caries
- K02.9 Dental caries, unspecified

K03 Other diseases of hard tissues of teeth
- K03.0 Teeth Excessive attrition
- K03.1 Abrasion of teeth
- K03.2 Erosion of teeth
- K03.3 Pathological resorption of teeth
- K03.6 Deposits [accretions] on teeth
- K03.8 Other specified diseases of teeth hard tissues
- K03.9 Diseases of teeth hard tissues, unspecified

K04 Diseases of pulp and periapical tissues
- K04.0 Pulpitis
- K04.1 Pulp Necrosis
- K04.2 Pulp degeneration
- K04.3 Abnormal hard tissue formation in pulp
- K04.4 Acute apical periodontitis of pulpal origin
- K04.5 Chronic apical periodontitis
- K04.6 Periapical abscess with sinus
- K04.7 Periapical abscess without sinus
- K04.8 Radicular cyst
- K04.9 Other and unspecified diseases of pulp and periapical tissues

K05 Gingivitis and periodontal diseases
- K05.0 Acute gingivitis
- K05.1 Chronic gingivitis
- K05.2 Acute periodontitis
- K05.3 Chronic periodontitis
- K05.4 Periodontosis
- K05.5 Other periodontal diseases
- K05.6 Periodontal diseases, unspecified

K06 Other disorders of gingiva and edentulous alveolar ridge
- K06.0 Gingival recession
- K06.2 Gingival and edentulous alveolar ridge lesions associated with trauma
- K06.3 Horizontal alveolar bone loss
- K06.8 Other specified disorders of gingiva and edentulous alveolar ridge
- K06.9 Disorder of gingiva and edentulous alveolar ridge, unspecified

K07 Dentofacial anomalies [including malocclusion]
- K07.0 Major anomalies of jaw size

K07.2 Anomalies of dental arch relationship
K07.4 Malocclusion, unspecified
K07.5 Dentofacial functional abnormalities
K07.6 Temporomandibular joint disorders
K07.8 Other dentofacial anomalies
K07.9 Dentofacial anomaly, unspecified
K08 Other disorders of teeth and supporting structures
K08.0 teeth Exfoliation due to systemic causes
K08.1 Loss of teeth due to accident, extraction or local periodontal disease
K08.3 Retained dental root
K08.8 Other specified disorders of teeth and supporting structures
K08.9 Disorders of teeth and supporting structures, unspecified
K09 Cysts of oral region, not elsewhere classified
K09.0 Developmental odontogenic cysts
K09.2 Other cysts of jaw
K09.8 Other cysts of oral region, not elsewhere classified
K09.9 Custs of oral region, unspecified
K10 Other diseases of jaws
K10.0 Developmental disorders of jaws
K10.1 Giant cell granuloma, central
K10.3 Jaws' Alveolitis
K10.8 Other jaws' specified diseases
K10.9 jaws' Diseases, unspecified
K11 Diseases of salivary glands
K11.2 Sialoadenitis
K11.3 Abscess of salivary gland
K11.7 Disturbances of salivary secretion
K11.8 Other diseases of salivary glands
K12 Stomatitis and related lesions
K12.0 Recurrent oral aphthae
K12.1 Other forms of stomatitis
K12.2 Cellulitis and mouth abscess
K13 Other diseases of lip and oral mucosa
K13.0 lips' Diseases
K13.1 Cheek and lip biting
K13.2 Leukoplakia and other disturbances of oral epithelium, including tongue
K13.4 Granuloma and granuloma-like lesions of oral mucosa
K13.7 Other and unspecified lesions of oral mucosa
K14 Diseases of tongue
K14.8 Other tongue diseases
K14.9 tongue Diseases, unspecified

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. In order 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 was 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 wasmade 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 of 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 diarrhoea (K58.9=462, 3.5%), depressive episode (F32.9=445, 3.3%), gastroenteritis and colitis of unspecified origin (A09.9=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 old, SD=12.61 vs., males=62.88 years old, 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 teeth disorders and supporting structures (K08.8=197, 1.47%), temporomandibular joint disorders (K07.6=195, 1.46%), dentofacial functional anomalies (K07.5=141, 1.05%), retained dental root (K08.3=110, 0.8%), anomalies of dental arch relationship (K07.2=108, 0.8%), teeth disorder and supporting structures, unspecified (K08.9=106, 0.79%), periapical abscess without sinus (K04.7=101, 0.76%), other dentofacial anomalies (K07.8=81, 0.61%), leukoplakia and other disturbances of oral epithelium, including tongue (K13.2=54, 0.4%), dentine 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%), embedded teeth (K01.0=35, 0.26%), deposits [accretions] on teeth (K03.6=33, 0.25%); teeth loss due to accidents, extraction or local periodontal disease (K08.1=29, 0.22%), other and unspecified lesions of oral mucosa (K13.7=29, 0.22%), teeth abrasion (K03.1=25, 0.19%), periapical abscess with sinus (K04.6=19, 0.14%), impacted teeth (K01.1=18, 0.13%), other specified disorders of gingiva and edentulous alveolar ridge (K06.8=18, 0.13%), other forms of stomatitis (K12.1=18, 0.13%), excessive teeth attrition (K03.0=15, 0.11), gingival and edentulous alveolar ridge lesions associated with trauma (K06.2=13, 0.1%), other and unspecified diseases of pulp and periapical tissue (K04.9=11, 0.08%), disturbances of salivary secretion (K11.7=11, 0.08%), other diseases of tongue (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 old (SD=9.99 years) and the median age was 57 years old (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: other specified teeth disorders and supporting structures (K08.8 and K08.9=29, 60.4%), caries limited to enamel (K02.0=28, 58.3%), dentofacial functional anomalies and other dentofacial anomalies (K07.5 and K07.8=12, 25.0%), periapical abscess without sinus (K04.7=10, 20.8%), retained dental root (K08.3=10, 20.8%), temporomandibular joint disorders (K07.6=9, 18.8%), dentine caries (K02.1=7, 14.6%), leukoplakia and other disturbances of oral epithelium, including tongue (K13.2=7, 14.6%), and hairy leukoplakia (K13.3=7, 14.6%). 14.6%), acute gingivitis (K05.0=6, 12.5%), and anomalies of dental arch relationship (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 diarrhoea (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 COVID-19 is higher in females (15.5%) compared to males (13.3%) (Table 1). Likewise, the probability of COVID-19 in patients with anomalies of dental arch relationship (K07.2 = 6.5%), dentofacial functional anomalies (K07.5 = 7.8%), temporomandibular joint disorders (K07.6 = 9.7%), retained dental root (K08.3 = 4.5%) and teeth disorder and supporting structures, unspecified (K08.9 = 6.6%) is lower compared to patients without the same anomalies or disorders (14.8%) (Table 1). Alveolitis of jaws (K10.3) increases the COVID-19 risk 11 times more compared to people without jaw alveolitis. In turn, age showed an inversely proportional association (beta= -0.084), indicating that the lower the age, the lower the likelihood of COVID-19 (Table 1). A multivariate logistic regression analysis was performed in order to identify the independent factors of COVID-19 in relation to oral cavity diseases, salivary glands and jaws. All codes (K00–K14) were included in the multivariate model. This first model showed that pathological resorption of teeth (K03.3) and pulpitis (K04.0) increase the risk of COVID-19 by 30 and 2 times more (Table 1). While the retained dental root (K08.3) continues to show an inversely (beta= -1.286) 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 old 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
K00.0(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K00.1(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K00.2(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K01.0(1)	0.963 (0.373-2.486)	0.939	0.916 (0.307-2.73)	0.875
K01.1(1)	0.340 (0.045-2.554)	0.294	0.22 (0.027-1.768)	0.154

K02.0(1)	0.997 (0.675-1.473)	0.987	1.134 (0.684-1.878)	0.626
K02.1(1)	0.627 (0.249-1.581)	0.323	0.669 (0.22-2.035)	0.478
K02.2(1)	5.784 (0.362-92.504)	0.215	$4.674E^{+25}$ (0-ND)	0.998
K02.3(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K02.9(1)	0 (0-ND)	0.999	0 (0-ND)	0.998
K03.0(1)	0.413 (0.054-3.140)	0.393	0 (0-ND)	0.998
K03.1(1)	0.788 (0.236-2.635)	0.699	0.58 (0.098-3.422)	0.547
K03.2(1)	1.928 (0.200-18.540)	0.570	2.381 (0.242-23.407)	0.457
K03.3(1)	2.892 (0.262-31.904)	0.386	30.488 (1.004-925.821)	0.050
K03.6(1)	0.372 (0.089-1.557)	0.176	0.156 (0.02-1.245)	0.080
K03.8(1)	2.892 (0.262-31.904)	0.386	3.854 (0.181-82.226)	0.388
K03.9(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K04.0(1)	1.723 (0.877-3.383)	0.114	2.446 (1.026-5.829)	0.044
K04.1(1)	0.964 (0.116-8.008)	0.973	4.146 (0.287-59.832)	0.296
K04.2(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K04.3(1)	2.892 (0.262-31.904)	0.386	2.975 (0.186-47.588)	0.441
K04.4(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K04.5(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K04.6(1)	0.321 (0.043-2.405)	0.269	0.387 (0.036-4.132)	0.432
K04.7(1)	0.930 (0.528-1.638)	0.801	0.793 (0.391-1.609)	0.520
K04.8(1)	0.723 (0.090-5.780)	0.759	0 (0-ND)	0.999
K04.9(1)	0.578 (0.074-4.517)	0.601	2.698 (0.254-28.645)	0.410
K05.0(1)	1.323 (0.613-2.856)	0.476	1.58 (0.632-3.954)	0.328
K05.1(1)	0.964 (0.116-8.008)	0.973	2.775 (0.213-36.101)	0.435
K05.2(1)	0.513 (0.184-1.428)	0.201	0.492 (0.138-1.751)	0.273
K05.3(1)	0.679 (0.241-1.917)	0.465	0.904 (0.236-3.469)	0.883
K05.4(1)	2.892 (0.262-31.904)	0.386	104.29 (0.413-26305.105)	0.100
K05.5(1)	9344156043.04 (0-ND)	1.000	4038131931.007 (0-ND)	1.000
K05.6(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K06.0(1)	9344156043.04(0-ND)	1.000	$6,160E^{+27}$ (0-)	0.999
K06.2(1)	0.482 (0.063-3.705)	0.483	0.558 (0.051-6.085)	0.632
K06.3(1)	0 (0-ND)	1.000	4.021 (0-)	1.000
K06.8(1)	0.722 (0.166-3.144)	0.665	0 (0-ND)	0.998
K06.9(1)	0 (0-ND)	0.999	13.629 (0-)	1.000
K07.0(1)	0 (0-ND)	0.999	0 (0-ND)	1.000
K07.2(1)	0.399 (0.185-0.859)	0.019	0.409 (0.118-1.419)	0.159
K07.4(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K07.5(1)	0.486 (0.262-0.902)	0.022	1.109 (0.376-3.276)	0.851
K07.6(1)	0.620 (0.386-0.998)	0.049	0.933 (0.489-1.782)	0.834
K07.8(1)	0.461 (0.200-1.060)	0.068	0.953 (0.293-3.096)	0.936
K07.9(1)	0 (0-ND)	0.999	0 (0-ND)	1.000
K08.0(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K08.1(1)	0.428 (0.102-1.800)	0.247	0.66 (0.145-2.993)	0.590
K08.3(1)	0.273 (0.111-0.672)	0.005	0.277 (0.083-0.916)	0.035
K08.8(1)	0.650 (0.408-1.034)	0.069	0.808 (0.452-1.443)	0.471
K08.9(1)	0.407 (0.189-0.877)	0.022	0.573 (0.23-1.427)	0.232
K09.0(1)	0 (0-ND)	1.000	0.523 (0-)	1.000
K09.2(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K09.8(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K09.9(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K10.0(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K10.1(1)	0 (0-ND)	1.000	$1,016E^{+16}$ (0-ND)	0.999
K10.3(1)	11.573 (1.049-127.692)	0.046	5039717125.38 (0-ND)	0.999
K10.8(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K10.9(1)	9344156043.04 (0-ND)	1.000	$6.837E^{+32}$ (0-ND)	0.999
K11.2(1)	2.892 (0.262-31.904)	0.386	0 (0-ND)	0.999
K11.3(1)	0 (0-ND)	1.000	0 (0-ND)	1.000
K11.7(1)	0.578 (0.074-4.517)	0.601	0 (0-ND)	0.999
K11.8(1)	2.892 (0.262-31.904)	0.386	0 (0-ND)	1.000

K12.0(1)	5.786 (0.815-41.100)	0.079	11.952 (0.993-143.798)	0.051
K12.1(1)	0 (0-ND)	0.998	0 (0-ND)	0.998
K12.2(1)	1.446 (0.307-6.813)	0.641	1.64 (0.149-18.026)	0.686
K13.0(1)	0 (0-ND)	0.999	16.398 (0-ND)	1.000
K13.1(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K13.2(1)	1.005 (0.474-2.133)	0.989	1.626 (0.618-4.282)	0.325
K13.4(1)	0 (0-ND)	0.999	0 (0-ND)	0.999
K13.7(1)	0 (0-ND)	0.998	0 (0-ND)	0.998
K14.8(1)	1.285 (0.277-5.952)	0.748	3.849 (0.506-29.279)	0.193
K14.9(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: K00.0: presence=1, absence=0, K00.1: presence=1, absence=0, K00.2: presence=1, absence=0, K01.0: presence=1, absence=0, K01.1: presence=1, absence=0, K01.2: presence=1, absence=0, K02.0: presence=1, absence=0, K02.1: presence=1, absence=0, K02.2: presence=1, absence=0, K02.3: presence=1, absence=0, K02.9: presence=1, absence=0, K03.0: presence=1, absence=0, K03.1: presence=1, absence=0, K03.2: presence=1, absence=0, K03.3: presence=1, absence=0, K03.6: presence=1, absence=0, K03.8: presence=1, absence=0, K03.9: presence=1, absence=0, K04.0: presence=1, absence=0, K04.1: presence=1, absence=0, K04.2: presence=1, absence=0, K04.3: presence=1, absence=0, K04.4: presence=1, absence=0, K04.5: presence=1, absence=0, K04.6: presence=1, absence=0, K04.7: presence=1, absence=0, K04.8: presence=1, absence=0, K04.9: presence=1, absence=0, K05.0: presence=1, absence=0, K05.1: presence=1, absence=0, K05.2: presence=1, absence=0, K05.3: presence=1, absence=0, K05.4: presence=1, absence=0, K05.5: presence=1, absence=0, K05.6: presence=1, absence=0, K06.0: presence=1, absence=0, K06.2: presence=1, absence=0, K06.3: presence=1, absence=0, K06.8: presence=1, absence=0, K06.9: presence=1, absence=0, K07.0: presence=1, absence=0, K07.2: presence=1, absence=0, K07.4: presence=1, absence=0, K07.5: presence=1, absence=0, K07.6: presence=1, absence=0, K07.8: presence=1, absence=0, K07.9: presence=1, absence=0, K08.0: presence=1, absence=0, K08.1: presence=1, absence=0, K08.3: presence=1, absence=0, K08.8: presence=1, absence=0, K08.9: presence=1, absence=0, K09.0: presence=1, absence=0, K09.2: presence=1, absence=0, K09.8: presence=1, absence=0, K09.9: presence=1, absence=0, K10.0: presence=1, absence=0, K10.1: presence=1, absence=0, K10.3: presence=1, absence=0, K10.8: presence=1, absence=0, K10.9: presence=1, absence=0, K11.2: presence=1, absence=0, K11.3: presence=1, absence=0, K11.7: presence=1, absence=0, K11.8: presence=1, absence=0, K12.0: presence=1, absence=0, K12.1: presence=1, absence=0, K12.2: presence=1, absence=0, K13.0: presence=1, absence=0, K13.1: presence=1, absence=0, K13.2: presence=1, absence=0, K13.4: presence=1, absence=0, K13.7: presence=1, absence=0, K14.8: presence=1, absence=0, K14.9: 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 dental root, and teeth disorder and 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 dental root, the probability is 21.2%, and in a person of the same age with a teeth disorder and supporting structures (unspecified), the probability is 18.6%, compared to a 40-year-old person who does not have

the same history indicated above (43.2%). Retained dental root and teeth disorder of and supporting structures (unspecified) 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
K03.3(1)	7.820 (0.509-120.162)	0.140		
K04.0(1)	2.319 (1.100-4.891)	0.027	2.198 (1.047-4.614)	0.037
K07.2(1)	0.416 (0.136-1.272)	0.124		
K07.5(1)	1.163 (0.444-3.044)	0.758		
K07.6(1)	0.809 (0.466-1.404)	0.451		
K08.3(1)	0.373 (0.145-0.959)	0.041	0.353 (0.139-0.900)	0.029
K08.9(1)	0.337 (0.147-0.776)	0.011	0.300 (0.132-0.679)	0.004
K10.3(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; K03.3: presence = 1, absence = 0, K04.0: presence = 1, absence = 0, K07.2: presence = 1, absence = 0, K07.5: presence = 1, absence = 0, K07.6: presence = 1, absence = 0, K08.3: presence = 1, absence = 0, K08.9: presence = 1, absence = 0, K10.3: presence = 1, absence = 0.

Variables included in the 3rd multivariate logistic regression model: Age (numerical variable). ICD-10 codes; K04.0: presence=1, absence=0, K08.3: presence=1, absence=0, K08.9: presence=1, absence=0.

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

3.4 Discussion.

The data shows 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, Qi et al. 2022). On the other hand, 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 common factors 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, Schwartz et al. 2024) 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 COVID-19 history (controls) (Cho et al 2023).

Approximately a 21% (311 of 1461) of the identified mRNA transcripts were in protein-coding genes (Cho et al 2023). From these genes, 252 (81%) were upregulated and 59 (19%) were downregulated in the COVID-19 group compared to controls (Cho et al 2023). Additionally, a 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 suggests that the dental pulp is vulnerable to SARS-CoV-2 infection and that SARS-CoV-2 infection of the Dental pulp may contribute to worsen 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. Thus, 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, Bellocchio et al. 2024). Besides, our data shows 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, increasing considerably the likelihood of COVID-19. Furthermore, a differential expression of genes associated with innate immune response, antibacterial activity and inflammatory response in patients with COVID-19 could partly explain this association. A 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, as well as 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 teeth disorders 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 generalizable 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. In order 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 were not assessed such as oral hygiene practices, diet, and lifestyle. These variables could play a crucial role in influencing both oral health and susceptibility to COVID-19. Therefore, future studies employing longitudinal designs and comprehensive data collection are needed to confirm these findings and investigate the underlying biological and environmental interactions. Additionally, a 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. On the other hand, 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. Besides, 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 teeth disorders and their supporting structures consistently exhibited an inverse association with COVID-19 risk. Thus, 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 it was obtained a no informed consent. 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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