JODR

VOLUME 11, ISSUE 1, 2024

JOURNAL OF ORAL and Dental Research

Iraqi Association for Oral Research
Iraqi Section of the IADR

Assessment of COVID-19-Related Oral Findings and Candida Species at Different Disease Severity

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Received 15 May, 2023.
Accepted for publication on August 23, 2023.
Published February 15, 2024.
Doi: https://doi.org/10.58827/828991jttrsx

Abstract

Background The management of coronavirus disease 2019 (COVID-19) has posed a significant challenge for healthcare providers worldwide, following the global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. The oral cavity is considered as a target site of SARS-CoV2. The two most reported oral symptoms of SARS-CoV2 infection were taste alteration and dry mouth. Individuals with COVID-19 are susceptible to opportunistic fungal infections, especially with acute respiratory distress syndrome (ARDS), prolonged hospitalization and administration of broad-spectrum antibiotics, corticosteroids, or immunosuppressants. **Objectives** 1-Assessment of oral findings including taste alteration (TA) and salivary flow rate (SFR) in patients with COVID-19. 2-Investigate the prevalence of candida species in COVID-19 patients. **Materials and Methods** This case-control study involved 30 individuals who tested positive for COVID-19 via reverse transcriptase-polymerase chain reaction, ages ranging from 25 to 59 years. Additionally, 30 healthy volunteers were included, matched according to age and sex with the patients. For TA an objective test includes standardized and validated solutions. For SFR calculation, saliva was collected from each participant to evaluate hyposalivation. An oral swap was collected from each participant and cultured on Sabouraud dextrose ager, candida albicans was identified using a Germ tube and via Vitek 2 compact machine. **Results** This study showed a significant difference in TA, SFR and frequency of candida albicans isolate (p= 0.001, p=0.0001 and p=0.0001 respectively, at level 0.05 using Pearson Chi-square and ANOVA tests) between COVID-19 and control, according to disease severity TA was significant in patients with mild cases then moderate and severe cases (p=0.001). While SFR was significantly decreased in patients with moderate and severe cases then in mild cases (p=0.0001) and the frequency of candida albicans isolation was more significant in moderate and severe cases than in mild cases (p=0.016). **Conclusions** Taste alteration and dry mouth are the most common oral findings in COVID-19 patients and statistically significant with disease severity, an increased prevalence of candida albicans in COVID-19 patients; likewise, statistically significant with disease severity.

Keywords: COVID-19; oral findings; candida species.

Introduction

Coronaviruses are enveloped, positive, single-stranded, huge RNA viruses that infect humans as well as a variety of other animals. Coronaviruses were identified for the first time in 1966 by Tyrell and Bynoe, who isolated them from individuals with a typical cold. They were called coronaviruses because they were spherical virions with a core-shell and external appendages that resembled a solar corona. Four coronavirus subfamilies—alpha, beta, gamma, and delta—exist. Gamma- and delta-subfamilies come from pigs and birds, whereas alpha- and beta-coronaviruses come from mammals, particularly bats. 26–32 kb is the genomic size. Beta-coronaviruses may cause serious sickness and death, whereas alpha-coronaviruses are asymptomatic or slightly symptomatic (Velavan, and Meyer, 2020). The coronavirus (SARS-CoV2) is a member of the genera Beta-coronavirus, which causes pneumonia in humans. Based on its genetic similarity to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), it is believed that this novel Beta-coronavirus originated from coronaviruses originated in bats and spread to human beings through an unknown intermediate mammalian host (Altemimy, 2020). The phrase "COVID-19" is composed of four different parts: "CO" stands for "coronavirus," "VI" stands for "virus," and "D" stands for "disease" and the number 19 refers to the year that the virus was identified; 2019 (Chams et al, 2020). In December 2019, in the city of Wuhan in China, the COVID-19 pandemic was initially identified. According to many reports, the infectious disease originated in seafood markets (Salah and Ahmed, 2021). COVID-19 was declared an international health emergency by the World Health Organization during their emergency summit on January 30, 2020 (Mohammed et al, 2021). Italy was the country that was hit the hardest by the COVID-19 outbreak when it first started, after China. As of the 24th of March, 2020, 69,176 persons in Italy have been confirmed to be infected with the virus, with 8326 recovering and 6820 passing away (Mohammed and Ali, 2020). 241 million verified cases of COVID-19 have been reported to WHO from October 19, 2021. Of these, little under 5 million people have lost their lives (Saleem, 2021). On February 24, 2020, in the province of Al-Najaf, a young man who had just travelled from Iran was found to be infected with (Covid-19), marking the first confirmed instance of the virus to be found in Iraq (Gadhi and Saleh, 2022). Fevers, exhaustion, and a dry cough are typical signs of this kind of pneumonia, followed by anorexia, myalgia, dyspnea, and so on. The novel coronavirus has been shown to impact a wide variety of tissues and organs in addition to the lungs, according to various studies (Zhou et al, 2021). About 80% of COVID-19 infections present with mild upper respiratory symptoms that can be handled as outpatient cases, 15% present with moderate-to-severe pneumonia that requires inpatient care, and 5% of the patients present with critical symptoms resulting in ARDS and septicemia, thus which demand intensive care, according to an analysis of about 72,000 COVID-positive cases by the Chinese Centre for Disease Control and Prevention (Ibrahim et al, 2022). An important factor in the viral entrance has been linked to the coronavirus S protein, which binds to the host cell receptor angiotensin-converting enzyme 2(ACE2) (Galib, 2020). The angiotensin-converting enzyme 2 (ACE2) receptor is utilized by both the 2019 coronavirus and the SARS coronavirus when they infect a host cell. As a direct result of this, this virus was eventually given the moniker SARS-CoV2 (Zhou et al, 2020). Zhou et al, (2020) study demonstrates that SARS-CoV2 can invade ACE2-expressing cells, but not ACE2-negative cells or cells displaying other coronavirus receptors including aminopeptidase N and dipeptidyl peptidase 4 (DPP4) (Zhou et al, 2020). Additional research revealed that the binding selectivity of the SARS-CoV2 spike glycoprotein to ACE2 is between 10 and 20 times greater than that of SARS-CoV to ACE2 (Wrapp et al, 2020). Since ACE2 is present in a variety of oral epithelial tissues, this entryway is being investigated for SARS-CoV2 transmission. Since the tongue, salivary glands, and floor of the mouth have the highest concentration of ACE2 receptors, followed by the buccal mucosa and the gingival epithelium, COVID-19 may lead to developing an oral manifestation by interacting with ACE2 in the oral mucosa (Bagley et al, 2020; Iranmanesh et al, 2021). Oral manifestations such as altered taste (gustatory dysfunction) and xerostomia are the most associated with COVID-19 and have been described by many previous studies (Fantozzi et al, 2020; Scotto et al, 2022). Patients infected with COVID-19 are at increased risk for developing opportunistic fungal infections especially if they suffer from acute respiratory distress syndrome (ARDS), require a prolonged rest in the intensive care unit, are treated with broad-spectrum antibiotics, corticosteroids, or immunosuppressants, and have their breathing assisted by invasive or non-invasive ventilation (Swain and Behera, 2020). Antibiotics were overused for the treatment of COVID-19 infection symptoms. Fungal infections caused by endogenous fungi, including candida species, are more likely to occur when patients with severe COVID-19 utilize a broad spectrum of antibiotics, either conventionally or as targeted therapy for hyperinflation (Du et al, 2020).

Aims of the study

1. Assessment of oral findings including altered taste (gustatory dysfunction) and salivary flow rate in patients with COVID-19 at different disease severity.
2. To investigate the prevalence of candida coinfection in COVID-19 patients at different disease severity.

Materials and Methods

A case-control study was conducted at the COVID-19 health isolation department, AL-Fallujah Teaching Hospital, Falluja City in the AL-Anbar government, Iraq from February 2022 until June 2022. The study was approved by the Research Ethics Committee of the College of Dentistry, University of Baghdad with reference number 443 (project number 443722 dated 3.1.2022). All participants gave written informed consent after receiving a thorough and understandable explanation of the study's objectives before being enrolled. This study involved 60 participants; they were split into two groups.

Group I (COVID-19 group) consisted of 30 patients with COVID-19, The World Health Organization guidelines for SARS-CoV2 infection were used to diagnose all patients (WHO.,2020). The SARS-CoV2 infection was identified using a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay.

Group II (control group) consisted of 30 healthy volunteers who have tested negative on RT-PCR for COVID-19 infection, show no signs of chronic or acute disease, and have no previous record of COVID-19 infection, have not yet received any COVID-19 vaccine.

Inclusion criteria patients older than 18 years with symptoms and signs of COVID-19 infection (fever, malaise, cough, and shortness of breath) and a positive RT-PCR result for COVID-19 were included in the study. Exclusion criteria included uncooperative patients, patients on aided ventilation, pediatric and pregnant patients, those with chronic viral infections and systemic diseases, allergic rhinitis and chronic sinusitis, and those unwilling to provide informed consent. Based on the signs and symptoms of clinical management guidelines outlined in the COVID-19 diagnosis and treatment protocol, the clinical presentation of patients was classified as mild, moderate, and severe by symptom of severity (COVID-19 Treatment Guidelines, 2023). On hospitalization, all recruited COVID-19 patients received antibiotic treatment, primarily azithromycin, patients with severe COVID-19 infection prescribe Corticosteroids primarily dexamethasone (Gautret et al, 2020; Lin et al, 2021).

Oral examination

The oral cavity was examined with a disposable mirror illuminated by lights was used for the oral examination and all patients were examined by a single examiner. wearing complete Personal Protective Equipment (PPE) comprising of complete body suits, sterile gloves, N95 masks, goggles and face shields, WHO guidelines were applied for oral examination (WHO,1987).

Taste Alteration (TA) was evaluated using a standardized and validated test that examines a person's ability to differentiate between four basic tastes: sweet, salty, sour, and bitter (Massarelli et al, 2018; Vaira et al, 2020). Following were the preparations for each of the four primary taste solutions:

Salted solution: 30 g of table salt was added to 1 L of deionized water. Sweet solution: 30 g of refined sugar was dissolved in 1 L of deionized water. Sour solution: 90 mL of commercial 100% lemon juice added to 1 L of deionized water. Bitter solution: unsweetened decaffeinated coffee. Deionized water is the control. Each solution was applied to the patient's tongue once. Each solution required a different cotton applicator, used once, and discarded. The patient was then asked to classify the flavour as sweet, salty, bitter, acidic, or neutral. The bitter taste was always provided last as it influences taste perception, but the other solutions were provided randomly (Vaira et al, 2020). Each answer was given a grade of correct or incorrect. Patients' ratings of taste scores, from 0 to 4, were used to categorize them into four groups. Normal (4) means all the tastes reported, Mild hypogeusia (3) means only 3 tastes were reported, Moderate hypogeusia (2) means only 2 tastes were reported, Severe hypogeusia (1) means only 1 taste reported and Ageusia (score 0) means no taste reported.

Salivary flow rate (SFR)

saliva samples were collected from each participant during the hours of 9 am to 11 am in an unstimulated state. As per the guidelines provided by Martinez et al, (2007), the participants were instructed to refrain from consuming any food or beverage, except water, for one hour before the collection of saliva. The salivary flow rate was calculated by dividing the milliliter volume of saliva obtained by the time it took to collect the sample (5 min).

Oral Microbiology

A sterile swab was spun and rubbed thoroughly over the mucosa while exerting pressure to gather deeply seated microorganisms from every participant. The swab is obtained from the inner surfaces of the upper and lower lips, cheeks, and tongue's dorsum and inserted in the package's transport media to preserve microbe viability until cultivation. In COVID-19 patients, oral swabs are collected between 9-11 am and the patient is asked not to drink or eat for at least one hour before the swab. The swabs are taken within 3-10 days of the first SARS-CoV2-positive nasopharyngeal swab or 3-10 days of the hospitalization to detect any shift in oral microorganisms if present at the pick point in the infection. For candida species growth, the swab was cultured on Saboroud's dextrose agar plate (Oxoid-CMOO4I-England) at 33°C (Lemos-Carolino et al,1982). Saboroud's dextrose agar is prepared by adding an antibiotic such as chloramphenicol 50 mg/l or gentamycin 500 mg/l to prevent bacterial growth (Coronado-Castellote and Jiménez-Soriano, 2013).

Identification of fungi

The morphological appearance on the Sabouraud plate.

After four to five days on the media, the colonies were medium-sized, wet, creamy, and yeasty-smelling as shown in Figure (1).

Germ tube fermentation test

A small quantity of an isolated colony's inoculum was suspended in 0.5 milliliters of normal human serum. After inoculating the tubes, they were kept in a 37°C incubator for three hours. A drop of yeast suspension was brought on a clean microscope slide, covered with a cover slip, and

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examined at low magnification for germ tubes after incubation. The production of germ tubes is a distinguishing feature of candida albicans as shown in Figure 2 (Davidson and Henry, 1974).

Vitek 2 compact machine

The Vitek 2 compact automated system is utilized for microbiological growth techniques, employing colorimetric reagent cards that undergo automatic incubation. (BioMérieux, Marcy l'Etoile, France).

• Isolated yeast cultured on a specified medium was incubated at 33°C for 48–72 hours.

• Using a sterile disposable loop, a few colonies were taken and added to a sterile plastic tube with 3.0ml of sterile saline (0.45% NaCl) and mixed with a vortex mixer. Check the McFarland turbidity with DensiCHEK plus (BioMérieux, Marcy l'Etoile, France) by inserting the tube and rotating it 360-clockwise. The result should be in the reference range: Yeats 1.80–2.20. When the turbidity was below the reference range, a tiny colony were added to the tube, mixed with a vortex mixer, and checked again until it reached the reference range. If it's above, the sample was discarded and the previous steps were repeated.

• Each Vitek identification card was used with the relevant colonies in the tube (i.e. Yeast). The suspension was inserted in the Vitek machine and took about 8-16 for fungal identification Figure (4).

Statistical Analysis

Using the available SPSS-28 statistical software, data analysis was conducted (Statistical Packages for Social Sciences- version 28). Simple measures of frequency, percentage, mean, standard deviation, and range were used to present the data (minimum-maximum values). The significance of percentage differences (qualitative data) was evaluated using the Pearson Chi-square test (2-test) with Yate's correction or Fisher Exact test, as appropriate and the ANOVA test for the difference between three or more independent means. When the P value was less than or equal to 0.05, statistical significance was considered

Results

Demographic Findings (Age and Gender)

The mean age of the COVID-19 patients was 43.4 years, with a standard deviation of 10.3 years with a range of ages from 25–59 years (n = 30). The mean age of healthy subjects was 40.6, with a standard deviation of 9.2 with a range of ages from 25–58 years (n = 30). Statistical analysis revealed no significant difference between groups regarding age at 0.05 level. regarding the gender studied groups had perfect similarity of gender distributions along different study groups as a result no significant difference accounted at 0.05 level, male (n = 15) and female (n = 15) of both COVID-19 patients and healthy subjects. Table (1). Based on the severity of COVID-19 symptoms, the current study revealed that 9 (30.0%) of patients have mild disease, 14 (46.7%) have moderate disease and 7 (23.3%) have severe disease, as illustrated in Figure (4).

Table (1): Comparison of age and gender between the study groups.

Parameters	COVID-19 group	Control group	P-value
Age (mean ± SD)	43.4 ± 10.3	40.6 ± 9.2	0.520
Male (N, %)	15 (50.0%)	15 (50.0%)	10000
Female (N, %)	15 (50.0%)	15 (50%)	

***Significant difference between percentages using Pearson Chi-square test (x^2-test) at 0.05 level.**

Table (2): Distribution of Taste alteration in the COVID-19 infected group and Control group with comparison significance.

Taste alteration	COVID-19 group (n=30)		Control group (n=30)		P value
	NO	%	NO	%	
Ageusia (No falvour recorded)	3	10.0	-	-	0.001*
Severe hypogeusia (Only 1 recorded)	7	23.3	-	-	
Moderate hypogeusia (only 2 recorded)	8	26.7	1	3.3	
Mild hypogeusia (only 3 recorded)	5	16.7	6	20.0	
Normal (All 4 recorded)	7	23.3	23	76.7	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table (3): Assessment of the relation between taste alteration and severity of COVID-19 with comparison significance.

Oral findings		COVID-19 symptoms Mild (n=9)		Moderate (n=14)		Severe (n=7)		P value
		NO	%	NO	%	NO	%	
Taste alteration	Ageusia (No flavor recorded)	2	22.23	1	7.14	-		0.001*
	Severe hypogeusia (Only 1 recorded)	4	44.43	3	21.42	-		
	Moderate hypogeusia (only 2 recorded)	3	33.34	3	21.42	2	28.57	
	Mild hypogeusia (only 3 recorded)	-		3	21.42	2	28.57	
	Normal (All 4 recorded)	-		4	28.57	3	42.85	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table (4): Clinical presentation of salivary flow rate in the COVID-19 and control groups.

Salivary flow rate (ml/min)	COVID-19 Infected (n=30)		Control (n=30)		P value
	No	%	No	%	
<0.20ml/min	4	13.3	-	-	0.0001*
0.200---	11	36.7	-	-	
0.300---	2	6.7	1	3.3	
0.400---	4	13.3	5	16.7	
0.500---	5	16.7	6	20.0	
0.600---	3	10.0	10	33.3	
0.700---	1	3.3	4	13.3	
0.800---	-	-	2	6.7	
=>0.90ml/min	-	-	2	6.7	
Mean±SD (Range)	0.366±0.173 (0.160-0.700)		0.636±0.139 (0.370-0.950)		0.0001^

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table (5): Assessment of the relation between salivary flow rate and severity of COVID-19 with comparison significance

COVID-19 symptoms	NO (n=30)	Salivary flow rate (ml/min) Mean ± SD
Mild	9	0.527±0.109
Moderate	14	0.341±0.165
Severe	7	0.211±0.043
P value		0.0001^

^Significant difference among more than two independent Means using ANOVA-test at 0.05 level.

Table (6): Distribution of the oral microorganism (Fungi) in different study groups with comparison significance.

Oral microorganism		COVID-19 group (n=30)		Control group (n=30)		P value
		NO	%	NO	%	
Candida albicans	Yes	21	70.0	9	30.0	0.0001*
	No	9	30.0	21	70.0	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Table (7): Frequency of candida albicans among COVID-19 patients.

Oral microorganism		COVID-19 symptoms Mild (n=9)		Moderate (n=14)		Severe (n=7)		P value
		NO	%	NO	%	NO	%	
Candida albicans	Yes	3	33.3	12	85.7	6	85.7	0.016*
	No	6	66.7	2	14.3	1	14.3	

*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.

Figure (1): Candida albicans on Sabouraud dextrose agar.

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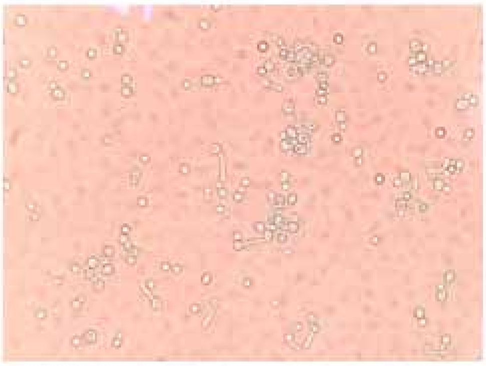

Figure (2): Germ tube formation indicating Candida albicans.

Microbiology Chart Report

Selected Organism : Candida albicans

Comments:

Identification Information

Analysis Time:

Status:

Final

Selected Organism

Candida albicans

ID Analysis Messages

Biochemical Details

Figure (3): Microbiological report for identification of Candida albicans via Vitek system.

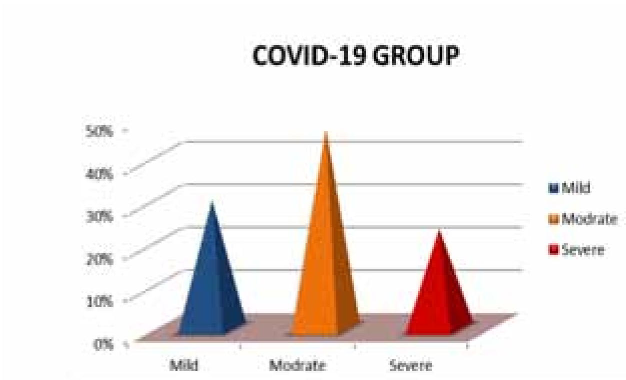

Figure (4): Distribution of patients according to COVID-19 severity.

Oral findings

Taste alteration (TA)

Regarding TA (Gustatory dysfunction) the current study shows a significant difference between the COVID-19 group and Control group, especially in the case of complete ageusia 3(10%) and severe 7(23.3%) and moderate 8(26.7%) hypogeusias which represent more in COVID-19 group than the control group as summarized in Table (2).

Salivary flow rate (SFR)

As illustrated in Table (4) the current study revealed that the mean of SFR in COVID-19 group was (0.366±0.1730) and ranged from (0.160-0.700); four patients (13.3%) SFR was <0.2ml/min, eleven patients (36.7%) SFR was between 0.2-0.3ml/min, two patients (6.7%) SFR was between 0.3-0.4ml/min, four patients (13.3%) SFR was between 0.4-0.5ml/min, five patients (16.7%) SFR was between 0.5-0.6ml/min, three patients (10.0%) SFR was between 0.6-0.7ml/min and one four patient (3.3%) SFR was between 0.7-0.8ml/min. The result for control group was indicated a mean SFR of (0.636±0.139) and ranged (0.370-0.959); one patient (3.3%) SFR was between 0.3-0.4ml/min, five patients (16.7%) SFR was between 0.4-0.5ml/min, six patients (20.0%) SFR was between 0.5-0.6ml/min, ten patients (33.3%) SFR was between 0.6-0.7ml/min, four patient (13.3%) SFR was between 0.7-0.8ml/min, four patients (13.3%) SFR was between 0.6-0.7ml/min, two patients (6.7%) SFR was between 0.8-0.9ml/min and two patients (6.7%) SFR was between ≥0.9ml/min. According to statistical analysis, salivary flow rate showed a significant difference between the COVID-19 and control groups in the table ($P < 0.05$) when percentages are compared using the Pearson Chi-square test. According to the ANOVA test, significant reduction in the mean of the COVID-19 group compared to the control regarding SFR. The results of oral findings (TA and SFR) and associations between COVID-19 patient groups (severe, moderate and mild) were illustrated in the table in which TA results show a significant difference among the patients at 0.05 level in which ageusia 2 (22.23%), severe hypogeusia 4 (44.45%) and moderate hypogeusia 3 (33.34%) are represent more in mild case then both moderate and severe cases, especially in the severe cases in which ageusia and severe hypogeusia are not even reported, surprisingly no patient with mild case report all taste that offered. Table (3). Regarding SFR the result shows a significant difference among the COVID-19 patients at 0.05 level using the ANOVA test in which the mean of SFR for mild patients was (0.527±0.109) while moderate and severe patients were (0.341±0.165 and 0.211±0.043), respectively as shown in Table (5).

Oral Microbiology

Candida albicans

The current study shows a significant difference in the isolation of candida albicans between COVID-19 patients and control groups at level 0.05. Candida albicans was present in 21(70.0%) COVID-19 patients and 9(30.0%) in control individuals. Table (6). Regarding the associations between the severity of COVID-19 patients and candida albicans the results show a significant difference among patients in which the isolation candida albicans are more prominent in severe cases 6 (85.7%) and 12 (85.71%) in moderate cases than the mild cases 3 (33.34%) as shown in Table (7).

Discussion

The scientific community worldwide has prioritized research on SARS-CoV2 infection, which is not unexpected. According to clinical evidence, the oral mucosa is identified as a primary entry point for SARS-CoV2 and is potentially highly vulnerable to infection by the 2019 novel coronavirus (Abubakr et al,2021). Nevertheless, there remains ambiguity regarding whether the oral manifestations stem from direct viral infection or systemic health decline and compromised immune function as a result the current study investigates objective evaluation of TA and SFR in COVID-19 patients. Additionally, the study aims to determine the frequency of candida albicans co-infection with SARS-CoV2 infection at varying degrees of infection severity. The most prevalent oral finding in the present study was TA, which is supported by an investigation by Fantozzi et al in 2020 that revealed that taste changes are the most frequent oral symptoms which account for 59.5% of COVID-19 patients, this research employed a questionnaire-based methodology also agree with the results from Italian research by Vaira et al in 2020, in which mild hypogeusia, moderate hypogeusia, severe hypogeusia, and ageusia were identified in 22.2%, 15.3%, 9.7%, and 1.4% of cases, respectively. This study employs the use of a standardized and validated test with prepared solutions, which is the same approach used in the current one. Taste alteration about the severity of COVID-19. This study revealed that the milder the case the more prominent the TA this was supported by a cross-sectional investigation conducted in Italy, it was observed that gustatory dysfunction was prevalent in 78.9% of individuals who were home-quarantined due to milder symptoms, whereas it was observed in 51.9% of individuals who were hospitalized due to severe or moderate symptoms (Paderno et al, 2020). The prevalence of ageusia in the current study was observed to be highest among patients with mild symptoms, followed by those with moderate symptoms surprisingly, no patients with severe symptoms developed ageusia this is supported by another study in Qatar (Al-Ani and Acharya, 2022). Xu et al, 2020, demonstrated that ACE2 receptors for SARS-CoV2 are expressed in mucosal epithelial cells of the oral cavity through an examination of public genomic databases. The researchers have verified that ACE2 is present in human oral tissues, with a higher concentration observed in the dorsal tongue compared to the gingival and buccal tissues. The infection caused by SARS-CoV2 has the potential to alter the functioning of ACE2, leading to a subsequent alteration in the levels of angiotensin II within the taste buds. This, in turn, may result in the development of taste dysfunction (Tsuchiya, 2021). The role of saliva as a solvent for taste substances and its ability to regulate the conditions of taste receptors suggests a potential correlation between alterations in saliva flow and variations in taste perception among COVID-19 patients (da Silva et al.,2021). According to Biadsee et al's findings in 2020, there exists a correlation between the incidence of xerostomia and gustatory dysfunction in individuals diagnosed with COVID-19. Taste disorders are characterized by the impairment of gustatory papillae and taste buds due to decreased saliva secretion. Given that ACE2 is expressed in human salivary glands, infection of these glands with SARS-CoV2 has the potential to impact the secretion of saliva and subsequently alter an individual's ability to taste (Tsuchiya, 2021). The S1 spike protein of SARS-CoV2 requires sialic acid binding to infect host cells. Sialic acid is an essential constituent of salivary mucin, which plays a vital role in safeguarding against the premature enzymatic breakdown of glycoproteins responsible for transmitting gustatory molecules through the pores of taste buds. A correlation has been observed between decreased levels of sialic acid and an elevation in the taste threshold. It is possible that SARS-CoV2 could occupy the binding sites for sialic acid in the taste buds, leading to an acceleration of gustatory particle degradation as a result taste alteration may develop (Harikrishnan, 2021). This runs in the same line as the current study that shows a decrease in SFR in COVID-19 patients. The medical condition of xerostomia, commonly referred to as dry mouth, has been observed in a significant number of individuals diagnosed with COVID-19, as reported in studies (Chen et al, 2020; Fathi et al, 2021). Xerostomia is a medical condition characterized by inadequate production of saliva or complete malfunction of the salivary glands. The current study shows a decrease in SFR in COVID-19 patients then the control groups this agree with Hanadi et al, (2023), who state that significant decrease in SFR in the COVID-19 group compared to the control group (Hanadi et al, 2023). Various studies have demonstrated that the SARS-CoV2 virus can be found in the whole saliva during the initial phases of the illness, and can also be identified in the saliva released from salivary gland ducts after a few days (Bagley et al, 2020). The study conducted by Liu et al. demonstrated that the quantity of SARS-CoV was comparatively greater in saliva samples as opposed to blood specimens, 48 hours following intranasal viral challenge (Liu et al, 2011). SARS-CoV2 tends to target ACE2-expressing cells. The salivary gland duct membrane expresses ACE2. COVID-19 may infect salivary glands. Researchers hypothesize that SARS-CoV2 can enter salivary gland epithelial cells, multiply, and disseminate to saliva. ACE-2 receptor virus activation causes acute and chronic sialoadenitis, salivary changes, and DM (Wang et al.,2020; Baghizadeh, 2020). A hypothesis has been made that an infection caused by the coronavirus in the salivary glands could create changes in the quantity and flow of saliva, either directly or indirectly (Belchior Fontenele and Pedrosa, 2021). According to the hypothesis infection with SARS-CoV2 leads to the development of inflammatory lesions in the salivary glands, which subsequently undergo lysis during the initial stages of infection. Furthermore, it is suggested that the salivary glands may be further damaged by immunopathological responses at a later stage (Abubakr et al, 2021). According to the literature, the neuropathic and mucotropic effects of this virus may disrupt salivary gland function, causing hyposalivation and xerostomia (dry mouth) (Iwabuchi et al, 2012). Based on the aforementioned data, it can be inferred that the infiltration of viruses into salivary glands has an impact on their functionality during the early phases of the illness, leading to alterations in both the flow and composition of saliva as a result dry mouth may arise as a consequence of COVID-19 infection (Bagley et al, 2020). The salivary flow rate and components may be subject to influence by psychological factors. Therefore, it is imperative to consider the potential psychological impacts of COVID-19 on salivary gland production and taste disturbances (da Silva et al, 2021). Salivary flow rate relation to the severity of COVID-19, our study revealed a relationship between the severity of COVID-19 and SFR in which severe COVID-19 patients had lower SFR than mild one this is supported by Hanadi et al (2023), which state that saliva volume was statistically significantly decreased in the severe COVID-19 patients compared to the mild COVID-19 patients this disagree Colombian study that states there was no significant difference among different COVID-19 symptoms (mild, moderate and severe) and xerostomia (Anaya et al, 2021). This may be attributed to the fact that xerostomia was evaluated using a quantitative scale in this study rather than a dichotomous variable (a yes/no answer), which was done in a previous study. Xerostomia, on the other hand, is a subjective complaint of dry mouth and does not necessarily correlate to insufficient salivary secretion. This is an essential point to keep in mind (Villa et al, 2014). Therefore, the amount of saliva that flows through the mouth is the most accurate indicator of dry mouth. The current study revealed increased isolation of candida albicans in the COVID-19 group than the control group, this was supported by Nambiar et al, that revealed that candida albicans was found to be the most dominant yeast, accounting for 70.7% of the cases of oropharyngeal candidiasis (OPC) in hospitalized COVID-19 (Nambiar et al.,2021) also supported by Another research in Iraq reported a similar incidence of candida coinfection with COVID-19 patients, 64.66 %, with candida albicans being the most frequent one (55.67 %) (Alkhuzaie and Jasim, 2022). Regarding the candida coinfection and severity of COVID-19. There are associations between the severity of COVID-19 and candida albicans coinfection in which patient with moderate and severe forms of the disease shows a higher rate of candida albicans coinfection than the mild form of the disease this is supported by Khalil et al, who reported individuals who have become infected with COVID-19 and are experiencing moderate to severe symptoms should be considered to be at a heightened risk of developing candida infection, particularly candida albicans, and subsequently developing oropharyngeal candidiasis. As a result, it is recommended that preventative measures be integrated into the treatment protocols (Khalil et al, 2022). The majority of patients exhibit concomitant risk factors, including the utilization of broad-spectrum antibiotics and corticosteroids, lymphocytopenia, admission to the intensive care unit, mechanical ventilation, or other localized risk factors such as inadequate oral hygiene practices, denture utilization, or reduced salivary flow leading to xerostomia due to the administration of specific medications all these risk factors that may promote candida overgrowth and coinfection (Nambiar et al, 2021).

Conclusions

The current investigation provides evidence that the oral cavity is among the most susceptible areas to SARS-CoV2. The symptoms of taste alteration and dry mouth may present themselves before other manifestations of COVID-19. These subjective complaints are commonly reported in asymptomatic or mild cases of the disease, with their prevalence being dependent on the severity of the illness. The present oral manifestations have the potential to exert a detrimental impact on the oral health of the affected individuals. Additionally, inadequate oral hygiene practices among COVID-19 patients who are hospitalized may exacerbate these oral symptoms. It is recommended that dental professionals, including dentists and dental hygienists, remain alert for any indications of taste alteration, or dry mouth, as these may be early symptoms of COVID-19. As of present, there exist no established pathogenic mechanisms that can account for the gustatory dysfunction and xerostomia observed in individuals afflicted with COVID-19. Additional investigations are required to explicate these phenomena, to enhance comprehension of the characteristics of SARS-CoV2 infection and to gain novel perspectives on the diagnosis and preventative strategies for COVID-19. The aforementioned data has the potential to facilitate rapid identification and isolation of individuals with paucisymptomatic COVID-19. The present shows an increased prevalence of candida albicans isolation from COVID-19 patients. The excessive use of corticosteroids and antimicrobial treatment among individuals diagnosed with COVID-19 may lead to the development of opportunistic fungal infection that may lead to worsening to severe form of COVID-19 infection as a result antifungal treatment should be considered.

References

(COVID-19 Treatment Guidelines. Clinical Spectrum of SARS-CoV-2 Infection. National Institutes of Health Last Updated: March 6, 2023,.2023).

Abubakr, N., Salem, Z. A., & Kamel, A. H. M. (2021). Oral manifestations in mild-to-moderate cases of COVID-19 viral infection in the adult population. Dental and medical problems, 58(1), 7–15. https://doi.org/10.17219/dmp/130814

Al-Ani, R. M., & Acharya, D. (2022). Prevalence of Anosmia and Ageusia in Patients with COVID-19 at a Primary Health Center, Doha, Qatar. Indian journal of otolaryngology and head and neck surgery: official publication of the Association of Otolaryngologists of India, 74(Suppl 2), 2703–2709. https://doi.org/10.1007/s12070-020-02064-9

Alkhuzaie, and Jasim, N. O. (2022). Candida spp. associated with COVID-19 and its Susceptibility to some Antifungals. Al-Qadisiyah Journal of Pure Science, 27(1), bio 26-38. https://doi.org/10.29350/qjps.2022.27.1.1517

Altemimy Hasan Mohammed. Clinical evaluation of selected Pharmacological Treatments used for Coronavirus (COVID-19) pandemic. JFacMedBagdad [Internet]. 2020 Jun. 16 [cited 2023 May 25];62(1.2):1-5.

Anaya, J. M., Rojas, M., Salinas, M. L., Rodríguez, Y., Roa, G., Lozano, M., Rodríguez-Jiménez, M., Montoya, N., Zapata, E., Post-COVID study group, Monsalve, D. M., Acosta-Ampudia, Y., & Ramírez-Santana, C. (2021). Post-COVID syndrome. A case series and comprehensive review. Autoimmunity reviews, 20(11), 102947. https://doi.org/10.1016/j.autrev.2021.102947

Baghizadeh Fini M (2020) Oral saliva and COVID-19. Oral Oncol 108:104821. https://doi.org/10.1016/j.oraloncology.2020.104821

Bagley, A. F., Ye, R., Garden, A. S., Gunn, G. B., Rosenthal, D. I., Fuller, C. D., Morrison, W. H., Phan, J., Sturgis, E. M., Ferrarotto, R., Wu, R., Liu, A. Y., & Frank, S. J. (2020). Xerostomia-related quality of life for patients with oropharyngeal carcinoma treated with proton therapy. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology, 142, 133–139. https://doi.org/10.1016/j.radonc.2019.07.012

Belchior Fontenele, M. N., & Pedrosa, M. D. S. (2021). Xerostomia and Taste Alterations in COVID-19. Ear, nose, & throat journal, 100(2_suppl), 186S–187S. https://doi.org/10.1177/0145561320982686

Biadsee, A., Biadsee, A., Kassem, F., Dagan, O., Masarwa, S., & Ormianer, Z. (2020). Olfactory and Oral Manifestations of COVID-19: Sex-Related Symptoms-A Potential Pathway to Early Diagnosis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery, 163(4), 722–728. https://doi.org/10.1177/0194599820934380

Chams, N., Chams, S., Badran, R., Shams, A., Araji, A., Raad, M., Mukhopadhyay, S., Stroberg, E., Duval, E.J., Barton, L.M. and Hajj Hussein, I., (2020). COVID-19: a multidisciplinary review. Frontiers in public health, 8, p.383. https://doi.org/10.3389/fpubh.2020.00383

Chen, L., Zhao, J., Peng, J., Li, X., Deng, X., Geng, Z., Shen, Z., Guo, F., Zhang, Q., Jin, Y., Wang, L., & Wang, S. (2020). Detection of SARS-CoV-2 in saliva and characterization of oral symptoms in COVID-19 patients. Cell proliferation, 53(12), e12923. https://doi.org/10.1111/cpr.12923

Coronado-Castellote, L., & Jiménez-Soriano, Y. (2013). Clinical and microbiological diagnosis of oral candidiasis. Journal of clinical and experimental dentistry, 5(5), e279–e286. https://doi.org/10.4317/jced.51242

da Silva Pedrosa, M., Sipert, C. R., & Nogueira, F. N. (2021). Altered taste in patients with COVID-19: The potential role of salivary glands. Oral diseases, 27 Suppl 3(Suppl 3), 798–800. https://doi.org/10.1111/odi.13496

Davidson I.; and Henry J.B. Clinical diagnosis by laboratory methods.15th edition.1974; Pp.1148.

Du, R. H., Liu, L. M., Yin, W., Wang, W., Guan, L. L., Yuan, M. L., Li, Y. L., Hu, Y., Li, X. Y., Sun, B., Peng, P., & Shi, H. Z. (2020). Hospitalization and Critical Care of 109 Decedents with COVID-19 Pneumonia in Wuhan, China. Annals of the American Thoracic Society, 17(7), 839–846. https://doi.org/10.1513/AnnalsATS.202003-225OC

Fantozzi, P. J., Pampena, E., Di Vanna, D., Pellegrino, E., Corbi, D., Mammucari, S., Alessi, F., Pampena, R., Bertazzoni, G., Minisola, S., Mastroianni, C. M., Polimeni, A., Romeo, U., & Villa, A. (2020). Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. American journal of otolaryngology, 41(6), 102721. https://doi.org/10.1016/j.amjoto.2020.102721

Fathi, Y., Hoseini, E. G., Atoof, F., & Mottaghi, R. (2021). Xerostomia (dry mouth) in patients with COVID-19: a case series. Future Virology, 10.2217/fvl-2020-0334. https://doi.org/10.2217/fvl-2020-0334

Gadhi MH, S. Saleh E. Measurement of the serum level of Elabela for the early detection of acute kidney injury in hospitalized Iraqi COVID-19 patients. JFacMedBagdad [Internet]. 2022 Oct. 17 [cited 2023 May 25];64(3):163-9.

Galib BA. SARS-CoV-2(COVID-19). JFacMedBagdad [Internet]. 2020 Apr. 15 [cited 2023 May 25];61(3,4).

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Tissot Dupont, H., Honoré, S., Colson, P., Chabrière, E., La Scola, B.,

Hanadi Abdullah Alwafi,Soad Shaker Ali,Sunil Babu Kotha,Layla Waleed Abuljadayel,Maha Ibrahim,Ibrahim Rashad Noor Elahi,Hebah Abdullah Alwafi,Matthew D. Finkelman,Nagla A. El-Shitany.(2023). Imbalanced salivary electrolytes, COVID-19 severity, and dysgeusia. Signa Vitae, 19(4);48-57.

Harikrishnan P. (2021). Etiogenic Mechanisms for Dysgeusia in SARS-CoV-2 Infection. The Journal of craniofacial surgery, 32(1), e111–e112. https://doi.org/10.1097/SCS.0000000000007021

Ibrahim S, Albadra M, Tadros F. Initial Chest X-ray scoring in the prediction of COVID-19 patients' outcome in the United Arab Emirates. JFacMedBagdad [Internet]. 2022 Jul. 24 [cited 2023 May 25];64(2):59-64. Available from:

Iranmanesh, B., Khalili, M., Amiri, R., Zartab, H., & Aflatoonian, M. (2021). Oral manifestations of COVID-19 disease: A review article. Dermatologic therapy, 34(1), e14578. https://doi.org/10.1111/dth.14578

Iwabuchi, H., Fujibayashi, T., Yamane, G. Y., Imai, H., & Nakao, H. (2012). Relationship between hyposalivation and acute respiratory infection in dental outpatients. Gerontology, 58(3), 205–211. https://doi.org/10.1159/000333147

Khalil, M. A. F., El-Ansary, M. R. M., Bassyouni, R. H., Mahmoud, E. E., Ali, I. A., Ahmed, T. I., Hassan, E. A., & Samir, T. M. (2022). Oropharyngeal Candidiasis among Egyptian COVID-19 Patients: Clinical Characteristics, Species Identification, and Antifungal Susceptibility, with Disease Severity and Fungal Coinfection Prediction Models. Diagnostics (Basel, Switzerland), 12(7), 1719. https://doi.org/10.3390/diagnostics12071719

Lemos-Carolino, M., Madeira-Lopes, A., & Van Uden, N. (1982). The temperature profile of the pathogenic yeast Candida albicans. Zeitschrift fur allgemeine Mikrobiologie, 22(10), 705–709. https://doi.org/10.1002/jobm.3630221004

Lemos-Carolino, M., Madeira-Lopes, A., & Van Uden, N. (1982). The temperature profile of the pathogenic yeast Candida albicans. Zeitschrift fur allgemeine Mikrobiologie, 22(10), 705–709. https://doi.org/10.1002/jobm.3630221004

Lin, Z., Phyu, W. H., Phyu, Z. H., & Mon, T. Z. (2021). The Role of Steroids in the Management of COVID-19 Infection. Cureus, 13(8), e16841. https://doi.org/10.7759/cureus.16841

Liu, L., Wei, Q., Alvarez, X., Wang, H., Du, Y., Zhu, H., Jiang, H., Zhou, J., Lam, P., Zhang, L., Lackner, A., Qin, C., & Chen, Z. (2011). Epithelial cells lining salivary gland ducts are early target cells of severe acute respiratory syndrome coronavirus infection in the upper respiratory tracts of rhesus macaques. Journal of virology, 85(8), 4025–4030. https://doi.org/10.1128/JVI.02292-10

Martinez, K.O., L.L. Mendes and J.B. Alves, (2007). Secretory a immunoglobulin, total proteins and salivary flow in recurrent aphthous ulceration. Rev. Bras Otorrinolaringol., 73: 323-328. https://doi.org/10.1590/S0034-72992007000300006

Massarelli, O., Vaira, L. A., Biglio, A., Gobbi, R., Dell'aversana Orabona, G., & De Riu, G. (2018). Sensory recovery of myomucosal flap oral cavity reconstructions. Head & neck, 40(3), 467–474. https://doi.org/10.1002/hed.25000

Mohammed, I. A., & Ali, A. H. (2020). Clinical course and disease outcomes in hospitalized patients with 2019 novel corona virus disease at Ibn-Al Khateeb Hospital in Baghdad, Iraq. Journal of the Faculty of Medicine Baghdad, 62(3). https://doi.org/10.32007/jfacmedbagdad.6231775

Mohammed, I. A., Hamdan, A. S., Jaber, O. A., & Abbas, G. H. (2021). Assessment of anxiety and depression status among health care workers from Baghdad post cure from COVID-19. Journal of the Faculty of Medicine Baghdad, 63(3). https://doi.org/10.32007/jfacmedbagdad.6331835

Nambiar, M., Varma, S. R., Jaber, M., Sreelatha, S. V., Thomas, B., & Nair, A. S. (2021). Mycotic infections - mucormycosis and oral candidiasis associated with Covid-19: a significant and challenging association. Journal of oral microbiology, 13(1), 1967699. https://doi.org/10.1080/20002297.2021.1967699

Paderno, A., Schreiber, A., Grammatica, A., Raffetti, E., Tomasoni, M., Gualtieri, T., Taboni, S., Zorzi, S., Lombardi, D., Deganello, A., Redaelli De Zinis, L. O., Maroldi, R., & Mattavelli, D. (2020). Smell and taste alterations in COVID-19: a cross-sectional analysis of different cohorts. International forum of allergy & rhinology, 10(8), 955–962. https://doi.org/10.1002/alr.22610

Rolain, J. M., Brouqui, P., & Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International journal of antimicrobial agents, 56(1), 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949

Salah, H. A., & Ahmed, A. S. (2021). Coronavirus Disease Diagnosis, Care and Prevention (COVID-19) Based on Decision Support System. Baghdad Sci. J, 18(3), 593-613. DOI: http://

dx.doi.org/10.21123/bsj.2021.18.3.0593

Saleem IA. The proportion and risk factors of fatal outcomes among severely and critically ill COVID-19 patients: A hospital experience, Baghdad, Iraq 2021. JFacMedBagdad [Internet]. 2022 Jan. 5 [cited 2023 May 25];63(4):145-51. Available from:

Scotto, G., Fazio, V., Lo Muzio, E., Lo Muzio, L., & Spirito, F. (2022). SARS-CoV-2 Infection and Taste Alteration: An Overview. Life (Basel, Switzerland), 12(5), 690. https://doi.org/10.3390/life12050690

Swain, S. K.., & Behera, I. C. (2020). Managing pediatric otorhinolaryngology patients in coronavirus disease-19 pandemic – A real challenge to the clinicians. Indian Journal of Child Health, 7(9), 357–362. https://doi.org/10.32677/IJCH.2020.v07.i09.001

Tsuchiya H. (2021). Characterization and Pathogenic Speculation of Xerostomia Associated with COVID-19: A Narrative Review. Dentistry journal, 9(11), 130. https://doi.org/10.3390/dj9110130

Tsuchiya H. (2021). Oral Symptoms Associated with COVID-19 and Their Pathogenic Mechanisms: A Literature Review. Dentistry journal, 9(3), 32. https://doi.org/10.3390/dj9030032

Vaira, L. A., Deiana, G., Fois, A. G., Pirina, P., Madeddu, G., De Vito, A., Babudieri, S., Petrocelli, M., Serra, A., Bussu, F., Ligas, E., Salzano, G., & De Riu, G. (2020). Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head & neck, 42(6), 1252–1258. https://doi.org/10.1002/hed.26204

Velavan, T. P., & Meyer, C. G. (2020). The COVID-19 epidemic. Tropical medicine & international health: TM & IH, 25(3), 278–280. https://doi.org/10.1111/tmi.13383

Villa, A., Connell, C. L., & Abati, S. (2014). Diagnosis and management of xerostomia and hyposalivation. Therapeutics and clinical risk management, 11, 45–51. https://doi.org/10.2147/TCRM.S76282

World Health Organization. 2020. Coronavirus disease 2019 (COVID-19).

World health organization, (1987). Oral health survey, Basic methods 4th edition, World Health Organization, Geneva, Switzerland.

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., Graham, B. S., & McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science (New York, N.Y.), 367(6483), 1260–1263. https://doi.org/10.1126/science.abb2507

Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., Li, T., & Chen, Q. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of the oral mucosa. International journal of oral science, 12(1), 8. https://doi.org/10.1038/s41368-020-0074-x

Zhou, J., Li, Y., Kong, C., Li, Y., & Liang, Y. (2021). Assessment of the Effects of SARS-CoV-2 Infection on Multiple Organs Using Laboratory Indices. AL-Kindy College Medical Journal, 17(2), 73–78. https://doi.org/10.47723/kcmj.v17i2.429

Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., … Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798), 270–273. https://doi.org/10.1038/s41586-020-2012-7