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Oral clinical courses of patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: A clinical follow up (a prospective prevalent cohort) study

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ABSTRACT

Introduction
Contemporary literature has revealed that SARS-CoV-2 causes acute sialadenitis and related symptoms, such as discomfort, pain, swelling, and secretory dysfunction in salivary glands. The secretory dysfunction is due to SARS-CoV-2 infection-induced xerostomia and other associated clinical courses such as sore tongue, mucosal ulcer, and gingivitis in the oral cavity. Furthermore, it has been reported that COVID-19 causes the development of other oral manifestations.

Purpose
This cohort study was initiated to identify the possible oral clinical manifestations of patients with SARS-CoV-2 infection admitted at Eka General Hospital COVID-19 treatment center in Addis Ababa, Ethiopia.

Materials and Methods
A prospective clinical follow-up (a prevalent cohort) study was conducted to identify the possible oral manifestations of SARS-CoV-2 infection among patients admitted at the Eka General Hospital COVID-19 treatment center. Patients were followed for an average period of 3.5 weeks.

Results
The findings of this cohort prevalent study were adjusted around the main objectives of the research. A total of 55 patients (36 males and 19 females) fulfilling the inclusion criteria were included in the cohort. The age of the cohorts ranged from 8 to 90 years. The overall prevalence of oral clinical courses in patients with SARS-CoV-2 was 0.18 (n=10). Oral mucosal lesions, xerostomia, thickening of saliva yielded prevalence data of 0.5 (n=6), 0.42 (n=5), and 0.08 (n=1), respectively. The oral mucosal lesions prevalence finding was further refined into aphthous lesions 0.5 (n=3), candidiasis 0.17 (n=1), geographic tongue 0.17 (n=1), and localized gingivitis 0.17 (n=1).

Conclusion
The findings of the study suggest the importance of initiating oral health care for patients with COVID-19. Therefore, multidisciplinary healthcare approaches to management should be promoted to assure optimal health outcomes. Accordingly, oral health care should be a substantial part of the multidisciplinary approach.

INTRODUCTION

Outbreaks of newly emerged respiratory infections are a continuing threat. Over the last two centuries, pandemics of influenza occurred at the rate of about once every thirty years (Lewnard, 2020). There is also a continuing threat of the emergence of new respiratory infections, as is illustrated by the emergence of SARS and its potential re-emergence. Outbreaks of diseases might occur over a vast area (several countries or continents) and usually affecting a large proportion of the population. The Spanish Influenza pandemic in 1918 is a good example (Arino et al., 2006).

In February 2019, the World Health Organization announced the official name of the illness caused by the new coronavirus as Covid-19, the virus is named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (World Health Organization [WHO], 2020). Although the new COVID-19 virus is different from SARS-CoV, it uses the same host receptor, namely human angiotensin-converting enzyme 2 (ACE2) (Fini, 2020). Following the rapid expansion of the disease globally, the world health organization declared the condition as pandemic on 11 March 2020 (WHO, 2020).

Transmission of viruses can generally occur in two ways: either through relatively large droplets of respiratory fluid (10–100 μm) or through smaller particles called aerosols (<10 μm) (Soldatova et al., 2020). The larger droplets are pulled to the ground by gravity quickly and hence transmission requires close physical proximity, whereas aerosolized transmission may occur over larger distances and does not necessarily require infected and susceptible individuals to be co-located at the same time (Han & Ivanovski, 2020). Respiratory and salivary droplets appear to be the main transmission routes of COVID-19 disease through inhalation, ingestion, and/or direct mucous contact (Centers for Disease Prevention and Control [CDC], 2020). Indeed, it has been suggested that such droplets can travel up to four meters with an uncovered cough (Schoeman & Fielding, 2019). It has also been shown that the SARS-CoV-2 virus can survive in aerosols in an experimental setting, but it is unclear to what extent such particles are generated in real-life situations, and whether such particles are sufficient to cause an infection (Meng et al., 2020). Therefore, the aerosol route for COVID-19 transmission requires further verification in clinical settings, taking into account the presence of patients and health workers, air circulation, and other environmental factors (Farooq & Ali, 2020).

The disease preventive approaches are designed to interrupt the SARS-CoV-2 virus transmission (CDC, 2020). Accordingly, getting a vaccine, wearing a face mask, social distancing, avoiding overcrowded spaces, proper handwashing, and using disinfectants are reported to be the main preventive measures to contain the disease transmission (Santosh & Muddana, 2020).

Patients with COVID-19 are reported to manifest several clinical symptoms. The characteristic symptoms of the disease are similar to the common flu: fever, dry cough, shortness of breath, and tiredness - it's not solely a running nose (WHO, 2020). Diarrhea may also manifest in some patients. These symptoms are usually mild (Lewnard, 2020). Older persons and people with pre-existing medical conditions (comorbidities) appear to develop a severe illness more often than others (Xu et al., 2020). In more severe cases, an infection can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death (Han & Ivanovski, 2020).

On the other hand, the majority of viral infections are reported to present a variety of oral manifestations (Verdoni et al., 2020). Oral manifestations of viral infections may present as a preliminary sign of disease, an important co-symptom of viral disease, or the only sign observed in such viral disease (Ather et al., 2020).

The most common reason for oral ulcerations and blisters is viral infections (Lzzetti et al. 2020). Blisters, ulcer, color variation, punctuated hemorrhages, bullae, erythematous plaques, surface/textural changes, Kaposi's sarcoma are reported to be the commonest clinical manifestations associated with different viral diseases such as HIV/AIDS, Chickenpox, and Zika (Santos et al., 2020). Hence, it is not surprising to expect potential oral clinical manifestations in patients with COVID-19 (Ather et al., 2020).

Moreover, a shred of contemporary literature has revealed the development of oral clinical courses in patients with SARS-CoV-2 infection (Dziedzic & Wojtyczka, 2020). In mild cases, oral mucosal lesions developed before or at the same time as the initial respiratory symptoms; however, in those who required medication and hospitalization, the lesions developed approximately seven to 24 days after

onset symptoms (Fini, 2020; Santos et al., 2020). Oral mucosal lesions are more likely to present as coinfections and secondary manifestations with multiple clinical aspects (Santos et al., 2020). Furthermore, various cutaneous manifestations including varicelliform lesions, pseudochilblain, erythema multiforme (EM)-liker lesions, urticaria form, maculopapular, petechiae and purpura, mottling, and livedo reticularis-like lesions are reported in patients with COVID-19 (Alharbi et al., 2020).

Despite the probable relationship between the oral cavity and SARS-CoV-2, to date, many variables could influence the presence of the oral manifestations (Xu et al., 2020). Most patients take a large number of drugs that may produce the oral manifestations, thus the need in evaluating in an observational study the oral manifestation of COVID-19 hospitalized patients (Biadsee et al., 2020). Hence, this prevalent cohort follow-up study aimed to fill such a potential scientific gap. On the other hand, the pandemic forced significant changes in the current approach to several practices globally (Fini, 2020). Several initiations have been enhanced to limit the spread of the virus throughout the world (Moulds, 2020). The application of a multidisciplinary approach to tackle the pandemic successfully is one of them. The same approach is also needed among health professionals to comprehensively treat patients with COVID-19 (Arino et al., 2020). This study aimed to suggest the involvement of dental practitioners in the healthcare team to treat patients with SARS-CoV-2 infection.

MATERIALS AND METHODS

Though the most common clinical symptoms of COVID-19 are fever, headache, sore throat, dyspnoea, dry cough, abdominal pain, vomiting, and diarrhea, several literatures reported a number of oral clinical manifestations in patients with SARS-CoV-2 infection. This prospective clinical follow-up (a prevalent cohort) study was conducted to identify the possible oral manifestations of SARS-CoV-2 infection among patients admitted at the Eka General Hospital, COVID-19 treatment center. Patients admitted to the Hospital were followed for an average period of 3.5 weeks.

Study Period

The study was conducted between 19 and 25 October 2020. Responsive and volunteer patients admitted to the Eka General Hospital COVID-19 treatment center were followed for an average of 3.5 weeks.

Exclusion criteria

- Patients with only conservative treatment (no drug)
- Confirmed cases of SARS-CoV-2 infection with oral clinical courses before admission
- Confirmed cases with SARS-CoV-2 infection and had a recent history of viral diseases such as HIV/AIDS, Hepatitis, Chickenpox, etc.
- All confirmed patients with SARS-CoV-2 infection that were not responsive or willing to voluntarily participate in the study
- Non intubated patients to rule out iatrogenic lesions

Sample size

The size of the cohort was determined using the prevalent cohort study sample size calculation formula. Accordingly, 55 confirmed cases with SARS-CoV-2 infection were selected.

Ethical clearance

Ethical clearance was obtained from the Addis Ababa Public Health Research and Emergency Management Directorate and the Eka General Hospital Ethics Committee.

Informed consent

The study participants were informed that the studyand they freely gave their consent to participate in it without any form of coercion. Thus, the participants were free from any form of duress related to the research. Furthermore, the researchers informed the participants regarding the purpose and the potential benefits of the research. The brief sessions emphasized that participation was voluntary and that the participants had the right to withdraw participation at any time without any prejudice.

Data Collection and Data Collection Instrument

Following the ethical approval by the responsible authorities and the Hospital Research Committee, the relevant primary data was collected by a calibrated dentist using the modified World Health Organization (WHO) oral health assessment forms (MOAF). The data collector used the required personal protective instrument (PPE). Furthermore, the data collector used a wooden spatula and headlight to examine the cohort's oral cavity. The number of examinations varied among patients depending on their

hospital admission duration. Patients were examined two times a week.

Data Management and Analysis

The completed MOAF was collected, cleaned, interpreted, and compiled into an excel sheet. The data cleaning in excel was carried out by the principal investigator using data cleaning software (STATA syntax). Eventually, the data were analyzed and described around the core objectives of the study.

RESULTS

The finding of this cohort prevalent study was adjusted around the main objective of the study. A total of 55 patients (36 males and 19 females) fulfilling the inclusion criteria were included in the cohort. The age of the cohorts ranged from 8 to 90 years. However, 78.2% of the cohorts were older than 40 years. The cohorts were followed for an average of 3.5 weeks.

Table 1:
Oral clinical courses (√) in patients with SARS-CoV-2 infection

Cohorts with oral clinical courses	Oral clinical courses manifested						Total clinical courses manifested
	Xerostomia	Thickening of saliva	Oral mucosal lesions				
			Aphthous lesion	Candidiasis	Geographic tongue	Erythematous and oedematous gingiva	
Females (n=3)	√ √ √	√					n=4
Males (n=7)	√ √		√ √ √	√	√	√	n=8
Total (n=10)	n=5	n=1	n=3	n=1 n=6	n=1	n=1	n=12

The prevalence of oral clinical courses in patients with SARS-CoV-2 infection was calculated. Furthermore, the prevalence finding was refined into prevalence data on xerostomia and prevalence data on oral mucosal lesions such as aphthous lesions, candidiasis, and geographic tongue. The overall prevalence of oral clinical courses in patients with SARS-CoV-2 was 0.18 (n=10). On the other hand, the prevalence of oral mucosal lesions and xerostomia were found to be 0.11 (n=6) and 0.91 (n=5), respectively.

The oral clinical courses were exhibited in 3 females and 7 males. The females to male ratio (3:7) who had manifested oral clinical courses were found to be comparable to the overall gender proportion of the cohort (34.5% females and 65.5% males). The proportion of cohorts (20%) who had presented oral clinical courses under the age of 40 years was also found to be comparable to their overall contribution (21.8%) to the total cohorts. Out of the total 10 cohorts who had presented oral symptoms, 2 had exhibited two oral manifestations each. Whereas, the remaining 8 cohorts had shown only one oral symptom each.

Out of the 12 reported oral clinical courses, oral mucosal lesions, xerostomia, thickening of saliva yielded prevalence data of 0.5 (n=6), 0.42 (n=5), and 0.08 (n=1), respectively. The oral mucosal lesions prevalence finding was further refined into aphthous lesions 0.5 (n=3), candidiasis 0.17 (n=1), geographic tongue 0.17 (n=1), and diffuse erythematous and oedematous gingiva 0.17 (n=1). Two of the aphthous lesions were developed on the buccal mucosa. The other aphthous lesion was seen on the dorsal midline of the tongue. The tongue 0.5 (n=3), buccal mucosa 0.33 (n=2), and upper anterior gingiva 0.17 (n=1) were the most common sites of presentation of the oral mucosal lesions in this prevalent cohort study.

DISCUSSION

Scholars have identified oral clinical courses in patients with HIV, Hepatitis, and Zika virus infections (Bezerra et al., 2020). Candidiasis, periodontitis, salivary gland disease, sarcoma, Kaposi's sarcoma, oral hairy leukoplakia, and aphthous ulcers are some of the oral clinical manifestations of HIV infection (Leao et al., 2009). Oral lesions such as petechiae and ulcers have been reported but scarcely described among patients with Zika virus infection (Khabadze et al., 2020). Similarly, oral mucosal manifestations have occasionally been described in published literature for dengue cases, including gingival ulcers and petechiae and vesicles at the junction of the hard and soft palate (Chen, 2018). Furthermore, hepatitis virus infections have also demonstrated significant oral manifestations such as gingivitis and gingival bleeding, pseudo-pocket formation, and a mucosal ulcer (Pérez-Elías, 2020).

On the other hand, several pieces of literature have outlined ACE2 as an important member of the renin-angiotensin system (Capaccio et al., 2020). ACE2 is widely distributed in the vasculature and participates in the regulation of blood pressure (Gherlone et al., 2021). ACE2 protein can also be found in other organs, such as the small intestine, testes, adipose tissue, thyroid gland, kidneys, heart muscle, colon, ovaries, and salivary glands (Wang, 2020). Accordingly, salivary glands could be the invasive target of SARS-CoV-2. Moreover, the salivary gland cells with ACE2 receptors may become host cells for the virus and further cause inflammatory reactions in related organs and tissues,

such as the tongue, the periodontal tissues, and oral mucosa (Capaccio et al., 2020). Furthermore, scholars have revealed oral clinical courses such as dysgeusia, petechiae, gingivitis, candidiasis, traumatic ulcers, geographical tongue, and thrush-like ulcers among patients with SARS-CoV-2 infection (Glavina et al., 2020). Other contemporary literature has ruled out acute sialidases which induced salivary glands dysfunction and related discomfort, pain, and swelling (Rodríguez et al., 2020). On the other hand, chronic sialadenitis causes xerostomia, sore tongue, mucosal ulcer, and gingivitis in patients with COVID-19 (EghbaliZarch & Hosseinzadeh, 2020). Xerostomia has been found mainly among COVID-19 patients, due to the neuroinvasive and neurotropic potential of SARS-CoV-2 (Chern et al., 2020).

On the other hand, a couple of observational studies across the world have reported several oral clinical courses in patients with COVID-19 (Fidan et al., 2021; Santos et al., 2020). Chinese researchers have identified xerostomia in a relatively high proportion of patients (Rekhtman et al., 2021). Similarly, a cross-sectional survey of 108 patients with confirmed SARS-CoV-2 in China observed that 46% of them reported dry mouth, among other symptoms. An observational human study of 20 patients has revealed nearly 30% of xerostomia during hospitalization (Tomo et al., 2020). An electronic literature review has reported that dry mouth, dysgeusia, oral ulcerations, and opportunistic infections as the most common oral manifestations expressed in COVID-19-positive patients (Coll & Elmahgoub, 2021). Similarly, the findings of this prevalent cohort study have revealed a considerable report of xerostomia. The prevalence of xerostomia was found to be 0.91 (n=5) among the cohorts involved in this follow-up study. Another literature review has revealed aphthous-like lesions, herpetiform lesions, candidiasis, and oral lesions of Kawasaki-like disease are the most common oral manifestations of COVID-19 disease (Iranmanesh et al., 2020). Iranmanesh et al. (2020) has also reported tongue (38%), labial mucosa (26%), and palate (22%) as the most common sites of oral clinical course presentation. In a similar fashion, tongue 0.5 (n=3), buccal mucosa 0.33 (n=2), and upper anterior gingiva 0.17 (n=1) were identified to be the most common sites of presentation of the oral mucosal lesions in this prevalent cohort study.

In a case report, a 67-year-old Caucasian man who was tested positive for coronavirus had presented with oral manifestations such as recurrent herpes simplex, candidiasis, and geographic tongue (Santos, et al, 2020). A systematic review and meta-analysis study have reported a 33% and 44% prevalence rate of oral lesions and xerostomia, respectively. This study also reported a 10% prevalence rate of aphthous lesions among patients with SARS-CoV-2 infection (Aragoneses, et al., 2021). In general, as much of the oral clinical course presentations reported in patients with COVID-19 are obtained through interviewing patients, the findings of this prevalent cohort study could play a substantial role to fill the gap in observational clinical reality in the subject matter (Fidan et al., 2021). This crucial reality might explain the observed variation in various prevalence data (Tapia et al., 2020). Moreover, many of the oral afflictions seen in COVID-19 patients might not be directly caused by SARS-CoV-2 infection and, thus, should not be classified as oral manifestations of this disease (Patel, 2021). Iatrogenic complications that occur in the course of the treatment of COVID-19 could be notable examples. This group includes lesions caused by mechanical trauma of prolonged intubation and other invasive procedures employed (Hocková et al., 2021). The other factor that could potentially justify the variation in prevalence data is a drug; drug reactions might also present in the form of oral lesions. Another group of oral lesions seen in patients with COVID-19, but not directly related to the pathologic processes of SARS-CoV-2 infection, are opportunistic co-infections that involve the oral cavity (Aragoneses et al. 2021). In those regards, this prevalent cohort study has executed rigor inclusion criteria to avoid potential confounding. Of note, the necessity of conducting further in-depth observational studies needs to be underlined.

CONCLUSIONS

The oral mucosal lesions were presented on the buccal mucosa, gingiva, tongue, and floor of the mouth. Therefore, the findings of this cohort study suggest that xerostomia and oral mucosal lesions are common manifestations in patients with COVID-19. However, further observational studies focusing on the causal relationships between oral lesions and COVID-19 need to be conducted among patients with SARS-CoV-2 infection. The findings of this study could be used as baseline data to conduct more comprehensive researches with more study participants and a longer follow-up period.

The results could be also used as a piece of scientific evidence to consider and initiate oral health care for patients with COVID-19. In other words, the findings will be crucial to advocate and optimize patients' overall healthcare at the COVID-19 treatment centers. The findings of this study promote the necessity of multidisciplinary healthcare approaches to assure optimal health outcomes. Thus, the importance of the clinical dental examination of patients with infectious disease in the OPD and ICU should be emphasized, considering the need for support, pain control, and quality of life. Furthermore, the dentist's relevance as part of the multi-disciplinary team in supporting critical patients in ICU, such as COVID-19, should be highlighted. Also, the need for oral cavity check-ups and follow-up should be underlined after patients are discharged from the treatment centers. On the other hand, the oral clinical courses of patients with COVID-19 could be used as potential early indicators of the SARS-CoV-2 infection.

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Ethical Approval: Ethical approval for this work was obtained from the Addis Ababa Public Health Research and Emergency Management Directorate and the Eka General Hospital Ethics Committee.

Conflicts of Interest: The authors declare no conflicts of interest.

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