

Long Term Oral Symptoms Systematization in Patients who Underwent COVID-19: Case Series Research

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Abstract

A number of common long-term morbidities have been reported following COVID-19, and question arises about oral symptoms.

In this case series we included 29 adult patients with oral mucosa symptoms ≥ 2 months after COVID-19 with the aim of highlighting potential interrelations between demographic, oral clinical symptoms and periods elapsed after COVID-19 and its severity.

Analysis of medical histories and demographic data showed the correlation between age and severity of previous COVID-19 ($r=.5$, $P=.01$), and the presence at least two chronic diseases such were gastrointestinal diseases, arterial hypertension, diabetes, etc. in all participants. Using clinical criteria of diagnosis, we found oral symptoms combined at least two: dry lips and edematose oral mucosa in all participants. The most common diagnosis was chronic candidal glossitis (Chi-square test, $P=.01$), presented in different forms and expansions, and correlated with COVID severity ($P=.001$, $r=.6$). The second most common symptom was halitosis which combined mainly with candidal glossitis and negatively correlated with COVID severity ($P=.001$, $r=-.6$). And the rarest finding was petechial rashes on the hard and soft palate, which also correlated with COVID severity ($P=.004$, $r=.5$).

After suffering COVID-19 on the background of chronic systemic diseases, it is expected long term incidence of oral mucosa morbidity during 8 months, with a significant prevalence of chronic candidal glossitis. All detected oral symptoms can be explained by concomitant pathology, in contrast to post-COVID syndrome.

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Introduction

Viral illnesses can cause a variety of oral manifestations, worsening the patient's health.¹ Oral mucosa disorders or lesions may be common symptoms in patients with relatively new SARS-CoV-2 infection and should be considered in the scope of the disease's onset and progression. Taste disorders/dysgeusia and/or dysosmia were the first, the most common, and recognized oral symptoms in patients with COVID-19, presenting a higher prevalence in Europe and North America than in Asia and a

significant association with COVID-19-positive diagnosis, mild/moderate COVID-19 severity, and female patients.² Review of thematic publications PubMed library and Google Scholar from December 2019 until September 2020 showed wide range of oral manifestations of COVID-19 such as an ulcer, erosion, bulla, vesicle, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, hemorrhagic crust, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement were the tongue (38%), labial mucosa (26%), and palate (22%).³ Assumed addition to the growing list of possible symptoms of the new coronavirus can be "COVID tongue".⁴ Last year Tim Spector, a professor of genetic epidemiology at King's College London, reported more cases of infected people complaining of tongue discoloration, enlargement and other mouth problems in the first 3 days of COVID (among

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other non-classic symptoms).⁴ In addition to SARS-CoV-2, higher rates of bacterial colonization, especially with *Streptococcus* species and *Klebsiella pneumoniae*, were detected on removable dental prostheses after infection.⁵

There is still doubt in relation above-mentioned manifestations as a direct oral mucosa infection primarily caused by SARS-CoV-2 or indirect reactions. The direct impact of SARS-CoV-2 suggested by evidence of dysgeusia that persists for up to 8 months, and by the distribution of ACE2 receptors (the angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serines 2 (TRMPRSS2) are potential targets of SARS-CoV-2) in such organs and tissues like the tongue mucosa and salivary glands.^{6,7} On the other hand, the current advances highlight the range of mechanisms that binds severity and/or complications of COVID-19 (thromboinflammation and/or cytokine storm) with individual characteristics and initial health of the patient.⁸⁻¹³ Based on last opinion, more researches considered symptoms in the oral cavity as consequences of the patient's systemic condition.¹⁴

A number of common long-term morbidities have been reported following COVID-19 and post-Covid syndrome (PCS).^{15, 16} According to clinical guidelines of the National Institute for Health and Care Excellence (NICE), PCS represents signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis.¹⁷ Therefore, the question arises about long-term oral symptoms after COVID-19.

The study aimed to systematize long-term oral symptoms in patients who underwent COVID-19 to optimize diagnosis and treatment. In this case series of oral mucosa morbidities after COVID-19, we analyzed patient demographics, COVID-19 severity, comorbidities, the association of oral symptoms with the time elapsed after COVID-19, and structured oral clinical diagnoses by frequency.

Materials and methods

Patient Population

This retrospective Case Series study was conducted in the Center of Diagnosis and Treatment of Oral Mucosa Diseases of the

Department of Postgraduate Education for Dentists, Poltava State Medical University.

In this case series we included patients with oral mucosa complains, who underwent COVID-19 ≥ 2 months ago. Twenty-nine adult patients (>18 years) with different oral mucosa complains and symptoms after recovery from COVID-19 between 2020 and 2021 were included in this study with the aim of highlighting potential interrelations between demographic, oral clinical symptoms and periods elapsed after COVID-19 and its severity.

We did not exclude any patients, and features of cases were tending to greater severity, more advanced illness, and greater comorbidity.

Demographic data were collected for each patient. Clinical and laboratory data and therapeutic management were analyzed for each patient at the time of the first visit and according to clinical presentation.

The authors obtained written informed consent from participants to present the materials from their case histories in the paper, in compliance with Ethical Approvals.

Diagnostic evaluation

We used mostly clinical criteria of oral mucosa symptoms and diseases diagnosis.

The symptoms of dryness of the red part of the lips were recorded based on presentations of exfoliation, painful commissural cracking, and erosion in place of Vermilion continuity with the mucosa, confirmed by complaints for lips dryness, tightness, recurrent cracks without improvement from cosmetic. Differential diagnoses included meteorological, actinic, contact/eczematous and exfoliative cheilitis. But typical causes for last were not identified.

The edema of oral mucosa was recorded on clinical presentation of clear, bright teeth imprints on the tongue and buccal mucosa.

The halitosis was diagnosed based on specific complaints combined with an intense white or white-gray plaque on the tongue and teeth. Halitosis was often accompanied, as shown below, by candidiasis glossitis.

Xerostomia was determined by a diagnostic "probe of the mirror" when it adheres to the buccal mucosa.

Petechial rashes were clinically presented in the form of specific elements without any pain or discomfort exclusively on the hard palate. Petechiae have been associated with complaints of increased bleeding, including intermittent

bleeding from the nasal cavity caused by light exercise.

Recurrent aphthous stomatitis (RAS) was presented as recurrent aphthous ulcer minor and diagnosed based on small superficial oval erosions with yellow pseudomembrane and an erythematous border, placed on the nonkeratinized surfaces (Fig. 2, B) and lateral surface of the tongue, and history of similar previous ulcerations during last 5-7 years with healing in 7-14 days. Clinical differential diagnoses included: 1) local traumatic ulceration, but insults were excluded; 2) environmental triggers: food (eg, figs, cheese, tomato, tomato sauce, vinegar, lemon, pineapple, milk, wheat flour); sodium lauryl sulfate; but correlation were not confirmed; 3) manifestations of herpes simplex, in which polygonal multiple superficial ulcers are typically localized on the attached keratinized areas of the oral mucosa, and differed from the detected ulcers on non-keratinized surfaces; 4) allergic contact stomatitis/dermatitis, but no clear association with drugs (nonsteroidal anti-inflammatory drugs, chemotherapy, and cytostatics) has been established. All patients with RAS had a background of chronic pathology: arterial hypertension (AH), diabetes mellitus (DM), chronic gastrointestinal (GI) diseases, the most often gastritis, which is considered one of the typical favorable factors for RAS.¹⁸

The recurrent herpetic gingivostomatitis was presented as typical manifestations: polygonal and/or multiple small ulcers localized on keratinized oral mucosa (Fig.2, C) and lips, and a history of the previous appearance of painful vesicles and itching at the site. The diagnosis was confirmed by the previous positive PCR test for EBV or HSV. Differential diagnosis was not necessary.

The clinical diagnosis of glossodynia, or burning mouth syndrome, was established on basis of complaints of continuous burning sensation of the mucosa of the mouth, typically involving the tongue, with or without extension. Patients had continuous symptoms during the day, regardless of food intake and its nature, and no symptoms at night. This type was associated with chronic anxiety, as evidenced by the neurologist. The clinical diagnosis was made via the exclusion of all other causes.¹⁹ Possible causes of the condition were excluded for differentiation such as mouth breathing/nasal

obstruction, alcohol-based mouthwash use, medication reaction (eg, ACE inhibitors, angiotensin receptor blockers, antiretrovirals, psychotropic, anticholinergic, clonazepam²⁰, chemotherapeutic agents). Differential diagnosis was performed with candidiasis (cytological microscopy showed absents of fungal/yeast-like microorganisms); with secondary manifestations of concomitant background diseases (such diagnoses as gastroesophageal reflux disease GERD and anemia were absent in the outpatient cards). Regarding differentiation with manifestation of DM, vitamin deficiency (B1, B2, B6, B12, folate, iron), and hypothyroidism, relevant specialists continue to work with patients.

Some of the participants have affected teeth and signs of developed chronic periodontitis. Screening of gingiva showed signs of inflammation, corresponding to dental plaque cumulating, and bleeding on probing >10%, as well as visible signs of advanced periodontitis, which did not include pyorrhea, aggressive or other unusual signs and additional complaints. We did not include the diagnoses of gingivitis and chronic periodontitis in this systematization, because their development is slow and may last for years.²¹

The diagnosis of chronic hyperplastic and/or atrophic candidal glossitis was based on range of complaints, such were halitosis, taste disorder, and clinical findings of abundant white-gray plaque on the tongue difficult to scrape off, or white hyperplastic areas intermittent with depapillated areas on the dorsum of the tongue (Fig.2), and identification of fungal-like microorganisms in direct microscopic examination of clinical brushing samples. Differential diagnoses included lichen planus, but except for white plaque on the tongue and sometimes cracks in oral commissures, the specific lesions/erosions of the retromolar areas and/or gums were not detected. Microscopic examination showed agglomerates of pseudomycelium and ovoid budding yeast-like cells presumably of *Candida* spp.; this confirmed the previous clinical diagnosis in 13 cases.²²

Statistical Analyses

Patients were assigned to subgroups based on the time after COVID-19 and its severity.

Data were analyzed with help of GraphPad Prism 5.0 (GraphPad Software, San Diego, USA) using descriptive statistics,

parametric (Pearson) correlation, Chi-square test, including Fisher's exact test, and Kaplan-Meier method. P values of <0.05 were considered statistically significant in all of the analyses.

The null hypothesis tested was that time after COVID-19 and its severity have no interrelations with oral mucosa symptoms and quantity of addresses to the dentistry department.

Results

Demographic Data

Patients (29 total; 12 men and 17 women, aged from 30 to 65 years, mean 46.5 ± 13) who met the inclusion criteria were included in this study. All suffered from COVID-19, and had various complaints about the oral mucosa. All participants have the history of earlier consultations with a dentist/dental professional and another clinician or physicians.

Complaints, medical history, previous treatment and its results are summarized in table 1.

We did not observe any significant correlations of COVID-19 severity with gender. But, a significant positive correlation was found between age and severity of previous COVID-19 ($r=.5$, $P=.01$).

Some of the complaints were present before COVID-19, and the generalized medical history is shown on the chronological scale in Figure 1.

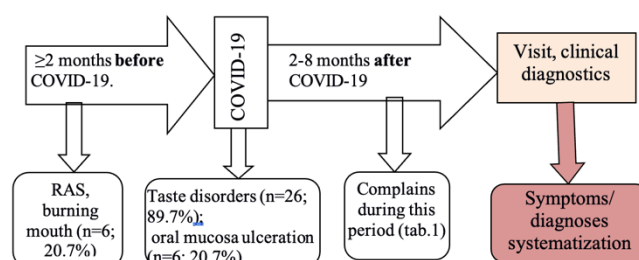


Figure 1. Chronological summary of the visits in case series, regarding COVID-19.

A subsequence of medical history showed that symptoms of burning mouth and recurrent aphthous stomatitis were observed before COVID-19 (Fig. 1) and previously treated with relative success (Table 1). During COVID-19 such symptoms as taste disorders in the majority of patients, $n=26$, and painful oral ulcers in 6 patients were developed (Table 1). Thus,

halitosis turned out to be the most frequent among the newly arisen complaints after suffering COVID-19.

All patients had chronic GI diseases, and in addition, in descending order: arterial hypertension, diabetes, neurogenic, herpetic (diagnosed serologically or by PCR before COVID-19), and oncological diseases after treatment (Table 1). Accordingly, all participants had a combination of at least two chronic common diseases, other than COVID-19, and besides from oral findings.

Almost all middle-aged and all elderly patients had AH, and the older had DM in addition. The combination of hypertension and diabetes is a common syntropy.²³

Clinical Presentation

Systematization of symptoms from the oral mucosa showed in table 2. A notable observation was the combination of signs of dry lips and mucosal edema in all participants, and halitosis in most patients: 25 from 29. According to clinical diagnosis, the following were established: recurrent herpetic gingivostomatitis, and chronic candidal glossitis. RAS (Fig. 2: C), HV infection (Fig. 2: B), and glossodynia existed before COVID-19. Table 2 summarizes the distribution of clinical findings according to the severity of previous COVID-19 and demonstrates significant correlations in the case series. These correlations, except the halitosis, with the severity of previous COVID-19, were positive. The statistical correlation did not reveal a significant relationship between oral symptoms/diagnoses and gender.





Figure 2. Clinical presentations of chronic candidal glossitis (A), recurrent aphthous stomatitis (B), recurrent herpetic gingivostomatitis (C), and petechiae (D).

Oral symptoms were combined with at least by two: dry lips and edematose mucosa, although this combination in all participants did not add much to the diagnosis.

The second most common symptom was halitosis which combined mainly with candidal glossitis and negatively correlated with COVID

severity (Table 2). And the rarest finding was petechial rashes on the hard and soft palate (Figure 2: D). The most common diagnosis was chronic candidal glossitis (Chi-square test, $P=0.01$), presented in different forms and expansions (Figure 2: A).

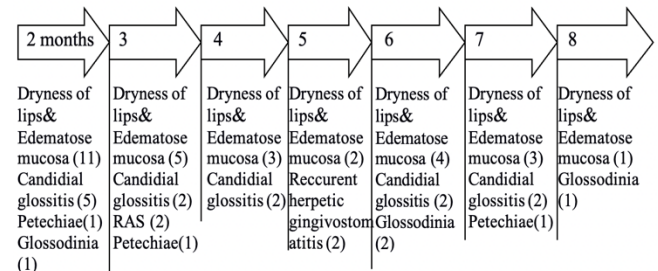


Figure 3. Chronology of objective oral symptoms and diagnoses after COVID-19.

Analysis of the chronology of visits to the clinic with oral diagnoses (Figure 3) showed that candidiasis occurred from the earliest visits. Together with frequent halitosis, this observation can suggest oral dysbiosis developed after undergoing COVID-19 and/or its treatment.

3 patients after mild and 8 after moderate COVID-19 severity visited the clinic with oral complaints in 2 months. Other patients after moderate and severe COVID-19, were asked later and during the longer period (not statistically confirmed: Fisher's exact test, $P=0.06$).

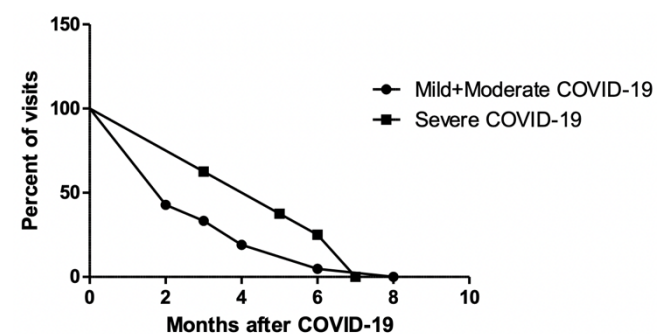


Figure 4. Survival of visits to the Center of Diagnosis and Treatment of Oral Mucosa Diseases after COVID-19 depending on its severity.

To analyze statistically the cumulative visits depending on the period duration after COVID-19, we divided all patients into 2 subgroups according to the severity: mild&moderate ($n = 22$) and severe ($n = 8$); the observation time was 8 months. In the first subgroup cumulative survival was 7.76%, and in

the second – 25%, which differed significantly (Gehan-Breslow-Wilcoxon Test, $P=,019$, Figure4). This means that the visits due to the oral symptoms were significantly lower after a mild or moderate COVID-19 severity, compare with severe.

Treatment and Outcome

According to the results of clinical examinations patients were referred for consultations and observations by specialists physicians: endocrinologists, gastroenterologists, neurologists, etc.

Dental care for patients necessarily included professional hygiene, treatment of individual teeth and periodontal inflammation, replacement of dentures (in some cases), and individual recommendations for home hygiene.

For patients with dry lips, lubrication of the red border with α -tocopherol acetate 10% three times a day for 7-10 days was prescribed. The symptoms disappeared after 10 days.

Patients with halitosis received treatment such were professional hygiene, home hygiene instruction (tongue cleaning, the appointment of a home hygiene complex with cetylpyridine chloride: toothpaste and rinse and/or spray Halita (Dentaid, Spain) (rinses for 2 weeks).

Patients with xerostomia received treatment such as professional hygiene and home oral hygiene complex of toothpaste and rinse with betaine and allantoin Dentaid Xerox (Dentaid, Spain) (rinses for 2 weeks). All of these patients reported improvement or disappearance of symptoms after 2 weeks.

Dental help for RAS included topical local 5% oil suspension of benzocaine on affected elements 5-6 times a day, oral baths with 0.2% chlorhexidine after meals, and home hygiene, followed by topical application of Solcoseryl dental adhesive paste (Legacy Pharmaceuticals, Switzerland) for up to a 10-14 days, following with rehabilitation/treatment of affected teeth/periodontal tissues and instruction for home oral hygiene. The lesions healed in 2 weeks. No recurrences were observed during the next 2 months. The prognosis for RAS depended on the prognosis of background GI diseases.

Recurrent herpetic gingivostomatitis treatment included the topical application of recombinant human interferon alfa-2b spray (100 000 IU) 5-6 times daily for 3-5 days. The pain decreased in 1-2 days, complete healing occurred during 3-5 days.

Glossodynia/burning mouth syndrome treatment provided a multidisciplinary approach. Dental help presumed drugs for local anesthesia: 5% oil suspension of benzocaine up to 5-6 times a day, oral baths of benzydamine every 1.5-3 hours, or benzydamine lozenges 3-4 times a day (Dileo Farma, Ukraine), hexetidinum solution (Bosnalijek, Bosnia and Herzegovina) rinsing for 2-3 times a day; alternate depending on symptoms reduction. Patients underwent rehabilitation of affected teeth/periodontal tissues, instructions on the home oral hygiene, and dental hygiene complex with betaine and allantoin Dentaid Xerox (Dentaid, Spain). After 1 month, patients reported modest decreasing pain. Prognostic characteristics were not favorable for glossodynia due to possible multifactorial etiology.²⁴

For local treatment of chronic candidal glossitis, after professional hygiene and home oral hygiene instruction (as mentioned in halitosis), the combination of topical azoles and NSAID with H1 antagonist and dietary supplement were prescribed: oral baths with 2% fluconazole (Yuria-Farm, Ukraine) 2-3 times a day for a 10-14 days; oral baths with benzydamine solution 3-4 times a day for a 10-14 days with next lubrication of oral mucosa with 1% clotrimazole (Glenmark, India) twice a day for a 10-14 days; oral cetirizine hydrochloride (Dr. Reddy's Laboratories Ltd, India) - 1 tablet 10 mg per day for 7-10 days; oral Echinacea purpurea syrup (Sandoz, Switzerland) - 20 drops 3 times a day for a 10-14 days; oral Lactic acid-producing organisms, combinations (Sandoz, Switzerland) - 1 tablet 3 times a day for 20 days, and multivitamins for 21 days. Dietary restrictions on sweets and fewer carbohydrates were prescribed.²⁵ In most cases, the duration of treatment was extended to a month, after which there was an improvement or recovery in patients. Prognosis depended on the systemic state of health. No side/negative effects from the dental prescriptions that would require drug withdrawal were observed in this study, according to patient self-reports.

Discussion

We have not seen reports describing long-term morbidity of the oral mucosa after COVID-19. But, patients' arrivals to the clinic with symptoms in oral mucosa related to undergoing

COVID-19 in the period 2020-2021, raised the question about the systematization of these symptoms. All of them have the history of earlier consultations with a dentist/dental professional and another clinician or physicians, which emphasizes the quite serious condition of the oral mucosa. This work has shed light on the question of the prolonged clinical impact of this new dangerous virus.

Firstly, a significant positive correlation was found between age and severity of previous COVID-19 ($r=0.5$, $P=0.01$), which was not surprising and widely reported previously.²⁶

The reported case series is associated with the emergence of new complaints, most of which were observed months after COVID-19, which may correspond to the development of PCS. The definition of PCS differs from the clinical guidelines of NICE, which call post-COVID syndrome a pathological condition after 12 weeks,¹⁷ and Infectious Diseases Society of America, emphasizes the absence of the pathogen in the presence of a pathological condition.^{27, 28} Regardless of the detection of the SARS-CoV-2, many organs and systems (lungs, heart, brain, kidneys and vascular system, etc.) are among the long-term persistent damage. Thus oral mucosa involvement was not surprising. After COVID-19, we found a combination of dry lips and mucosal edema in all participants and halitosis in most of them. A significant correlations were found between COVID-19 severity and halitosis ($P=0.001$; $r=-0.6$), petechiae ($P=0.004$; $r=0.5$), RAS, recurrent herpetic gingivostomatitis ($P=0.03$; $r=0.4$), and chronic candidal glossitis ($P=0.001$; $r=0.6$). The most common clinical diagnosis was chronic candidal glossitis (chi-square, $P=0.01$), which agrees with recent review.³

Various mechanisms of long-term persistent damage of organs and systems after COVID-19 are studied, including inflammatory reactions, thrombotic microangiopathy, venous thromboembolism, oxygen deficiency, autoimmune processes, pneumofibrosis, or persistence of the pathogen.^{15,16} Among these mechanisms, inflammatory reactions, thrombotic microangiopathy, and direct damaging effects of viral infection on the endothelium are suitable to explain, for example, the observed symptoms of petechiae among our patients. Systemic hyperinflammation, with neuroinflammation, autoimmune aggression, hypoxic trauma due to

direct exposure of the virus to the cardiorespiratory center, and possible direct entry of SARS CoV 2 into the CNS, with infection of astrocytes and microglia, are possible explanations for glossodynia symptoms. Regarding the actual symptoms at the level of the organism, musculoskeletal, digestive (i.e., diarrhea) and neurological symptoms including depression (by Zung scale) were the most frequent observed in PCS patients.²⁹ The last two are candidates for understanding oral candidal infections/dysbiosis and glossodynia / burning mouth syndrome exacerbation from our study.

Finally, systemic hyperinflammation contributes to the pre-existing diseases and such manifestations in the oral cavity as candidal glossitis, RAS, recurrent herpes viruses gingivostomatitis. In addition, all participants had a combination of at least two concomitant chronic common diseases. The combination of chronic gastrointestinal diseases, often hypertension and diabetes reflect the prevalence in the population and related problems with oral mucosa. And only the dryness of the red border of the lips can be associated with mechanical irritation due to wearing a mask, including improper.

Thus, all detected symptoms in the case series can be explained by concomitant pathology, in contrast to post-COVID syndrome. The recent report about increased biofilm on dentures,⁵ supports the concept of promoting the development of oral candidiasis. Another case of a patient who tested positive for coronavirus and presented oral manifestations such as recurrent herpes simplex, candidiasis, and geographic tongue, supports the argument that some oral conditions could be secondary to the deterioration of systemic health or due to treatments for COVID-19,² which coincides with our assumptions. Antibiotics, which are widely incorrectly used in COVID-19 treatment, make a significant contribution to later oral dysbiosis or candidiasis development. And, finally, recent evidence suspects host gene variability associated with COVID-19 can affect the disease pathogenesis, individual susceptibility to SARS-CoV-2 infection, severity and complications.³⁰ Therefore, we believe that oral symptoms were a group of secondary or symptomatic diseases or conditions depending on systemic state.

The management of the patient was differentiated related to the symptoms/diagnoses and based on classical approaches, except for

the features such as prolonged treatment or healing as in RAS and candidal glossitis, which, however, is possible in common conditions despite to COVID-19. Based on the results of treatment, we have not found indications for additional measures, although such targets may appear in the future.

Limitations

Some limitations should be highlighted. First, the definition of each level of severity for COVID-19 based on the patients' self-reporting. The second weakness of the study can be considered the undiagnosed presence of SARS CoV 2 at the time of examination of participating patients. Third, the traditional using of clinical criteria of diagnosis included specific limitations, such as the limitation of direct microscopic examination of clinical brushing samples; moreover remains unclear how long exactly the patients' complaints lasted. Also, we did not include an assessment of the oral health-related quality of life and therefore failed to assess the patients' real significance of the clinical findings. But the condition of the patients was quite serious, given that this was not their first visit to the physician. In addition, statistical results have some limits due to the case series design of the study.

Conclusions

After suffering COVID-19 on the background of chronic systemic diseases, it is expected long term incidence of oral mucosa morbidity during 8 months, with a significant prevalence of chronic candidal glossitis. Most oral symptoms depend on age and severity of the previous COVID-19. All detected oral symptoms can be explained by concomitant pathology, in contrast to post-COVID syndrome.

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Declaration of Interest

The authors declare that they have no competing interests.

Primary concerns and symptoms in the oral mucosa n=29 (100%)	Medical history, previous interventions and outcomes n(%)	Men (%)	Age (yr; mean ± SD)
Dryness of the Vermillion 29 (100), Halitosis 25(86.2), Taste disorders 26(89.7)	COVID-19 severity mild: 3(10.3)	0	29.3±1.2
Xerostomia 5(17.2), Burning mouth 4(13.8), Painful lesions 4(13.8)	COVID-19 severity moderate: 18(62)	47	46.7± 11.5
	COVID-19 severity severe: 8(27.5)	43	52.6±13.5
	COVID-19 was diagnosed and treated by primary care physicians based on the guideline including antibiotics, GCS, vitamins/minerals, and anticoagulants. Recovery.		

	<p>Ulceration of oral mucosa during COVID-19: alveolar bone/hard palate areas: 3 (10.3%), lower lip mucosa: 3 (10.3%).</p> <p>Healing without treatment, or topical NSAIDs</p>	
	<p>Burning mouth during 0,5-2 yr before: 4(13.8).</p> <p>Treatment by physicians, neurologists, and endocrinologists with effects of minor relief, or relief after prolonged treatment.</p>	
	<p>RAS during 5-7 yr before: 2(6.9).</p> <p>Treatment by the dentist results in relief of pain, and disappearance of symptoms.</p>	
	<p>Chronic comorbidities: 29 (100): GI diseases (gastritis, GERD, cholecystitis, pancreatitis); DM: 8 (27.5); AH: 19 (65.5); Neurogenic diseases: 5 (17.2); EBV/HSV positive PCR: 3 (10.3); Oncological: 3 (6.9).</p> <p>Treatment by specialists, resulting in compensated or subcompensated condition with periodic exacerbations.</p>	

Table 1. The presenting concerns and relevant demographic information.
 RAS – recurrent aphthous stomatitis, GI – gastrointestinal, GERD – *gastroesophageal reflux disease*, DM – *diabetes mellitus*, AH – arterial hypertension, EBV – *Epstein-Barr virus*, HSV – *Herpes simplex virus*, GCS – glucocorticosteroids.

COVI D-19 severity	n (%)	Symptoms, n					Clinical dental diagnoses, n			
		Dryness of lips	Edematose mucosa	Halitosis * (P=.001 r=-.6)	Xerostomia	Petechiae *(P=.01 r=.5)	RAS *(P=.03 r=0.4)	Recurrent herpetic gingivostomatitis *(P=.03 r=.4)	Glossodynia / burning mouth syndrome	Chronic Candidial glossitis *(P=.001 r=.6)
Mild	3 (10.3)	3	3	3	-	-	-	-	-	-
Moderate	18 (62)	18	18	18	3	1	-	4	7	
Severe	8 (27.5)	8	8	4	2	2	2	2	6	
Total	29 (100)	29	29	25	5	3	4	2	4	13

Table 2. Long term oral symptoms systematization and significant correlations with previous COVID-19 severity.

References

1. Brady MP. Cutaneous and Mucosal Manifestations of Viral Diseases. [Internet]. Medscape [update 2021 Sep 22; cited 2022 Jun 18]. Available from: <https://reference.medscape.com/slideshow/viral-skin-6002995>.
2. Amorim Dos Santos J, Normando AGC, Carvalho da Silva RL, et al. Oral Manifestations in Patients with COVID-19: A Living Systematic Review. *J Dent Res* 2021; 100(2):141-154.
3. Iranmanesh B, Khalili M, Amiri R, Zartab H, Aflatoonian M. Oral manifestations of COVID-19 disease: A review article. *Dermatol Ther* 2021; 34(1):e14578.
4. 'COVID Tongue' May Be a Symptom, Professor Says [Internet]. *WebMD Health News* [updated 2021 Jan 29; cited 2022 Jun 18]. Available from: <https://www.medscape.com/viewarticle/944962/>.
5. Karimzadeh F, Sajedi SM, Taram S, Karimzadeh F. Comparative evaluation of bacterial colonization on removable dental prostheses in patients with COVID-19: A clinical study. *J Prosthet Dent* 2021; S0022-3913(21)00252-3.
6. Doyle ME, Appleton A, Liu QR, Yao Q, Mazucanti CH, Egan JM. Human Taste Cells Express ACE2: a Portal for SARS-CoV-2 Infection. Preprint. *bioRxiv*. 2021;2021.04.21.440680. Published 2021 Apr 21. doi:10.1101/2021.04.21.440680.
7. Zhu F, Zhong Y, Ji H, et al. ACE2 and TMPRSS2 in human saliva can adsorb to the oral mucosal epithelium. *Journal of Anatomy* 2022; 240: 398-409.
8. Kichloo A, Dettloff K, Aljadah M, et al. COVID-19 and Hypercoagulability: A Review. *Clin Appl Thromb Hemost* 2020; 26: 1076029620962853.
9. Antoniak S, Mackman N. Multiple roles of the coagulation protease cascade during virus infection. *Blood* 2014; 123(17): 2605-13.
10. Grobbelaar LM, Venter C, Vlok M, et al. SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: implications for microclot formation in COVID-19. *Biosci Rep* 2021 27; 41(8): BSR20210611.
11. Abou-Ismael MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. *Thromb Res* 2020; 194: 101-115.
12. Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. *JCI Insight* 2020; 5(11): e138999.
13. de Bont CM, Boelens WC, Pruijn GJM. NETosis, complement, and coagulation: a triangular relationship. *Cell Mol Immunol* 2019; 16(1): 19-27.
14. Cruz Tapia RO, Peraza Labrador AJ, Guimaraes DM, Matos Valdez LH. Oral mucosal lesions in patients with SARS-CoV-2 infection. Report of four cases. Are they a true sign of COVID-19 disease? *Spec Care Dentist* 2020; 40(6): 555-560.
15. Holubovska OA. Postkovidnyi syndrom: patohenez ta osnovni napriamy reabilitatsii. [Internet]. *Health-ua.com* 2021 [update 2021 Mar 14; cited 2022 Jun 18]. Available from: <https://health-ua.com/article/64069-postkovdnij-sindrom-patogenez--ta-osnovn-napryami-reabltac>.
16. Maltezou HC, Pavli A, Tsakris A. Post-COVID Syndrome: An Insight on Its Pathogenesis. *Vaccines* 2021; 9(5): 497.
17. COVID-19 rapid guideline: managing the long-term effects of COVID-19. [Internet]. NICE guideline [update 2020 Dec 18; cited 2022 Jun 18]. Available at: www.nice.org.uk/guidance/ng188.
18. Mirowski GW. Aphthous Stomatitis [Internet]. Medscape [updated 2020 Sep 25, cited 2022 Jun 18]. Available at: <https://emedicine.medscape.com/article/1075570-overview#a5>.
19. Bender SD. Burning Mouth Syndrome. *Dent Clin North Am* 2018; 62(4): 585-596.
20. Culhane NS, Hodle AD. Burning mouth syndrome after taking clonazepam. *Ann Pharmacother* 2001; 35(7-8): 874-6.
21. Papapanou PN, Sanz M, Buduneli N, et al. Periodontitis: Consensus report of Workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol* 2018; 45 (Suppl 20): S162- S170.
22. Holubka OV. The abundance of candidiasis, the general characteristics of the pathogen, approaches to the laboratory diagnostic. *Annals of Mechnikov Institute* 2011; (2): 51-9.
23. Rasin MS, Kaidashev IP. The role of nuclear transcription factors in modern syntropy internal pathology (review). [Internet]. *Ukrainskyi medychnyi chasopys* 2014; (1): 17-21. [update 2014 Jen 2; cited 2022 Jun 18]. Available at: <https://www.umj.com.ua/article/70824/rol-yadernyx-transkripcionnyx-faktorov-v-sintropii-sovremennoj-vnutrennej-patologii-obzor-literatury>.
24. Liu YF, Kim Y, Yoo T, Han P, Inman JC. Burning mouth syndrome: a systematic review of treatments. *Oral Dis* 2018; 24(3): 325-334.
25. Rodrigues CF, Rodrigues ME, Henriques MCR. Promising Alternative Therapeutics for Oral Candidiasis. *Curr Med Chem* 2019; 26(14): 2515-2528.
26. Davies NG, Klepac P, Liu Y. et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med* 2020; 26: 1205-1211.
27. Arbour N, Côté G, Lachance C, Tardieu M, Cashman NR, Talbot PJ. Acute and persistent infection of human neural cell lines by human coronavirus OC43. *J. Virol* 1999; 73: 3338–3350.
28. Arbour N, Ekané S, Côté G, et al. Persistent infection of human oligodendrocytic and neuroglial cell lines by human coronavirus 229E. *J. Virol* 1999; 73: 3326–3337.
29. Anaya JM, Rojas M, Salinas ML, et al. Post-COVID syndrome. A case series and comprehensive review. *Autoimmun Rev* 2021; 20(11): 102947.
30. Kaidashev I, Shlykova O, Izmailova O, et al. Host gene variability and SARS-CoV-2 infection: A review article. *Heliyon*. 2021 Aug;7(8):e07863.