RESEARCH ARTICLE

The effect of interleukin-6 and procalcitonin level on the development of oral manifestation in hospitalized COVID-19 patients

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Abstract

Objective: To evaluate the effect of interleukin-6 and procalcitonin levels in plasma on the development of oral manifestation in patients of coronavirus disease-2019.

Methods: The case-control study was conducted from January to September 2021 at Kafrelsheikh University Hospital, Egypt, and comprised severe coronavirus disease. One hundred patients of either gender aged 30-60 years were included.. The patients were divided into two equal groups, with group I having patients with oral manifestations, and group II had those without any oral symptoms. Plasma samples from both the groups were used to determine serum interleukin-6 and procalcitonin levels using electrochemiluminescence immunoassay. Data was analysed using SPSS 20.

Result: Of the 100 patients, 50(50%) were in each of the two groups. Group I had 29(58%) males and 21(42%) females with overall mean age 44.83±6.12 years. Group II had 26(52%) males and 24(48%) females with overall mean age of 43.68±4.62 years. Interleukin 6 was significantly high in group I than in group II ($p<0.05$), while there was no significant difference between the groups for procalcitonin level ($p>0.05$).

Conclusion: Interleukin-6 level could play an important role in the development of oral manifestation in coronavirus disease-2019 patients.

Keyword: Interleukin, Procalcitonin, Ageusia, COVID-19, Gingivitis, Candidiasis, Mucous membrane, Immunoassay.

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Introduction

The single-chain ribonucleic acid (RNA) virus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the coronavirus disease-2019 (COVID-19), which spread quickly throughout the globe by the direct touch, saliva in the form of tiny droplets, and aerosol formation routes of transmission. Fever, headache, sore throat, dyspnoea, dry cough, abdominal pain, vomiting and diarrhoea are the most typical clinical symptoms.[1] The earliest identified oral symptom of COVID-19 is loss of taste, which the virus can also cause along with symptoms in the oral cavity. Among the observed oral symptoms during and after COVID-19 are taste impairment, oral mucosal abnormalities, like petechiae, ulcers, plaque-like lesions, recurrence of the herpes simplex virus 1 (HSV1), geographical tongue, desquamative gingivitis and mucormycosis, as well as dry mouth. The most typical locations for mucosal lesions are tongue, palate and labial mucosa. The precise aetiology of these oral symptoms is uncertain.[2]

There are four different types of COVID-19 pneumonia: mild, moderate, severe and critical. Mild pneumonia is defined as infections without symptoms or minor clinical signs without abnormal chest imaging findings. Moderate pneumonia is thought to be indicated by both clinical symptoms and atypical chest imaging findings. Patients are diagnosed with severe pneumonia when the infection gets so bad that any of the following criteria is met: 93% oxygen saturation at rest, a significantly increased breathing rate of roughly 30 breaths per minute (bpm), or a partial pressure of oxygen (PaO_2) /fraction of inspired oxygen (FiO_2) reading of <300mmHg (1mmHg = 0.133 kPa). If any of the following symptoms exist and the illness worsens quickly, critical pneumonia may result: shock, other organ failure necessitating monitoring in a critical care unit (CCU), respiratory failure necessitating mechanical ventilation.[3]

The pathophysiology of COVID-19 is presumed to be particularly dependent on interleukin-6 (IL-6). It is crucial for regulating a number of viral infections and is mostly produced by macrophages and T lymphocytes in response to viruses. While IL-6 at homeostatic levels helps heal tissue wounds and infections, its exaggerated production significantly fuels cytokine storms. In COVID-19, radiological alterations and illness stages have a positive correlation with IL-6.[4,5] Hospitalised individuals with moderate to severe types of COVID-19 usually have high levels of procalcitonin (PCT), the hormone's 116-amino acid precursor. PCT has been interpreted as a biomarker for secondary bacterial infections in COVID-19 and is typically used to identify systemic bacterial infections.[6]

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The current study was planned to examine if oral manifestations in hospitalised COVID-19 patients correlated with IL-6 and PCT levels.

Patients and Methods

The case-control study was conducted from January to September 2021 at Kafrelsheikh University Hospital, Egypt. After approval from the institutional ethics review committee, the sample size was calculated using the equation:[7]

$$N = \frac{(Z\alpha)2 * (SD)2}{(d)2}$$

N was the total sample size; Zα was the standard normal variant and was equal to 11.68 at p<0.05; SD was standard deviation of the variable; and d was the absolute error or precision.

Zα	SD	d
11.68	1.21	2

The sample was raised by Non probability convenient sampling from among male and female COVID-19 patients aged 30-60 years who had severe pneumonia, as indicated by a respiratory rate of <30bpm, oxygen saturation <93% at rest, or PaO2/FiO2 <300mmHg. The subjects had no other medical complaint and furnished informed consent to participate in the study.

Patients were excluded if they had any systemic illness, like diabetes and autoimmune disorders that affect the oral cavity. Also, heavy smokers (>10 smokes per day) and alcohol abusers were excluded. Pregnant females and those who received any inflammatory medications, antibiotics, immunosuppressors, or corticosteroids during the preceding month were also excluded.

According to the presence of oral manifestation, the patients were separated into two groups, with group I having COVID-19 patients with oral manifestations, while group II had COVID-19 without oral manifestations.

In accordance with the diagnosis and treatment procedure for COVID-19, all the patients received conventional care.

Prior to therapy, plasma samples from all the subjects were tested for IL-6 and PCT using electrochemiluminescence immunoassay (Elecsys® model E411; Roche Diagnostics GmbH, Mannheim, Germany).

PCT level 0.5-2 suggests systemic inflammation and sepsis risk is significant at 2, while the reference level if IL-6 is up to 7.0.[8,9]

Data was analysed using SPSS 20. Chi-Square and independent samples student t-tests were used for inter-group comparisons. Spearman coefficient was used to correlate between quantitative variables at the level of 5% significance.

Results

Of the 100 patients, 50(50%) were in each of the two groups. Group I had 29(58%) males and 21(42%) females with overall mean age 44.83±6.12 years. Group II had 26(52%) males and 24(48%) females with overall mean age 43.68±4.62 years (Table 1).

Several oral lesions at various locations in the oral cavity were noted in group I (Figure).

IL-6 was significantly high in group I than in group II (p<0.05), while there was no significant difference between the groups for procalcitonin level (p>0.05) (Table 2). There was no association between oral manifestation and procalcitonin, but the correlation between oral manifestation and IL-6 was significantly positive (Table 3).

Table-1: Demographic characteristics.

	Group 1 (n = 50)	Group 2 (n = 50)	*p-value*
Sex	29male/ 21 female	26 male/ 24 female	0.267#
Age	44.83± 6.12	43.68 ± 4.62	0.292*

p-values determined: *using independent samples t-test, #using Chi-Square test
Statistically significant at p<0.05

Table-2: Interleukin-6 (IL-6) and procalcitonin levels in the study groups.

	Group 1 (n = 50) Mean ± SD	Group 2 (n = 50) Mean ± SD	t-test	*p-value*
IL-6 (pg/ml)	138.20±46.69	29.41±21.70	15.036	0.000*
Procalcitonin (ng/ml)	0.73± 0.37	0.87±0.41	1.818	0.072

* Statistically significant at p<0.05.

Table-3: Correlation of oral manifestations with interleukin-6 ((IL-6) and procalcitonin.

	rs	*p-value*
IL-6 (pg/ml)	0.840*	<0.001*
Procalcitonin (ng/ml)	-0.187	0.063

rs: Spearman coefficient
* Statistically significant at P < 0.05

Figure: Oral manifestation in coronavirus disease-2019 (COVID-19) patients. A, B: Erosion in hard and soft palate. C, D, E: Ulcer in gingiva, labial mucosa and lip. F: Median rhomboid glossitis (Candida infection).

Discussion

The oral manifestations noted in the current study among COVID-19 patients included erosion, ulceration, gingivitis, loss of taste and smell, oral mucosal tissue inflammation and candida colonisation. COVID-19 resolution and the healing of oral lesions are inter-related, suggesting a link between the infection and oral manifestations.[10]

There is still no clear understanding of the specific connection between several of the oral lesions and the pathological features of SARS-CoV-2 infection. Some theories have been put forth, such as the virus itself[11], the lesions would be secondary to the medications used for treatment[12], due to the weakened and deteriorated immune system, which also allows for opportunistic infections, or could be related to psychological factors, like limited social interaction because of quarantine.[13]

In a susceptible host, immune dysregulation is a key factor in the development of oral illnesses. Studies revealed that SARS-CoV patients had higher serum levels of pro-inflammatory cytokines, including IL-1, IL-6 and IL-12.[14] The multipurpose cytokine IL-6 is created in response to environmental triggers, including infection and trauma. The creation of antibodies and autoantibodies, T cell activation, B cell differentiation, an increase in acute-phase proteins, haematopoiesis, angiogenesis, vascular permeability and osteoclast differentiation are just a few of the biological processes that IL-6 can induce.[15]

In the current study, the most frequent oral side effects related to COVID-19 were ulcers and erosions. Studies concluded that ulcerative lesions of the oral cavity were connected with COVID-19, and the current findings are similar in this regard.[16-19]

In the current study, group I had a greater increase in IL-6 than group II. IL-6 production may be an important aetiological factor for a recurrent aphthous ulcer (RAU) and may explain the elevated IL-6 plasma levels observed in RAU.[19,20]

Interleukin networks were studied by Sosroseno et al.[21] in relation to the immunopathogenesis of a few mouth illnesses. Interleukins, like IL-1 and IL-6, may be to blame for tissue deterioration in periapical inflammation and chronic inflammatory periodontal disorders. Increased levels of IL-6 may be related to the function of Langerhans cells in presenting autoantigens in autoimmune-related oral illnesses like lichen planus.[21]

Studies showed that gingival changes, like generalised erythematous and oedematous gingivae, gingiva-peridontal bleeding, necrotic interdental papillae and desquamative gingivitis, are noted in COVID-19 patients.[22-24] Gingivitis, one of the most common types of periodontal disease, was observed in the current study. Higher levels of both local and systemic IL-6 were linked to periodontitis. Another theory is that the gingivitis linked to COVID-19 is brought on by inadequate dental care while a patient is in the hospital. [25]

Several studies discovered a relation between periodontal disease (PD) and COVID-19. Additionally, pathophysiological mechanisms linked to a cytokine storm brought on by an unbalanced immune response and excessive production of proinflammatory cytokines and chemokines like IL-1, IL-6, tumour necrosis factor (TNF), macrophage inflammatory protein 1a, IL-10 and interferon (IFN), have been implicated in the signs and symptoms of COVID-19.[26-28]

Loss of smell and taste between 2- and 14-days post-infection is one of the most notable symptoms of COVID-19.[29] The specific mechanisms behind the

alterations in smell and taste caused by the infection are unknown.

There is a significant viral load in the saliva during the beginning of infection, and the titres decline as the illness worsens, suggesting a relationship between the presence of the virus in the saliva and the manifestation of the disease.[14] The loss of taste and smell in COVID-19 may be caused by a viral disruption of cranial nerves 1, VII, IX and X, as well as an inflammatory exudate that affects the cells that maintain neural transmission.[30] An important receptor for COVID-19, angiotensin-converting enzyme 2 (ACE-2) is widely expressed on cells in the mouth and the nose. The loss of taste and smell in COVID-19 may help to explain potential harm caused by the infection to the epithelial cells of the salivary glands, which are thought to be a target of the virus due to ACE-2 expression. [31]

Candida infection in the current study was found in COVID-19 patients, with the tongue being the most prevalent site of infection. Studies have linked COVID-19 with oral candidiasis.[32,33] IL-6 levels in plasma were statistically higher in human immunodeficiency virus (HIV) patients with oral candidiasis compared to HIV patients without oral candidiasis.[34]

Extended use of broad-spectrum antibiotics and prolonged mechanical ventilation in intensive care settings, and long-term use of corticosteroids, which can cause immunosuppression, may be to blamed for the development of oral mucocutaneous lesions, like candidiasis in COVID-19 patients.[35]

Regarding PCT, there was no significant difference between the two groups. Procalcitonin test has been shown to be ineffective in identifying sepsis of maxillofacial infections. As a result, in addition to routine laboratory testing, the PCT test should be performed in patients with mandibular infection to diagnose their systemic inflammatory status.[36]

Conclusion

COVID-19 oral lesions occurred in part as a result of higher IL-6 levels. Procalcitonin had no effect in this regard.

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