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LETTER TO THE EDITOR

Prevalence of dry mouth in COVID-19 patients with and without Sicca syndrome in a large hospital center

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The ACE-2 receptor is abundantly expressed on the epithelial cells of the salivary glands, and when infected by SARS-CoV2, these receptors are over expressed [1]. It is speculated that signaling of the ACE-2 receptor by the virus triggers a cascade of inflammatory processes, ending in acute and chronic sialoadenitis and causing disruption in salivary secretion and dry mouth [2, 3].

However, there is a dearth of information on the extent of the association between COVID-19 and dry mouth. Most of the existing literature is comprised of individual case reports or surveys reporting on symptoms from COVID -19 patients [4, 5]. It was suggested that the reported xerostomia is caused by fibrosis repairment [4] or due to the neuroinvasive and neurotropism potential of SARS-CoV-2 [6].

COVID -19 is an infectious disease with a strong inflammatory response as demonstrated by the phenomenon of "cytokines storm" [7]; therefore, it is intriguing to speculate that the reports on positive SSA antibodies in these patients [8, 9] may indicate the existence of autoimmune inflammatory response similar to the one described in Sjogren's syndrome [10, 11] that can result in dry mouth as well.

The purpose of the present study was to evaluate the prevalence of the association between COVID-19 and dry mouth in Sicca and non-Sicca patients, as well as to evaluate the association between SSA and COVID-19 and CRP and COVID-19.

The study was exempted by the University of Florida Institutional Review Board (IRB).

We used the University of Florida Health Center Integrated Data *i2b2* provided by the University of Florida Health Office of the Chief Data Officer for the period of June 2015–September 2020. Diagnoses of COVID-19 (ICD10 U07.1), Sicca syndrome (ICD10 M35.0), Dry mouth (ICD10, R62.8), positive SSA antibody (CPT 86235), elevated CRP (CPT 86140), and total hospital population by age and sex were searched by using the appropriate international classification of diseases (ICD 10). The total hospital population was 987849 patients, 46% male and 54% females. From 889 patients that were diagnosed with COVID-19, 43% were male and 57% were females. A total of 1772 (0.18%) of patients were diagnosed with dry mouth, 30% were males and 70% females. Nine patients (1.01%) were diagnosed with both COVID-19 and dry mouth. Most of the patients were adults and 100% of both COVID-19 and dry mouth were adults (Table 1).

The OR for COVID-19 with dry mouth was 5.153 (95% CI 2.9220 to 10.9008, $p < 0.001$).

The OR for COVID-19 in the presence of Sicca syndrome dry mouth was 2.01, not statistically significant (0.7525 to 5.3753, $p = 0.1636$). The OR for COVID-19 in the presence of non-Sicca dry mouth was 3.5661 (95% CI 1.4786 to 8.6009, $p = 0.0046$) (Table 2). The OR for COVID-19 in the presence of positive SSA was 2.2519 (95% CI 1.2418 to 4.0835, $p = 0.0075$. The OR for COVID-19 in the presence of elevated CRP was 4.3237 (95% CI 2.0523 to 9.1091, $p < 0.0001$) (Table 3).

Table 1 Demographic data of patients with dry mouth in COVID-19, COVID-19 patients only, dry mouth in hospital patients, and all hospital patients

	Dry mouth and COVID-19	COVID-19	Dry mouth (ICD10 R68.2)	Hospital
Total	6	889	1772	987849
Male	0	385 (43%)	534 (30%)	455230 (46%)
Female	6 (100%)	504 (57%)	1238 (70%)	532165 (54%)
Children < 18 years	0	38	151	156063
Adults > 18 years	6 (100%)	851 (96%)	1621 (91%)	831786 (84%)

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Table 2 Odds ratio for COVID-19 in the presence of dry mouth, Sicca dry mouth, and non-Sicca dry mouth

	COVID-19	Hospital
Dry mouth (R68.2)	9 (1.01%)	1772 (0.179%)
Hospital	889	987849
OR	5.153	
95% CI	2.9220 to 10.9008	
p	< 0.0001	
Dry mouth Sicca (M35.00)	4 (0.45%)	2210 (0.22%)
Hospital	889	987849
OR	2.0112	
95% CI	0.7525 to 5.3753	
p	*p* = 0.1636	
Dry mouth non-Sicca	5 (0.56%)	1558 (0.158%)
Hospital	889	987849
OR	3.5661	
95% CI	1.4786 to 8.6009	
p	0.0046	

Dry mouth is a condition that may result from many causes, including autoimmune, endocrine and neurological conditions, and the use of a variety of medications. In addition, it is clear that the intensive medical therapies especially in intensive care units may contribute significantly to the subjective and objective complaints of dry mouth.

Several studies of self-reported complaints of COVID-19 patients have documented oral symptoms such as dry mouth and dysgeusia [4, 5]. Few authors have suggested that SARS-CoV-2 binds to ACE-2 receptors on the epithelium of salivary glands, replicate, lyse cells, and propagate signs and symptoms, such as discomfort, inflammation, and pain in major salivary glands and resulting in chronic sialoadenitis [2, 3]. Some authors have suggested that the dry mouth results from the neurotoxic effects of the virus on target organs with effects on CNS [4].

Patients with rheumatic diseases are known to be at higher risk of infections such as COVID-19. This might be attributed to their rheumatic disease activity, comorbidities, and immunosuppressive therapy [12]. COVID-19 shares a similar inflammatory immune response with autoinflammatory and autoimmune conditions. Viruses can share immune responses with autoimmune diseases such Kawasaki disease, vasculitis, and Sjögren's-like syndrome [9, 13].

In conclusion, dry mouth related to Sicca and not related to Sicca are strongly associated with COVID-19. The causes for this association are not clear and may include autoimmunity causes as well as increased risk for infection and the impact of other comorbidities and therapies. Clinician should be aware of the association and treat the patients accordingly.

Table 3 Odds ratio for COVID-19 in the presence for positive SSA and elevated CRP

	COVID-19	Hospital
SSA	11 (1.23%)	5428 (0.55%)
Hospital	889	987849
OR	2.2519	
95% CI	1.2418 to 4.0835	
p	= 0.0075	
CRP	7 (0.78%)	1799 (0.182%)
Hospital	889	987849
OR	4.3237	
95% CI	2.0523 to 9.1091	
p	= 0.0001	

Compliance with ethical standards

The study was exempted from approval by the Institutional Review Board (IRB) of the Health Center at the University of Florida as it does involve any disclosure of personal health information (PHI). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest Dr. Katz is a consultant for HT Bioimaging on an unrelated project.

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