

Review Article

Olfactory and Gustatory Dysfunction in COVID-19 Patients – A Current Review

Tay Yong Boon Ernest¹, Ho Ching Wen Dawn², Rebecca Low Pei Kee³, Bharath Raj Varatharaj Palraj⁴, Ramkumar Sekar⁵, Muhammad Bilal Abid⁶, Veeraraghavan Meyyur Aravamudan⁷, Charn Tze Choong⁸

¹Medical Officer, Department of Otolaryngology – Head and Neck Surgery, Sengkang General Hospital

²Medical Officer, Department of Ophthalmology, National Healthcare Group Eye Institute, Khoo Teck Puat Hospital

³Medical Officer, Department of Ophthalmology, National Healthcare Group Eye Institute, Tan Tock Seng Hospital

⁴Assistant Professor of Medicine and Consultant, Division of Infectious Diseases, Mayo Clinic College of Medicine and Science.

⁵Consultant, Cardiology, Khoo Teck Puat Hospital, Singapore

⁶Assistant Professor of Medicine, Divisions of Infectious Diseases & Hematology/Oncology, Medical College of Wisconsin

⁷Consultant, Department of Medicine, Woodlands Health Campus

⁸Head and Consultant, Department of Otolaryngology – Head and Neck Surgery, Sengkang General Hospital

***Corresponding author:** Veeraraghavan Meyyur Aravamudan, Consultant, Department of Medicine, Woodlands Health Campus, Singapore. E-mail: aravamudan_veeraraghavan_meyyur@whc.sg

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus that has caused a global pandemic. Initial reported symptoms include fever, cough, dyspnoea, fatigue, and myalgia. There has been increasing evidence that sudden olfactory and gustatory dysfunction may be another common symptom. This review will look at the prevalence of olfactory and gustatory dysfunction in COVID-19, the utility of this symptom as a screening tool for the disease, postulated disease mechanisms resulting in olfactory and gustatory dysfunction, and the recovery rate of

Methods

A review of relevant articles was conducted via a search through MEDLINE, EMBASE, CENTRAL, and Web of Science. References of articles were also examined to identify other relevant publications.

Results

There is a high prevalence for olfactory or gustatory dysfunction among COVID-19 patients, although clinical data may represent indigenous variability in geographical regions, demographic features, and clinical severity. And patients exhibiting these disturbances as the first or only symptom may have a milder disease course. SARS-CoV-2 is postulated to be a neurotropic virus with a specific tropism for the olfactory system.

Conclusion

Current literature suggests olfactory and gustatory dysfunction is prevalent in COVID-19. Longer term data is required to draw definitive conclusions about this association.

Keywords: SARS-CoV-2, Coronavirus; Smell; Taste; Disturbance

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus which first emerged in Wuhan, China in December 2019 [1, 2]. A progressive global outbreak in coronavirus disease (COVID-19) in early 2020 resulted in the World Health Organization first calling this a Public Health Emergency of International Concern on 30 January 2020, and then declaring this a pandemic on 11 March 2020 [3].

The public health strategy used to mitigate the outbreak involves screening individuals for symptoms suggestive of disease, test for infection, and isolate infected individuals. Initial commonly reported symptoms include fever, cough, dyspnoea, fatigue, and myalgia [4].

However, there has been increasing evidence that sudden olfactory and gustatory dysfunction may be associated with COVID-19. On 22 March 2020, the American Academy of Otolaryngology—Head and Neck Surgery (AAO – HNS) released a statement that anosmia, hyposmia, and dysgeusia have been reported by patients who ultimately tested positive for the disease and proposed to add these symptoms to the list of screening tools for infection [5].

Olfactory dysfunction is defined as an altered sense of smell [6]. This encompasses anosmia (complete loss of smell), hyposmia (partial loss), and dysosmia (distortion in the perception of an odorant). Gustatory dysfunction is defined as an altered sense of taste. This includes ageusia (complete loss of taste), hypogeusia (partial loss), and dysgeusia (distortion in the perception of taste).

As olfactory and gustatory systems are interlinked, it is not uncommon for patients to develop concurrent olfactory and gustatory disturbance. In the context of COVID-19, such dysfunction can occur in isolation or together with other

Olfactory and gustatory dysfunction have been described as specific early symptoms, and hence may potentially be harnessed as an effective screening tool for diagnosis.

This review will look at the prevalence of olfactory and gustatory dysfunction in COVID-19, the utility of this symptom as a screening tool for the disease, postulated disease mechanisms resulting in olfactory and gustatory dysfunction, and the recovery rate of smell or taste dysfunction in these patients.

For the purpose of this comprehensive narrative review, we searched MEDLINE, EMBASECENTRAL and Web of Science using the following keywords: COVID-19, SARS-CoV-2, coronavirus, olfactory, anosmia, gustatory, ageusia. We also examined the references of articles found and included those that were considered appropriate for this review.

1.1 Prevalence of olfactory and gustatory dysfunction in COVID-19 disease Epidemiology

The prevalence of olfactory and gustatory dysfunction in patients diagnosed with COVID-19 has been well researched. A meta-analysis by Tong et al. [7], reported an overall prevalence of 52.7% for olfactory dysfunction and 43.9% for gustatory dysfunction. Sub-group analysis revealed that studies which used validated reporting instruments reported higher smell or taste disturbance (86.60%, 95% confidence interval (CI): 72.95%-95.95%) compared to those which did not (36.64%, 95% CI, 18.31%-57.24%). There have since been more prevalence studies conducted after the meta-analysis was published and we have included a comprehensive updated list in table 1.

Clinical data thus far remains heterogenous and can be in part explained by reasons which were not fully explored in the meta-analysis. Firstly, available prevalence data represent the indigenous variability in geographical regions and the setting in which patients were sampled. Patients sampled in the outpatient setting for instance are likely to have less severe respiratory symptoms and hence other symptoms such as olfactory or gustatory disturbance may be more prominent. Secondly, the use of varied tools for assessment of olfactory and gustatory dysfunction contribute to its heterogeneity. There is an element of reporting bias for self-reported surveys. The variety of questionnaires used, ranging from pre-existing ones (like the Sino-nasal Outcome Test) to newly developed ones (like the Anosmia Reporting Tool developed by the AAO-HNS) also likely leads to variabilities in data. Pre-existing questionnaires were developed for other purposes and are not validated for COVID-19. Newly developed ones may be more specific for COVID-19, but the majority also suffer from a lack of rigorous validation. Lastly, prevalence data obtained earlier at the start of the pandemic via medical records (which are likely less complete for such symptoms) or via non-validated questionnaires (at a time where there was little or less insight into the relationship between olfactory/gustatory dysfunction) are likely to be different compared to data obtained from prevalence studies later.

1.2 Patterns of dysfunction

Many studies have since reported olfactory dysfunction as an early manifestation of COVID-19, with a small proportion reporting it as the only symptom of the disease. According to Kaye et al. [8], anosmia or hyposmia was found to be the initial presenting symptom in 27% of patients, while 73% reported such symptoms prior to the diagnosis of COVID-19.

Author	Study design	Population	Means of assessment	No.	Olfactory dysfunction (%)	Gustatory dysfunction (%)	Olfactory AND Gustatory Dysfunction (%)	Olfactory OR Gustatory Dysfunction (%)	Anosmia as first or only presenting symptom (%)
Vaira et al. [9]	Case series	Patients at a single centre, Italy	Connecticut Chemosensory Clinical Research Centre olfactory test	72	83.3	48.6	41.6	-	19.4
Moein et al. [10]	Cross-sectional	Hospitalised patients, Iran	University of Pennsylvania Smell Identification Test	60	98.3	23.3	16.7	35	-
Hornuss et al. [11]	Cross-sectional	Hospital, Germany	Sniffin' Sticks Test	45	84.4	-	-	-	-
Altin et al. [12]	Case control	Patients at a single centre, Turkey	Sniffin' Sticks Test	8	61.7	27.2	-	-	-

1.1 Via objective assessment

Table. 1: Prevalence of olfactory or gustatory dysfunction.

Spinato et al. [13]	Cross-sectional	Patients at a single centre, Italy	Sino-nasal Outcome Test 22	202	-	-	-	64.4	14.9
Menni et al. [14]	Cross-sectional	General community, United Kingdom	COVID RADAR Tracker app	579	Not reported	Not reported	59.1	-	-
Lechien et al. [15]	Case series	ENT patients, Belgium	Non-validated questionnaire	417	85.6	82	-	-	11.8
Kaye et al. [8]	Cross-sectional	Patients in USA	Non-validated questionnaire	237	73	-	-	-	26.6
Sakalli et al. [16]	Cross-sectional	Patients in a single centre in Turkey	Non-validated questionnaire	172	51.2	47.1	-	-	4.54
Fontanet et al. [17]	Retrospective cohort study	High school, France	Non-validated questionnaire	171	34.5	34.5	-	-	-
Beltrán-Corbellini et al. [18]	Case control	Hospitalised patients, Spain	Non-validated questionnaire	79	31.6	35.4	-	39.2	13.9
Bénézit et al. [19]	Cross-sectional	Patients at three centres, France	Non-validated questionnaire	68	75	92.6	63.2	-	94.1
Yan et al. [20]	Cross-sectional	Patients at a single centre, USA	Non-validated questionnaire	59	67.8	71.2	-	-	22
Wee et al. [21]	Cross-sectional	Patients at emergency department, Singapore	Verbal interview	154	-	-	-	22.7	1.9
Giacomelli et al. [22]	Cross-sectional	Hospitalized patients, Italy	Verbal interview	59	23.7	28.8	18.6	33.9	-
Mao et al. [23]	Case series	Hospitalised patients from 3 centres, China	Electronic records audit	214	5.61	5.14	-	-	-
Yan et al. [24]	Case series	Patients at a single centre, USA	Electronic records audit and phone interview	128	58.6	54.7	-	-	-

1.2 Via non-objective assessment (-) denotes information that was not reported in the study.

1.3 Olfactory and gustatory dysfunction as a screening tool for disease diagnostic utility of sudden onset olfactory and / or gustatory dysfunction

The gold standard test for the diagnosis of COVID-19 is a reverse transcriptase polymerase chain reaction (RT-PCR) performed via oropharyngeal and / or nasopharyngeal swabs. However, limitations to testing exist due either to lack of access to validated diagnostic test kits or due to bottlenecks with the scale of testing involved. Clinical symptoms have hence become an important screening tool to streamline testing efforts and ensure cost-efficient and equitable healthcare delivery in current times of crisis.

While there is an increasing body of evidence that show a high prevalence of sudden onset olfactory and gustatory disturbance among COVID-19 patients [7], François Bénézit et al. first described the potential diagnostic utility of these symptoms. They reported that sudden onset hyposmia (odds ratio (OR) 7.44, 95% CI 3.63-15.6) and hypogeusia (OR 13.4, 95% CI 6.61-28.3) were strongly associated with COVID-19 [19]. The best diagnostic performance was obtained with patients without any past medical history of ear, nose, or throat (ENT) disorders who had combined smell and taste dysfunction (sensitivity 42%, specificity 95%).

A review of several other studies [10, 14, 17, 19-21] in which diagnostic values can be calculated corroborates this finding. Across these studies (table 2), there are consistently high values for the specificity of olfactory and gustatory dysfunction in relation to COVID-19 (range 81 – 100%). The high specificities strongly support the use of acute smell or taste disturbance as a screening symptom for COVID-19. We have since seen this being demonstrated with the incorporation of this symptom either as part of screening questionnaires for COVID-19, or as an isolated screening tool such as the previously mentioned Anosmia Reporting Tool.

Author	Symptom	Sensitivity	Specificity	PPV	NPV	Positive likelihood ratio	Negative likelihood ratio
Altin et al. [12]	Olfaction	0.62	1	1	0.56	-	0.38
Altin et al. [12]	Gustation	0.73	1	1	0.65	-	0.27
Bénézit et al. [19]*	Olfaction	0.46	0.9	0.62	0.82	4.53	0.6
Bénézit et al*. [19]	Gustation	0.62	0.89	0.68	0.87	5.84	0.43
Bénézit et al*. [19]	Both	0.43	0.93	0.69	0.82	6.2	0.62
Fontanet et al. [17]	Olfaction	0.29	0.98	0.85	0.8	15.92	0.72
Fontanet et al. [17]	Gustation	0.3	0.99	0.88	0.8	21.29	0.71

Menni et al. [14]	Both	0.59	0.81	0.62	0.79	3.13	0.5
Moein et al. [10]^	Olfaction	0.59	0.81	0.62	0.79	3.13	0.5
Salmon et al. [25]	Olfaction	0.41	0.9	0.79	0.64	4.21	0.66
Wee et. al. [21]	Both	0.23	0.99	0.8	0.86	18.08	0.78
Yan et al. [20]	Olfaction	0.68	0.84	0.55	0.9	4.17	0.38
Yan et al [20].	Gustation	0.71	0.83	0.55	0.91	4.13	0.35

1.4 Diagnostic utility in comparison with other symptoms of COVID-19

Sporadic evidence has emerged [15, 22, 26] that sudden onset of olfactory or gustatory dysfunction has a stronger association with COVID-19 as compared to more commonly described symptoms of fever, cough, dyspnoea, or fatigue/myalgia. In comparing common presenting symptoms of COVID-19, Yan et al. demonstrated that smell and taste disturbances showed the strongest association with the disease. A multivariable logistic regression showed that both smell and taste impairment were the strongest independent factors associated with COVID-19 positivity (anosmia: OR 10.9, 95% CI: 5.08- 23.5; ageusia: OR 10.2 95% CI 4.74-22.1) [20].

This was subsequently corroborated in two racially distinctive cohorts. In an Asian cohort of patients with PCR-proven acute respiratory viral infections, Wee et al. demonstrated that those patients who tested positive for COVID-19 had significantly higher odds of olfactory or gustatory dysfunction as compared to those positive for other respiratory viruses (OR = 10.14, 95% CI 2.37–43.49) [21]. Beltrán-Corbellini et al. demonstrated in a case control study that sudden onset of smell or taste dysfunction was more frequently observed in the COVID-19 group (39.2%, 95% CI 28.9-50.6) than in the control group comprising of influenza patients (12.5 %, 95% CI 5.1-27.6), with an adjusted OR of 21.4 (95% CI, 2.77-165.4) [18].

1.5 Diagnostic utility in comparison with other risk factors for COVID-19

Traditional risk factors for communicable diseases including COVID-19 include a history of close contact with confirmed cases. Wee et al [21]. found that olfactory and gustatory dysfunction were equally sensitive and specific as a history of close contact with a confirmed COVID-19 case (specificity: 94.8%, 95% CI 93.0–96.3%; sensitivity: 27.3%, 95% CI 20.4–35.0%). This indicates that actively inquiring about smell or taste disturbances in an individual suspected of disease may be as effective as epidemiological contact-tracing, though more work needs to be done to study this association.

1.6 Diagnostic utility of olfactory and gustatory dysfunction for clinical severity of COVID-19

It is now known that COVID-19 can cause a spectrum of disease severity. Risk factors for severe disease [27] include advanced age, people with a vulnerable social set-up such as those staying in nursing homes or in overcrowded areas,

and people with medical conditions which may predispose to an immunocompromise state, or having less physiological reserves. Isolated case reports and case series appear to suggest that alterations in smell or taste may signify a milder clinical course of COVID-19 [13, 28, 29]. This may particularly be the case if these manifestations were the only presenting symptoms.

In a retrospective review involving 169 patients, Yan et al. found that patients who were hospitalized were less likely to report smell (26.9% vs 66.7%), and taste abnormalities (23.1% vs 62.7%) than those who were managed outpatient [24]. Multivariable logistic regression demonstrated that self-reported intact olfactory function and positive chest radiograph findings were the only factors independently associated with hospital admission. Patients with altered smell and taste were ten times less likely to be admitted than those with normosmia (OR: 0.09, 95% CI: 0.01-0.74).

We recommend that results suggesting a relationship between olfactory/gustatory dysfunction and clinical severity should be interpreted with caution due to various limitations. Existing studies mostly involve small samples, and data is often self-reported leading to recall bias. Patients who require hospitalization may also display more prominent symptoms such as high fever or dyspnoea requiring oxygen supplementation or even mechanical ventilation and thus may not notice qualitative differences in olfactory or gustatory function.

1.7 Proposed mechanisms resulting in olfactory and taste dysfunction

Olfactory dysfunction can affect between 3 to 20% of the general population [30]. Post-viral dysfunction is a common aetiology [14]. The exact mechanistic pathways in which viruses (including SARS-CoV-2) may lead to changes in smell and taste perception are poorly understood. However, a few plausible explanations have been proposed.

Firstly, these viruses produce local inflammation of the sinonasal mucosa, thereby resulting in nasal obstruction and changes in the perception of smell (and taste). Akerlund et al previously found that for a significant proportion (49%) of their subjects with experimentally induced common cold after nasal inoculation with human coronavirus 229E, the magnitude of the change in smell was correlated with the severity of nasal obstruction (measured via nasal peak expiratory flow and by acoustic rhinometry) [31]. Suzuki et al found a similar correlation in their cohort [32]. However, both studies also had a proportion of infected individuals who had olfactory dysfunction but minimal subjective nasal obstruction or normal acoustic rhinometry. This suggests that sinonasal inflammation is not the only factor underlying post-viral olfactory and gustatory dysfunction. Furthermore, it has been observed that SARS-CoV-2 does not appear to generate clinically significant nasal congestion or rhinorrhoea in comparison with other respiratory viruses [33].

Secondly, SARS-CoV-2 is a neurotropic virus with a specific tropism for the olfactory system [33]. Some viruses that affect the respiratory tract are hypothesized to either infect olfactory receptor neurons or diffuse through channels formed by olfactory ensheathing cells [34]. Previous studies have demonstrated the presence of viruses in nasal secretions and post-mortem biopsy samples of the olfactory bulb, suggesting viral replication within the nasal cavity and olfactory system [34].

Coronaviruses are known to be neurotropic amidst a growing body of evidence [33]. In 2003, tissue samples from patients with severe acute respiratory syndrome (SARS) demonstrated the presence of SARS-CoV in the central

nervous system [35]. The angiotensin-converting enzyme II (ACE2) is known to be the cell receptor for SARS-CoV-2 [36] to gain entry at the cellular level. The human ACE2 protein is widely expressed in the upper aerodigestive tract (on mucosal epithelial cells of the nasal and oral cavity). It is also expressed in epithelial cells of the lower airway as well as the intestines and kidneys. Neural mechanisms of the virus have been hypothesized, although the extent to which the olfactory epithelium could serve as a nose-brain entry path is uncertain.

Experimental studies using transgenic mice expressing the ACE2 receptor previously demonstrated trans neural penetration and spread to connected areas of the brain through the olfactory bulb after intranasal inoculation with either SARS-CoV or MERS-CoV. One mice model notably revealed that the detection of virus antigen was most abundant in the olfactory bulb [37]. Still, to date, our understanding of the neurotropism of the virus remains limited by small study samples, as well as difficulties in obtaining histopathological tissue specimens and viral cultures of infected olfactory neuroepithelium.

1.8 Prognosis

There has been limited literature assessing the long-term prognosis of post-viral smell and taste dysfunction in general. A case-control study by Lee et al [38] showed that 80% of patients with post-viral dysfunction reported subjective recovery after one year. Favourable prognostic factors include the female gender, and patients with follow-up duration of 2 years or longer. A retrospective analysis of 791 patients by Cavazzana showed 46% of anosmic and 35% of hyposmic patient exhibiting clinically significant improvement in smell test scores over a mean follow-up period of 1.94 years [39].

For COVID-19, given that this is caused by a novel coronavirus, there is limited data regarding recovery rate. Existing studies suggest a highly variable complete recovery rate, ranging from 11.5 – 74% (Table 3). Data related to the time of recovery was equally variable but suggested that a large proportion of patients who generally made early recovery.

Author	Olfactory dysfunction	Gustatory dysfunction
Beltrán et al. [18]	Complete recovery: 40% • Mean duration 7.4 days • Range 5.1 to 9.7 days,	Not documented
Hopkins et al. [40]	Complete recovery (at 1 week): 11.5%	
Lechien et al. [15]	Complete recovery: 37% Recovery time in days: •1-4 (33%) •5-8 (47.5%) •9-14 (24.2%) 15 or more days (3.4%)	Among patients with residual dysfunction, 53.9% had isolated olfactory dysfunction, 22.5% had isolated gustatory dysfunction, 23.6% had both
Salmon et al. [25]	Complete recovery: 72.9%	Not documented
Sakalli et al. [16]	Complete recovery: 22.7% Mean duration: 8.02 days	Complete recovery: 23.4%

Vaira et al. [9]	<p>Complete recovery: 66%</p> <ul style="list-style-type: none"> - 19 in less than 5 days - 16 in 5 days or more <p>Among these patients, 28 (80%) had residual hyposmia or hypogeusia on objective assessment</p>	Complete recovery: 20.5%
Yan et al. [20]	Complete recovery: 74%	Not documented

Table 3: Recovery from olfactory and gustatory dysfunction.

Accurate analysis is complicated by the fact that most studies on SARS-CoV2 and olfactory or gustatory dysfunction is based on subjective self-evaluations. Disparity between subjective and objective assessment was highlighted in a rare study of objective olfactory dysfunction relating to COVID-19 by Vaira et al [9], where 66% of patients self-perceived complete recovery, but on objective assessment, 80% of these patients still showed residual hyposmia or hypogeusia.

2. Conclusion

Current evidence suggest that acute olfactory or gustatory dysfunction is prevalent and can be utilised as a screening tool for COVID-19. There is a plausible biological pathway leading to dysfunction. It remains to be seen how longer-term data will affect the overall recovery rate, and how this compares to other respiratory viruses which cause olfactory and gustatory dysfunction.

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