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ORIGINAL ARTICLE

Clinical significance of olfactory dysfunction in patients of COVID-19

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Abstract

Background: Currently, as the coronavirus disease (COVID-19) has become a pandemic, rapidly obtaining accurate information of patient symptoms and their progression is crucial and vital. Although the early studies in China have illustrated that the representative symptoms of COVID-19 include (dry) cough, fever, headache, fatigue, gastrointestinal discomfort, dyspnea, and muscle pain, there is increasing evidence to suggest that olfactory and taste disorder are related to the COVID-19 pandemic. Therefore, we conduct this study to review the present literature about the correlation between anosmia or dysgeusia and COVID-19.

Methods: A comprehensive literature search in 2020 of the electronic journal databases, mainly PubMed or Web of Science, was performed using the keywords COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with hyposmia, anosmia, dysgeusia, olfactory disorder, or olfactory dysfunction. The country, study period, case number, inpatient or outpatient medical visit, evaluation method (subjective complaints of dysfunction or objective evaluation), and occurrence rate of olfactory or gustatory function were reviewed.

Results: Many studies reported that the recoverable olfactory or gustatory dysfunction may play an important role as the early clinical symptom of COVID-19. It is associated with better prognosis, although further investigation and validation should be carried out.

Conclusion: Studies have shown that smell and taste disturbances may represent an early symptom of COVID-19 and healthcare professionals must be very vigilant when managing patients with these symptoms. In the pandemic era, this implies testing for COVID-19 by healthcare workers with full personal protective equipment.

Keywords: Anosmia; COVID-19; Hyposmia; Olfactory dysfunction

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1. INTRODUCTION

The coronavirus disease 2019 (COVID-19), is a new global public health crisis and the entire world is rapidly suffering from its effect. Initially, the new virus was also known as 2019 novel coronavirus (2019-nCoV). As the new virus is very similar to the previous one that caused the severe acute respiratory syndrome (SARS) outbreak (SARS-CoV), the experts of the International Committee on Taxonomy of Viruses first named it as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] On January 15, 2019, this disease was also named by Taiwan CDC, the Ministry of Health as Severe Pneumonia with Novel Pathogens, which was a notifiable communicable disease of the fifth category.[2] As of April 20, 2021, there were more than 140 800 263 confirmed cases of COVID-19 and 3 045 849 deaths reported globally.[3] While fever, cough, headache, fatigue, and dyspnea were regarded as the most and dominant symptoms in the early disease stage of COVID-19, olfactory dysfunction of COVID-19 has been additionally recognized. Although olfactory impairment can occur due to several reasons, such as inherited causes, aging process, chronic sinonasal diseases, head trauma, upper respiratory infections, and neurodegenerative diseases, several kinds of viruses (eg, Epstein-Barr virus, parainfluenza, rhinovirus, and some coronavirus) may also affect the upper aerodigestive tract and lead to olfactory dysfunction in which most of them are related to inflammatory reactions of the nasal mucosa. The previous reports stated that the recovery rate of short-duration olfactory dysfunction was around 44%, of which 72.6% of patients had an average duration of olfactory and gustatory disorders to be 7.5 days. Thus, several cases of short-duration olfactory dysfunction were not reported, and only patients with long-lasting symptoms sought for medical advice.[4,5] However, a previous study has indicated that reduced olfaction occurred in about 74% of COVID-19 patients, on average at the fourth day after the first symptoms had been noted.[6] In addition, little is known regarding the pathophysiology of COVID-19 on the olfactory system, which may possess the significance in early diagnostics. In particular, this may identify the disease spread may be majorly driven by asymptomatic carriers.

Although olfactory dysfunction is not a life-threatening emergency, it can affect the quality of life significantly. This well-known symptom has been discussed robustly in previous articles. Anosmia, the inability to smell, which can result from many underlying diseases, may afflict 3% to 20% of the population.[7,8] Up to 40% of anosmia has been caused by post-viral infection which is the most likely underlying etiology.[9] Walker et al[10] investigated searches related to loss of smell by using Google Trends during the early COVID-19 outbreak and found that the incidence of smell-related disorder is strongly correlated with the onset of SARS-CoV-2 infection in Europe, the United Kingdom, the United States, and the Middle East. Bagheri et al[11] reported that during the COVID-19 epidemic, there is a surge of olfactory dysfunction in Iran which correlates with the patient numbers of COVID-19 around the country. In South Korea, an informal phone survey by the Daegu City Council found that 15.3% of a total of 3191 confirmed COVID-19 cases had anosmia or dysgeusia.[12] In Germany, Hendrik Streeck, a virologist, reported that clinicians at the University Hospital in Bonn found that up to two-thirds of 100 patients with SARS-CoV-2 described olfactory and taste dysfunction lasting several days.[13] A multicenter European study even showed that olfactory dysfunction appeared before the appearance of general or ear-nose-throat symptoms of COVID-19 in 11.8% of patients.[4]

Evidence on the evolutionary changes related with COVID-19 has been reported. The neurologic manifestations of COVID-19 such as nausea, headache, and vomiting, and even the development of acute respiratory failure have been considered to be associated with the role of neurologic damage from the virus.[14] A previous study has described that coronavirus (human strains) have also been shown to invade the central nervous system (CNS) and propagate within the olfactory bulb (OB).[15] Angiotensin-converting enzyme 2 (ACE2) is highly expressed in olfactory epithelial support cells and nasal respiratory epithelial cells and has been adapted as the entry point for SARS-CoV-2 to infect cells.[16] In this cohort of patients, hyposmia or anosmia followed fever or occurred solitary (ie, without any systemic disorder), and most of them were young patients without gender differences.[14] Early outcomes showed that patients may recover completely or partially in a few weeks (around 80% of patients described their sense of smell recovered within a few weeks of onset, with a plateau appearing after 3 weeks).[14,17]

As we continue to face this pandemic, recognizing the early representative symptoms of COVID-19 to accelerate timely identification of patients who are already infected but transmit the virus asymptomatically is crucial due to the shortage of valid treatments and vaccine for COVID-19.[18] As a consequence, the aim of this article is to review the present literature about the relationship between gustatory or olfactory dysfunction with COVID-19 and to understand the occurrence rate in different countries.

2. METHODS

A literature review was performed up to April 10, 2021 by searching in the electronic databases, mainly PubMed and Web of Science. The search strings used were the following: "COVID-19 or SARS-CoV-2" with "anosmia or hyposmia or olfactory dysfunction or olfactory disorder or dysgeusia." Variations of these terms were also searched. We also considered the "Related articles" option on the PubMed Web search homepage. The references of those retrieved articles were also searched manually to prevent the relevant studies lost in the initial literature search. Articles were limited to those having titles and abstracts available in English and published in peer-reviewed journals were screened initially. After deduplication, the identified full-text articles were examined for original data, and we also retrieved and checked for the related references for further studies.[19]

Articles having the following criteria were included: (1) English was the main published language; (2) full-text articles can be obtained on electronic databases; (3) patients enrolled in the studies were all laboratory-confirmed positive testing for SARS-CoV-2 infection; and (4) articles included studies reporting detailed occurrence rates about olfactory or gustatory dysfunction.

3. RESULTS

The article search was started on June 20, and the last day to search was on April 10, 2021. Fig. 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature selection process to identify clinical studies regarding "anosmia or hyposmia or olfactory dysfunction or olfactory disorder or dysgeusia" use in COVID-19 or SARS-CoV-2. A total of 91 articles were retrieved. Among them, 66 articles were excluded after detailed screening due to the mismatched inclusion criteria. The remaining 25 articles were considered eligible for our reviewing process.

Among 25 included articles, 11 were from Europe (including four studies from Italy, two studies from France, one study from Germany, one study from Switzerland, two studies from Spain, and one study from 12 European hospitals), 10 were from Asia (including four studies from Iran, three studies from India, one study from Singapore, and two studies from China), one was from middle East, one was from Brazil, and two were from the United States. The study from China was the only one conducted from January to February 2020, and the most studies were conducted between March and October 2020.[20]

In regard to the evaluation of olfactory function, three articles used objective methods. In the article by Vaira et al, an orthonasal olfaction test by Connecticut Chemosensory Clinical Research Center was used. This simple test has been validated and is the most frequently used. It includes a butanol threshold assessment and an odor identification test using common odors to evaluate olfactory function.[21] Another article by Moein et al, the Persian version of the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT) was adopted in the research.[22] The UPSIT is a well-validated and trustworthy test that employs microencapsulated "scratch and sniff" odorants. The other eight

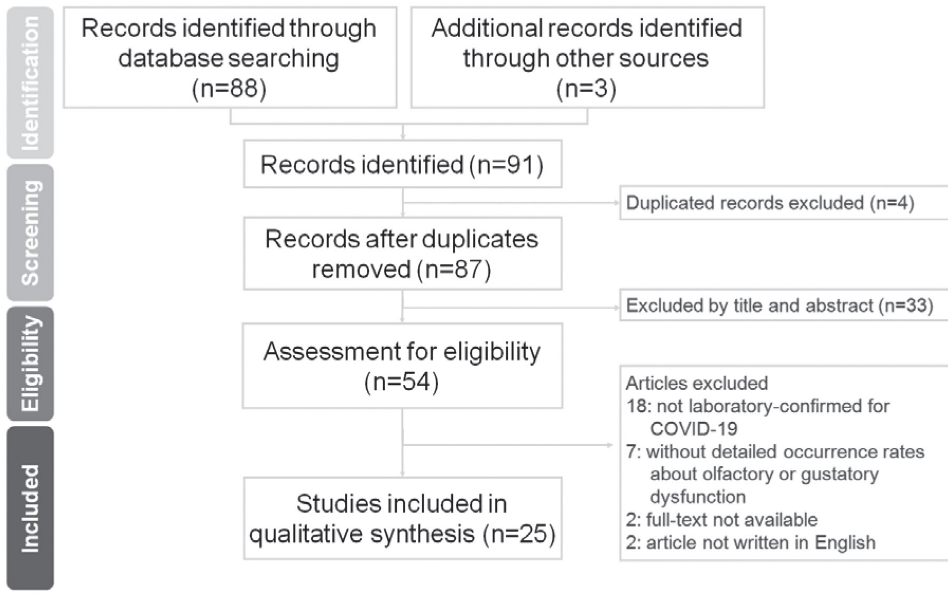

Fig. 1 The PRISMA flow diagram of the literature selection process regarding this study on "anosmia or hyposmia or olfactory dysfunction or olfactory disorder or dysgeusia" use in COVID-19 or SARS-CoV-2. PRISMA = preferred reporting items for systematic reviews and meta-analyses; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

articles retrieved clinical information about olfactory and gustatory function by retrospective electronic medical records review or questionnaire.

The number of patients in these articles ranged from 43 to 873 (one report of 10 069 participants was from Iran, in which 80.38% of participants reported concomitant olfactory and gustatory dysfunctions).[11] These included both outpatient and hospitalized patients in eight articles. The other articles only enrolled admitted inpatients, but there was no clear information about inpatients or outpatients in the rest of the studies. Some articles reported that olfactory and gustatory impairment as the first clinical manifestation, ranging from 4% to 35.5% of their studied patients, respectively.[5,13,23] The study conducted by Wee et al reported that 35 out of 154 (22.7%) COVID-19 positive patients had concomitant olfactory and taste disorders (OTDs). Among these patients with OTDs, three patients (8.6%) presented with isolated anosmia without any other clinical symptoms.[24] The recovery rate of the chemosensory dysfunction was mentioned in several articles with the percentage of 62% to 100%, respectively.[5,13,21,25–27]

In addition to the typical symptoms of COVID-19 related to respiratory symptoms (include fever, coughing, dyspnea, fatigue, shortness of breath, and muscle soreness), gastrointestinal (anorexia, nausea, vomiting, abdominal pain, and/or diarrhea) and hepatic manifestations (abnormal liver enzymes) have been indicated in clinical reports.[28,29] In the clinical diagnosis, gastrointestinal symptoms in COVID-19 patients have been associated with a longer duration of illness,[29] in which a few of them (around 5.5%) experienced taste or smell impairment. Because some patients only had mild fever, mild fatigue, or even no symptoms, fever becomes a critical but not the only initial symptom of infection.[29] Also, hypogeusia and hyposmia were suggested as early signs of infection.

A very wide range of the occurrence rate of olfactory or gustatory dysfunction has been shown. The lowest one is the study from Wuhan China in which the frequencies of neurologic manifestations were analyzed in 214 patients. They reported that only 5.1% of patients presented with anosmia and 5.6% of patients with ageusia.[20] However, Moein et al[22] described up to 98% of patients exhibited some degree of measured olfactory dysfunction by using UPSIT. According to the current evidence, subjective olfactory dysfunction was reported in up to 80% of patients, which suggested high prevalence rate of olfactory dysfunction in SARS-CoV-2.[30] In addition, higher prevalence may be indicated by subjective olfactory dysfunction and objective olfactory testing.

In M. Otte's report, only 62% of patients recovered from olfactory dysfunction. They stated that olfactory dysfunction may persist in patients after recovering from SARS-CoV-2.[31] Indeed, their recovery rate is the second-lowest from our study. Interestingly, in Paderno's report, the percentages of patients having olfactory or gustatory dysfunction are similar where the recovery rates for both dysfunctions are similar, too.[32] Although the case number is much smaller in the Paderno's report, this Italian report also showed similar recovery rates for olfactory dysfunction.[33] Unlike Paderno's report, where data were collected from outpatients, Jalessi's was collected from inpatients and had pretty low occurrence rates of olfactory and gustatory dysfunction.[34] Interestingly, two studies from France and Switzerland recruited >100 patients and have similar occurrence rates of olfactory and gustatory dysfunction (54%-65%).[35,36] Li and co-workers reported that olfactory dysfunction may last >3 months, especially in elderly patients.[37]

In Amanat's study, the most common non-neurologic manifestations were fever (81.1%), cough (76.1%), fatigue (36.1%), and shortness of breath (27.6%). The partial or full recovery of smell and taste dysfunctions was found in 95.2% of patients after 8 weeks and almost all the patients (97.3%) after 16 weeks. Patients with confirmed dysgeusia were mainly females (69.7%) and nonsmokers (66.7%).[38] However, in Thakur's study, over 70% of patients were diagnosed with olfactory dysfunction in which the majority of them were males and above 40 years of age.[39] Even in children, male patients showed significantly larger disturbances than girls.[40] The duration of olfactory and taste dysfunction varied from 2 to 15 days with an average of 5.7 days.[27] Mostly patients recovered their sense of smell within 1–2 weeks from the day of onset of anosmia.[40] Nevertheless, another report indicated that the fully recoverable olfactory dysfunction and dysgeusia had a mean duration of 2.5 days.[26] Olfaction dysfunction was significantly more prevalent in patients with mild flu syndrome in COVID-19, which may be a predictor of a good prognosis for this infection.[41]

Pooled data regarding study countries, study periods, case numbers, inpatient or outpatient medical visits, evaluation methods (subjective complaints of dysfunction or objective evaluation), and occurrence rate of olfactory or gustatory function are reported and listed in Tables 1 and 2.

4. DISCUSSION

Olfactory dysfunction has been classified into three general categories.[42,45,46] One is a conductive or transport impairment due to inflammation of the nasal mucosa since allergic rhinitis and rhinosinusitis (chronic or acute) may cause disruption of the mechanical function of olfaction. Another is a sensorineural impairment which is due to post-viral or drug-induced damage to the olfactory epithelium and nerves. The last one is central olfactory dysfunction which is common in CNS disorders such as head injury or neurodegenerative diseases.[43,45,46] Both neurotrophic targeting of olfactory neurons and infection on non-neural olfactory epithelial cells were suggested by previous articles investigating the pathophysiology of olfactory loss in COVID-19.[16,47] The COVID-19 may affect oral and nasal nervous systems and cause olfactory dysfunction. Until now, it is still not clear which olfactory mucosa cells are affected by COVID-19 and whether the virus can attack sensory cells or the OB directly. The improvement of the chemosensory function over time was reported in many studies.[5,13,21,24] This would favor a model that the olfactory epithelium may repair and regenerate rapidly after the removal of SARS-CoV-2, rather than permanent cell damage. Olfactory and gustatory dysfunctions are closely related to SARS-CoV-2 infection. Most cases were characterized as temporary olfactory dysfunction with restoration of normal olfaction within days to weeks after the COVID-19 recovery. However, the percentage of cases of permanent olfactory dysfunction is unclear.[44]

The pathophysiology of neuroinvasiveness and neurotropism of SARS-CoV-2, other than anosmia and dysgeusia, may be related to the CNS. In Freni's study, 46 of 50 patients had olfactory dysfunction.[48] They suggested that SARS-CoV-2 is likely having neuroinvasiveness and probably affects CNS through intranasal inoculation or trans-synaptic pathways because such alterations of sense (taste and smell) along with other discomforts point to the linkage of neurotropism to the virus.[44] Olfactory receptor neurons may connect the nasal cavity with the CNS where SARS-CoV-2 may act similar to other viruses since it has been known that several viruses utilize the olfactory nerve as an easy access to the CNS.[49] The possible mechanisms of transport are infection of olfactory receptor neurons or diffusion from channels of olfactory ensheathing cells and the damage may be from infection itself or the immune response. The symptoms may include severe meningoencephalitis or neurodegenerative diseases. Indeed, mild and severe neurologic symptoms, such as hyposmia, hypogeusia, headache, dizziness, acute necrotizing encephalopathy, meningitis and encephalitis, Guillain-Barre Syndrome, and altered mental status have been reported.[50,51] Galougahi's study demonstrated that patients with anosmia showed normal magnetic resonance imaging (MRI) of the olfactory tract in the early phase of COVID-19.[52] Thus, to find possible temporal evolution of the imaging, OB MRI may be performed both in the acute phase and in the follow-up as well as applying hybrid imaging (ex. single-photon emission computed tomography-MRI).[53]

Giacomelli et al[54] revealed that females were reported with OTDs more frequently than males. Klopfenstein et al[55] also described that younger patients and female patients were more likely to suffer from anosmia. Lechien et al revealed that hyposmia or anosmia as well as gustatory dysfunction occurred more frequently in females compared with males.[4] Moreover, patients with olfactory or taste disorder were younger. Beltrán-Corbellini et al[5] reported the age of patients with COVID-19 and new-onset smell and/or taste disorder were significantly younger than those COVID-19 patients without smell and/or taste disorder. Also, previous studies have shown that morbidity rate and symptoms are usually less severe in children and infants than those in adults.[29,56] Regarding these results, it will require more studies to evaluate the possible gender and age differences in the development of chemosensory disorder.

The gender differences in inflammatory reaction processes and the expression of the SARS-CoV-2 receptor, that is, ACE2, could be the important tracks which need further investigation. The high expression of ACE2 in the salivary glands may be the main cellular receptor of SARS-CoV-2, which supports viral fusion and subsequent inflammation. ACE2 is expressed from the type II alveolar cells of the lung and the epithelial cells of gastrointestinal tract. This indicates that the symptoms of gastrointestinal tract may be from the direct infection by the virus instead of being the immune response of the pulmonary infection. Thus, clinicians should be careful to suspicious symptoms (eg, fever, respiratory symptoms, olfactory disorder, or olfactory dysfunction) because patients may develop with new symptoms of gastrointestinal tract.[28,57] The roles of ACE2 and transmembrane protease serine 2 were indicated as the major key host-specific cellular moieties responsible for the cellular entry of the virus.[58] Previously, the direct infection of sensory neurons by SARS-CoV-2 causing the imbalance of angiotensin II has been indicated.[59] Also, Interleukin-6 may be involved in dysgeusia since it could affect the nearby thalamus and eventually both the gustatory and olfactory nerve pathways.[60] Thus, these reports suggest that inflammatory cytokines, angiotensin II accumulation, and even the subsequent dysfunction of supporting non-neuronal cells in the mucosa due to the cytotoxicity all lead to the olfactory dysfunction of COVID-19.[58–60]

Discrepancy of self-reported and quantitative olfactory dysfunction was reported by Moein et al. They revealed a high rate of objective olfactory dysfunction (about 98%) of COVID-19 patients measuring by UPSIT. However, patients who were sensitive to the olfactory deficit before receiving the evaluation measured only 35% dysfunction.[22] This is considered owing to a general unawareness or under-reporting of hyposmia.[46] The prognostic significance of olfactory dysfunction in COVID-19 patients is an interesting and to-be-discussed issue. A study by Moein et al,[22] using the COVID-19 treatment guidance algorithm of Massachusetts General Hospital, disclosed that there was no correlation of the UPSIT scores with the disease severity. Beltrán-Corbellini et al[5] revealed that, regarding the COVID-19 severity criterion (needed for mechanical ventilation and tocilizumab usage), there was no significant difference between patients who presented new-onset smell and/or taste disorder and those who did not. However, Yan et al reported that COVID-19 patients being anosmic/hyposmic were >10-fold less likely to be admitted than those who were normosmic on multivariable logistic regression analysis.[61] They also found that anosmia and sputum production associated inversely with odds ratio of 0.26 which suggested that anosmic COVID-19 patients are not likely to have the symptoms presented when a more serious lower respiratory tract inflammation occurred.[62] We also noticed that the reported proportions of chemosensory loss were around half the level in the hospital-based survey compared to an outpatient-based survey.[5,25,54] The data collected in the current study are retrospective and limited by lack of objective testing for smell and taste disturbance. It needs to be evaluated through further clinical studies on a global research to discover its pathogenesis, prognosis, and the correlation between disease severity and olfactory dysfunction. Also, since nasal and gustatory symptoms are early signs, even before fever, they can be exploited as criteria for quarantining patients in an earlier stage or for performing the swab for virus

Table 1

List of the reviewed studies regarding the olfactory or taste dysfunction in patients with COVID-19

No.	Country	Study type	Study period in 2020	Subjective or objective	COVID+ patient number	Inpatient/outpatient numbers	Symptoms (%)				Recovery rate (%)	First symptom (%)
							OD or TD	OD	TD	OD and TD		
1	Italy	Single center	31 March to 6 April	Objective	72	25/47	73.6	14.4	12.5	41.7	66	18.1
2	Singapore	Single hospital	26 March to 10 April	Subjective	154	Both	22.7					8.6
3	Iran	Single hospital	21 March to 5 April	Objective	60	Inpatients		98				
4	Italy	Single hospital	19 March	Subjective	59	Inpatients	33.9	5.1	10.2	18.6		
5	USA	Single institute	3-29 March	Subjective	59	Mostly outpatients		67.8	71.2		72.5	
6	Spain	2 centers	23-25 March	Subjective	79	Inpatients	39.2	31.7	35.4	39.2	56.7	35.5
7	Europe	12 hospitals	N/A	Subjective	417	N/A		85.6	88.8		72.6 (for OD)	11.8
8	China	3 centers	16 January to 19 February	Subjective	214	Inpatients		5.1	5.6			
9	USA	Single hospital	3 March to 8 April	Subjective	128	26/ 102		I: 26.9 O: 66.7	I: 23.1 O: 62.7			
10	France	Single hospital	1-17 March	Subjective	114	Both		47				
11	Germany	Single hospital		Objective	50	Outpatients		94			62	
12	Italy	home-quarantined	27 March to 5 May	Subjective	151	Outpatients		83	89		87 (OD)/82 (TD)	14-OD/16-TD
13	Italy	Single hospital	1 Febuary to 24 April	Subjective	43	20/23		60			85	
14	Iran	Single hospital	February to March	Subjective	100	Inpatients		24	16		95 (OD)	7-OD
15	France	Single hospital	1-31 March	Subjective	229	Mostly outpatients		61	54		96 (OD)/95 (TD)	4
16	Switzerland	Single hospital	3 March to 17 April	Subjective	103	Inpatients and outpatients		61	65			9
17	China	Multicenter	N/A		145	N/A					89	
18	Turkey	2 centers	25 March to 20 April	Subjective	81	Inpatients	35.8	61.7	27.2	27.7		
19	Iran	Single Medical Council	12 March to 17 March	Objective	10,069	Participants		60.9	76.2	80.4		
20	Iran	3 hospitals	7 April to 18 November	Objective	873	Inpatients		58.6	41.4	64.3	95.2	
21	India	Single hospital	September to October	Objective	250	Inpatients	71.6	49.6	68.5	66.4		
22	India	Single hospital	March	Objective	203	Inpatients	37.8	18.4	13.1		100	7.23
23	Spain	Single center	March to May		126	N/A	54.7					
24	Brazil	Single hospital	March to January		261	Inpatients	66.28					
25	India	Single hospital	May to August		141	N/A	28.4	24.1	24.1	19.8	100	13.5

OD = olfactory dysfunction; TD = taste dysfunction.

Table 2

The characteristics and references regarding the olfactory or taste dysfunction in patients with COVID-19

No.	Country	Other characteristics	Reference no.
1	Italy	No indication	14
2	Singapore	Fever (60%), cough (28.5%)	20
3	Iran	Fever (77%), cough (58%), shortness of breath (52%), headache (37%), myalgia (8%)	15
4	Italy	Fever (72.8%), cough (37.3%), dyspnea (25.4%), sore throat (1.7%), arthralgia (5.1%)	42
5	USA	Fatigue (81.4%), fever (69.5%), myagia or arthralgia (62.7%), cough (66.1%), headache (66.1%), dyspnea (54.2%), diarrhea (47.5%)	21
6	Spain	No indication	16
7	Europe	Cough, myalgia, loss of appetite, diarrhea, fever, headache, asthemia	13
8	China	Fever 61.7%, cough 50%, anorexia 31.8%, diarrhea 19.2%	4
9	USA	Fatigue, diarrhea, fever, cough, dyspnea, sore throat, nasal obstruction, headache, sputum production	16
10	France	Fatigue 93%, cough 87%, headache 82%, fever 74%, myalgia 74%, arthralgia 72%, diarrhea 52%	43
11	Germany	An established smelling test (ex. Sniffin' Sticks test) may be necessary to characterize olfactory dysfunction objectively	31
12	Italy	Patients had a recurrence of OD and GD after complete resolution of symptoms (2%)	32
13	Italy	Olfactory dysfunction suffered headaches (52%)	33
14	Iran	Fever and myalgia were the most common symptoms (30%)	34
15	France	47 patients (33.57%) reported sore/dry/tingling (nasal cavity)	35
16	Switzerland	The severity of shortness of breath was strongly correlated with olfactory dysfunction	36
17	China	Olfactory dysfunction is more common in the elderly population	37
18	Turkey	In all such cases, SARS-CoV-2 was confirmed by 2019 nCoV real-time PCR laboratory testing	44
19	Iran	10.55% of responders had a history and about 1.1% were hospitalized due to respiratory problems. The duration of anosmia ranged from 0 to 30 days	11
20	Iran	64.3% of patients were with smell and taste dysfunctions, which were more common among females and non-smokers	38
21	India	179 patients were diagnosed with Olfactory dysfunction, of which the majority were males. Most of the patients were above 40 years old	39
22	India	Mean duration of symptoms was around 2.5 days	26
23	Spain	Male patients showed significantly larger disturbances than girls in both groups	40
24	Brazil	In approximately 56.58% of the individuals, the smell alterations lasted between 9 days and 2 months	41
25	India	The duration of olfactory and taste dysfunction varied from 2 to 15 days with an average of 5.7 days	27

detection. Future prospective studies with a larger population and standardized smell and taste tests are essential to investigate whether ambulatory and hospitalized COVID-19 patients present differential clinical course due to diverse viral spread routes. Moreover, the need to clarify the relationship between anosmia or ageusia and the prognostic potential on the severity of COVID-19 is waiting to be fulfilled.

In conclusion, olfactory dysfunction has been recognized as a significant COVID-19 symptom and has growingly acquired acceptance as a public health means to confirm SARS-CoV-2 infection. It presents as one of the early clinical symptoms of COVID-19, and is associated with better prognosis. The clinical evaluation and functional tests of olfactory dysfunction including precise grading and duration of the complaints are becoming a high priority. Further study and validation regarding the symptom's severity, gene, age and gender susceptibility, as well as prognostic significance should be executed as the pandemic progresses. This article is a narrative review with the aim of analyzing current literatures on post-viral olfactory dysfunction related to COVID-19 and may facilitate future research on the diagnosis and treatment of SARS-CoV-2 infection.

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REFERENCES

1. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. *Features, Evaluation, and Treatment of Coronavirus (COVID-19)*. 2021 In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
2. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: an overview. *J Chin Med Assoc* 2020;**83**:217–20.
3. Coronavirus Outbreak. Available at https://www.worldometers.info/coronavirus/. Accessed April 20, 2020.
4. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020;**277**:2251–61.
5. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. *Eur J Neurol* 2020;**27**:1738–41.
6. Luers JC, Rokohl AC, Loreck N, Wawer Matos PA, Augustin M, Dewald F, et al. Olfactory and gustatory dysfunction in coronavirus disease 2019 (COVID-19). *Clin Infect Dis* 2020;**71**:2262–4.
7. Hoffman HJ, Rawal S, Li CM, Duffy VB. New chemosensory component in the U.S. National Health and Nutrition Examination Survey (NHANES): first-year results for measured olfactory dysfunction. *Rev Endocr Metab Disord* 2016;**17**:221–40.

8. Landis BN, Hummel T. New evidence for high occurrence of olfactory dysfunctions within the population. *Am J Med* 2006;**119**:91–2.
9. Welge-Lüssen A, Wolfensberger M. Olfactory disorders following upper respiratory tract infections. *Adv Otorhinolaryngol* 2006;**63**:125–32.
10. Walker A, Hopkins C, Surda P. Use of google trends to investigate loss-of-smell-related searches during the COVID-19 outbreak. *Int Forum Allergy Rhinol* 2020;**10**:839–47.
11. Bagheri SH, Asghari A, Farhadi M, Shamshiri AR, Kabir A, Kamrava SK, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak in Iran. *Med J Islam Repub Iran* 2020;**34**:62.
12. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny JC 3rd. COVID-19 anosmia reporting tool: initial findings. *Otolaryngol Head Neck Surg* 2020;**163**:132–4.
13. Brodwin E. Doctors warn an inability to smell could be a symptom of COVID-19 - but caution the evidence is preliminary. Available at https://www.statnews.com/2020/03/23/coronavirus-sense-of-smell-anosmia/. Published March 23, 2020. Accessed April 15, 2020.
14. Garavello W, Galluzzi F. Olfactory dysfunction in COVID-19. *Otolaryngol Head Neck Surg* 2020;**163**:182.
15. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol* 2018;**92**:e00404–18.
16. Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv* 2020;**6**:eabc5801.
17. Printza A, Katotomichelakis M, Metallidis S, Panagopoulos P, Sarafidou A, Petrakis V, et al. The clinical course of smell and taste loss in COVID-19 hospitalized patients. *Hippokratia* 2020;**24**:66–71.
18. Ho TC, Wang YH, Chen YL, Tsai WC, Lee CH, Chuang KP, et al. Chloroquine and hydroxychloroquine: efficacy in the treatment of the COVID-19. *Pathogens* 2021;**10**:217.
19. Rocke J, Hopkins C, Philpott C, Kumar N. Is loss of sense of smell a diagnostic marker in COVID-19: a systematic review and meta-analysis. *Clin Otolaryngol* 2020;**45**:914–22.
20. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;**77**:1–9.
21. Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck* 2020;**42**:1252–8.
22. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol* 2020;**10**:944–50.
23. Gómez-Iglesias P, Porta-Etessam J, Montalvo T, Valls-Carbó A, Gajate V, Matías-Guiu JA, et al. An online Observational Study of patients with olfactory and gustory alterations secondary to SARS-CoV-2 infection. *Front Public Health* 2020;**8**:243.
24. Wee LE, Chan YFZ, Teo NWY, Cherng BPZ, Thien SY, Wong HM, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. *Eur Arch Otorhinolaryngol* 2020;**277**:2389–90.
25. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol* 2020;**10**:806–13.
26. Yadav V, Bhagat S, Sharma DK, Sibia RPS, Pandav R, Sandhu VP. Olfactory and gustatory dysfunction in COVID-19 patients: a tertiary care institute experience in India. *Indian J Otolaryngol Head Neck Surg* 2021:1-8.
27. Kumar L, Kahlon N, Jain A, Kaur J, Singh M, Pandey AK. Loss of smell and taste in COVID-19 infection in adolescents. *Int J Pediatr Otorhinolaryngol* 2021;**142**:110626.
28. Guo JY, Chen CY. How is the digestive system affected by coronavirus disease? *J Chin Med Assoc* 2020;**83**:795–6.
29. Tsai PH, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, et al. Clinical manifestation and disease progression in COVID-19 infection. *J Chin Med Assoc* 2021;**84**:3–8.
30. Sedaghat AR, Gengler I, Speth MM. Olfactory dysfunction: a highly prevalent symptom of COVID-19 with public health significance. *Otolaryngol Head Neck Surg* 2020;**163**:12–5.
31. Otte MS, Klussmann JP, Luers JC. Persisting olfactory dysfunction in patients after recovering from COVID-19. *J Infect* 2020;**81**:e58.
32. Paderno A, Mattavelli D, Rampinelli V, Grammatica A, Raffetti E, Tomasoni M, et al. Olfactory and gustatory outcomes in COVID-19: a prospective evaluation in nonhospitalized subjects. *Otolaryngol Head Neck Surg* 2020;**163**:1144–9.
33. D'Ascanio L, Pandolfini M, Cingolani C, Latini G, Gradoni P, Capalbo M, et al. Olfactory dysfunction in COVID-19 patients: prevalence and prognosis for recovering sense of smell. *Otolaryngol Head Neck Surg* 2021;**164**:82–6.
34. Jalessi M, Barati M, Rohani M, Amini E, Ourang A, Azad Z, et al. Frequency and outcome of olfactory impairment and sinonasal involvement in hospitalized patients with COVID-19. *Neurol Sci* 2020;**41**:2331–8.
35. Gorzkowski V, Bevilacqua S, Charmillon A, Jankowski R, Gallet P, Rumeau C, et al. Evolution of olfactory disorders in COVID-19 patients. *Laryngoscope* 2020;**130**:2667–73.
36. Speth MM, Singer-Cornelius T, Oberle M, Gengler I, Brockmeier SJ, Sedaghat AR. Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics. *Otolaryngol Head Neck Surg* 2020;**163**:114–20.
37. Li J, Long X, Zhu C, Wang H, Wang T, Lin Z, et al. Olfactory dysfunction in recovered coronavirus disease 2019 (COVID-19) patients. *Mov Disord* 2020;**35**:1100–1.
38. Amanat M, Rezaei N, Roozbeh M, Shojaei M, Tafakhori A, Zoghi A, et al. Neurological manifestations as the predictors of severity and mortality in hospitalized individuals with COVID-19: a multicenter prospective clinical study. *BMC Neurol* 2021;**21**:116.
39. Thakur K, Sagayaraj A, Prasad KC, Gupta A. Olfactory dysfunction in COVID-19 patients: findings from a tertiary rural centre. *Indian J Otolaryngol Head Neck Surg* 2021. [Online ahead of print].
40. Concheiro-Guisan A, Fiel-Ozores A, Novoa-Carballal R, González-Duran ML, Portugués de la Red M, Martínez-Reglero C, et al. Subtle olfactory dysfunction after SARS-CoV-2 virus infection in children. *Int J Pediatr Otorhinolaryngol* 2021;**140**:110539.
41. Mendonça CV, Mendes Neto JA, Suzuki FA, Orth MS, Machado Neto H, Nacif SR. Olfactory dysfunction in COVID-19: a marker of good prognosis? *Braz J Otorhinolaryngol* 2021; S1808-8694:30240-8.
42. Liu J, Pinto JM, Yang L, Li L, Sun J, Miao X, et al. Gender difference in Chinese adults with post-viral olfactory disorder: a hospital-based study. *Acta Otolaryngol* 2016;**136**:976–81.
43. Imamura F, Hasegawa-Ishii S. Environmental toxicants-induced immune responses in the olfactory mucosa. *Front Immunol* 2016;**7**:475.
44. Altin F, Cingi C, Uzun T, Bal C. Olfactory and gustatory abnormalities in COVID-19 cases. *Eur Arch Otorhinolaryngol* 2020;**277**:2775–81.
45. Miwa T, Ikeda K, Ishibashi T, Kobayashi M, Kondo K, Matsuwaki Y, et al. Clinical practice guidelines for the management of olfactory dysfunction - secondary publication. *Auris Nasus Larynx* 2019;**46**:653–62.
46. Schwartz JS, Tajudeen BA, Kennedy DW. Diseases of the nasal cavity. *Handb Clin Neurol* 2019;**164**:285–302.
47. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci* 2020;**11**:995–8.
48. Freni F, Meduri A, Gazia F, Nicastro V, Galletti C, Aragona P, et al. Symptomatology in head and neck district in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2. *Am J Otolaryngol* 2020;**41**:102612.
49. van Riel D, Verdijk R, Kuiken T. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol* 2015;**235**:277–87.
50. Abboud H, Abboud FZ, Kharbouch H, Arkha Y, El Abbadi N, El Ouahabi A. COVID-19 and SARS-Cov-2 infection: pathophysiology and clinical effects on the nervous system. *World Neurosurg* 2020;**140**:49–53.
51. Baig AM, Sanders EC. Potential neuroinvasive pathways of SARS-CoV-2: deciphering the spectrum of neurological deficit seen in coronavirus disease-2019 (COVID-19). *J Med Virol* 2020;**92**:1845–57.
52. Galougahi MK, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. Olfactory bulb magnetic resonance imaging in SARS-CoV-2-induced anosmia: the first report. *Acad Radiol* 2020;**27**:892–3.
53. Shiga H, Taki J, Yamada M, Washiyama K, Amano R, Matsuura Y, et al. Evaluation of the olfactory nerve transport function by SPECT-MRI fusion image with nasal thallium-201 administration. *Mol Imaging Biol* 2011;**13**:1262–6.
54. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute

respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis* 2020;**71**:889–90.
55. Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. *Med Mal Infect* 2020;**50**:436–9.
56. Jeng MJ. Coronavirus disease 2019 in children: current status. *J Chin Med Assoc* 2020;**83**:527–33.
57. Luo YH, Chiu HY, Weng CS, Chen YM. Overview of coronavirus disease 2019: treatment updates and advances. *J Chin Med Assoc* 2020;**83**:805–8.
58. Gupta K, Mohanty SK, Mittal A, Kalra S, Kumar S, Mishra T, et al. The cellular basis of loss of smell in 2019-nCoV-infected individuals. *Brief Bioinform* 2021;**22**:873–81.
59. Mahmoud MM, Abuohashish HM, Khairy DA, Bugshan AS, Khan AM, Moothedath MM. Pathogenesis of dysgeusia in COVID-19 patients: a scoping review. *Eur Rev Med Pharmacol Sci* 2021;**25**:1114–34.
60. Mastrangelo A, Bonato M, Cinque P. Smell and taste disorders in COVID-19: From pathogenesis to clinical features and outcomes. *Neurosci Lett* 2021;**748**:135694.
61. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol* 2020;**10**:821–31.
62. Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ. Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. *Arch Clin Neuropsychol* 2011;**26**:260–9.