



COVID-19 Viral Load in the Severity of and Recovery From Olfactory and Gustatory Dysfunction

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Objectives/Hypothesis: This study investigated olfactory and gustatory dysfunction in the 2020 novel coronavirus disease (COVID-19) patients, and their correlations with viral load evaluation.

Study Design: Prospective cross-sectional cohort study.

Methods: One hundred forty-three symptomatic patients being screened for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were invited to participate. The clinical data of 83 confirmed COVID-19 subjects were collected, with 60 patients who were symptomatic but negative for COVID-19 recruited as controls. The prevalence and severity of and recovery time for olfactory and gustatory dysfunction, and cycle threshold (Ct) values from a SARS-CoV-2 polymerase chain reaction assay of nasopharyngeal and deep throat swabs were collected. Their correlations with Ct values were reported.

Results: Thirty-nine (47.0%) and 36 (43.4%) COVID-19 patients reported olfactory and gustatory dysfunction, respectively. The results of one-way analysis of variance did not show statistically significant relationships between the Ct values and severity of olfactory and gustatory dysfunction ($P = .780$ and $P = .121$, respectively). Among the COVID-19 patients who reported smell and taste loss, 28/39 (71.8%) and 30/36 (83.3%) experienced complete recovery, respectively. The mean recovery time was 10.3 ± 8.1 days for olfactory dysfunction and 9.5 ± 6.8 days for gustatory dysfunction. The recovery time was not correlated with the Ct values (Pearson correlation coefficient, smell: -0.008 , $P = .968$; taste: -0.015 , $P = .940$).

Conclusions: There is a high prevalence of olfactory and gustatory dysfunction in COVID-19. However, the severity of and recovery from these symptoms have no correlations with the viral load of SARS-CoV-2.

Key Words: Olfactory, gustatory, COVID-19, viral load.

Level of Evidence: 4

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INTRODUCTION

The 2020 novel coronavirus disease (COVID-19) pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and is considered a worldwide threat to human health. The 124th situation report issued by the World Health Organization on May 23, 2020 listed 5,103,006 confirmed COVID-19 cases and 333,401 deaths worldwide.¹ Although the classical

respiratory symptoms of COVID-19 such as fever, cough, expectoration, dyspnea, and sore throat are widely used to screen suspected patients with strong contact history or travel history,² acute olfactory and gustatory loss have aroused significant attention and discussion for their potential application in the diagnosis of this viral illness during the pandemic.^{3–6} In response to the United States and European countries reporting a high prevalence of smell (68%–85.6%) and taste dysfunction (71%–88%) among patients with COVID-19,^{7–9} the American Academy of Otolaryngology–Head and Neck Surgery has advocated the addition of anosmia, hyposmia, and dysgeusia to the list of screening tools for possible infection.¹⁰

Given the strong evidence that olfactory and gustatory dysfunction may be important presenting symptoms of COVID-19 infection, researchers have paid increasing attention to the pathophysiology and prognosis of these sensory impairments. In some studies, it has been observed that the prevalence and severity of COVID-19 infection have an association with the viral load of SARS-CoV-2 as determined from the sputum and nasopharyngeal swab (NPS).^{11,12} However, there have been insufficient studies in patients with COVID-19 to provide enough detail to understand the relation between disease severity and viral RNA load kinetics. Whether this

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relationship is also valid for olfactory and gustatory impairment should be an interesting topic for further investigation.

COVID-19 diagnosis is confirmed by reverse transcriptase polymerase chain reaction (PCR), which detects viral nucleic acid in either sputum, saliva, or nasal discharge from patients.¹³ Real-time PCR yields a cycle threshold (Ct) value, which is defined as the number of amplification cycles required to reach a threshold for detection of the viral nucleic acid. The Ct level is inversely proportional to the amount of the virus in a sample. Consequently, the Ct level may indirectly indicate the viral replication activity level, which affects the infectivity of SARS-CoV-2 in a patient.¹⁴ Higher SARS-CoV-2 loads have been detected in the nose than in the throat.¹⁵ However, at the time of writing, no study has investigated the correlation between Ct values, which indirectly reflect the viral load or activity, and the severity of or recovery from olfactory or gustatory impairment in individual patients. Here, we describe our evaluation of olfactory and gustatory dysfunction and the prognosis of both symptoms in patients with COVID-19 in Hong Kong, and their correlation with the viral load as detected by combined NPSs and throat swabs (TSs).

MATERIALS AND METHODS

The prospective study was approved by the Research Ethics Committee of Kowloon Central and Kowloon East Cluster of the Hospital Authority of Hong Kong. Informed consent was obtained from all patients. Patients who had been tested for SARS-CoV-2, whether positive or negative, and were admitted to the United Christian Hospital and Tseung Kwan O Hospital between February 8 and April 15, 2020 were recruited. The inclusion criteria were age ≥ 18 years and a SARS-CoV-2 test history. The exclusion criteria were age < 18 years and having preexisting olfactory and gustatory disturbances. In Hong Kong, the reporting criteria for a suspected COVID-19 case are fever, respiratory symptoms, or pneumonia and a recent history of travel from any country with active community transmission of COVID-19 or close contact with any confirmed case within 14 days. All suspected cases are tested for SARS-CoV-2, and positive cases are admitted to the hospital for surveillance and isolation. The COVID-19 group represented symptomatic patients with a positive test result for SARS-CoV-2 from combined NPS + TS. The control group represented symptomatic patients with suspected COVID-19 who had a negative SARS-CoV-2 test result.

A Chinese-language questionnaire was distributed to the wards to collect the patients' clinical data via phone contact or online submission. Information was collected on the onset and severity of any nasal and respiratory symptoms such as rhinorrhea, purulent nasal discharge, nasal blockage, epistaxis, cough, sputum, dyspnea, fever, anosmia, hyposmia, and dysgeusia. The questionnaire for smell and taste loss was combined and used a visual analog scale of 1 (anosmia/ageusia) to 10 (normal). The patients were asked to rate the severity of smell and taste loss separately. Follow-up phone interviews with patients at 4 to 6 weeks were arranged to enquire about their recovery from smell and taste impairments.

The participants' demographic characteristics, travel history, occupation, contact history, and laboratory findings were extracted from electronic medical records. Of particular

importance were the Ct values from a SARS-CoV-2 PCR assay of combined NPS + TS.

All statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY). Symptom variables included in the comparisons were rhinorrhea, purulent nasal discharge, nasal blockage, epistaxis, cough, sputum, dyspnea, fever, and olfactory and gustatory changes. Pearson χ^2 test and the Mann-Whitney *U* test were used to compare the demographic statistics and questionnaire results between the groups. The relationship between olfactory and gustatory dysfunctions was analyzed using Spearman's rank correlation coefficient. The effects of NPS + TS PCR results on olfactory and gustatory dysfunction were analyzed using one-way analysis of variance (ANOVA). The relationship between the NPS + TS PCR result and recovery time was analyzed using Pearson's correlation coefficient. A *P* value of $< .05$ was considered statistically significant.

RESULTS

Ninety-nine confirmed COVID-19 patients were invited to participate, and 83 were eventually recruited. Ninety-one control patients were invited to participate, but only 60 were eventually recruited. The COVID-19 group comprised 48 men and 35 women, whereas the control group comprised 26 men and 34 women, and no statistically significant difference was found between the two groups (*P* = .087). The mean ages were 36.4 ± 16.3 years in the COVID-19 group and 38.4 ± 14.2 years in the control group (*P* = .305). The COVID-19 and control groups did not differ significantly in terms of basic demographics. The most common presenting symptoms of the COVID-19 group were cough (59.0%), fever (50.6%), and expectoration (41.0%), whereas only 3% to 6% reported purulent and blood-stained nasal discharge. Dyspnea and fever were more common among the confirmed cases than among the controls (dyspnea: confirmed, 21.7% vs. control, 8.3%; *P* = .032) (fever: confirmed, 50.6% vs. control, 23.3%; *P* = .001). The presence of rhinorrhea, nasal blockage, purulent nasal discharge and epistaxis, cough, and expectoration did not differ significantly between the groups (Table I).

In terms of smell impairment, 39 of the COVID-19 patients (47.0%) reported olfactory dysfunction, with 18 (21.7%) reporting anosmia and 21 (25.3%) reporting hyposmia. Moreover, 31 (79.4%) of these patients reported reduction in smell by 5 out of 10 or less. Four patients presented with olfactory dysfunction as their only symptom. Nine patients reported olfactory dysfunction as the earliest symptom, among others. In contrast, none of the control patients reported any olfactory dysfunction, and this effect was statistically significant (*P* $< .05$). The mean age of patients who reported olfactory dysfunction was 29.8 ± 11.2 years, and there was no sex predilection in this subgroup (*P* = .255). Rhinorrhea, nasal blockage, and fever were more commonly reported within the olfactory dysfunction subgroup (*P* = .025, *P* $< .01$, and *P* = .021, respectively).

In taste impairment, 36 COVID-19 patients (43.4%) reported a gustatory dysfunction, with seven (8.4%) reporting ageusia and 29 (34.9%) reporting hypogeusia. Of these 36 patients, 29 (80.6%) reported reduction in taste by 5 out of 10 or less. Again, none of the patients in

TABLE I.
Demographic Data and Presenting Symptoms of Patients.

Characteristics	COVID-19 Group, n = 83	Control Group, n = 60	P Value
Male: female ratio	48:35	26:34	.087*
Age range, yr	18–71	18–65	
Mean age, yr	36.4 ± 16.3	38.4 ± 14.2	.305†
History of allergic rhinitis, no./total no. (%)	16/83 (19.3)	16/60 (35)	.295*
Medication for nasal symptoms, no./total no. (%)	4/83 (4.8)	6/60 (10)	.231
History of nasal surgery, no./total no.	0/83	0/60	
Rhinorrhea, no./total no. (%)	32/83 (38.6)	27/60 (45)	.440*
Nasal blockage, no./total no. (%)	31/83 (37.3)	21/60 (35)	.773*
Purulent nasal discharge, no./total no. (%)	3/83 (3.6)	1/60 (1.67)	.486*
Epistaxis, no./total no. (%)	5/83 (6.0)	3/60 (5.0)	.793*
Cough, no./total no. (%)	49/83 (59.0)	28/60 (46.7)	.143*
Expectorant, no./total no. (%)	34/83 (41.0)	25/60 (41.7)	.933*
Dyspnea, no./total no. (%)	18/83 (21.7)	5/60 (8.3)	.032*
Subjective fever, no./total no. (%)	43/83 (50.6)	14/60 (23.3)	.001*
Documented fever on admission, no./total no. (%)	23/83 (27.7)	7/60 (13.2)	.020*
Smell change, no./total no. (%)			
1 (anosmia)	18/83 (21.7)	0/60 (0)	
2–5	13/83 (15.7)	0/60 (0)	
6–9	8/83 (9.6)	0/60 (0)	
10 (normal)	44/83 (53)	60/60 (100)	<.001*
Taste change, no./total no. (%)			
1 (ageusia)	7/83 (8.4)	0/60 (0)	
2–5	22/83 (26.5)	0/60 (0)	
6–9	7/83 (8.4)	0/60 (0)	
10 (normal)	47/83 (56.6)	60/60 (100)	<.001*

*Pearson χ^2 test.

†Mann-Whitney *U* test.

the control group reported any gustatory dysfunction ($P < .05$). The mean age of patients who reported a taste dysfunction was 30.6 ± 11.9 years. There was a significant correlation between pronounced olfactory dysfunction and pronounced gustatory dysfunction (Spearman's correlation coefficient = 0.797, $P < .01$).

The mean Ct value of SARS-CoV-2 PCR tests in the COVID-19 group was 28.3 ± 6.7 . Subgroup analysis was performed according to the severity of olfactory and gustatory loss (1: anosmia and ageusia, 2–5: severe hyposmia and hypogeusia, 6–9: mild to moderate hyposmia and hypogeusia, 10: normal). The Ct values of different subgroups of patients ranged from 27.3 ± 6.3 to 34.0 ± 2.5 . The results of the one-way ANOVA did not show statistically significant relationships between the Ct value and the severity of olfactory and gustatory impairment ($P = .780$ and $P = .121$, respectively) (Table II).

TABLE II.
Ct Values From SARS-CoV-2 Polymerase Chain Reaction Assays in Patients With Confirmed COVID-19.

	No. of Patients, n = 83	Ct Value	P Value
Smell change			
1 (anosmia)	18	29.6 ± 5.8	
2–5	13	28.6 ± 7.4	
6–9	8	28.0 ± 7.2	
10 (normal)	44	27.7 ± 6.8	.780*
Taste change			
1 (ageusia)	7	34.0 ± 2.5	
2–5	22	27.3 ± 6.3	
6–9	7	27.7 ± 5.6	
10 (normal)	47	27.9 ± 7.1	.121*

*One-way analysis of variance.

Ct = cycle threshold; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

TABLE III.
Ct Values From SARS-CoV-2 Polymerase Chain Reaction Assays in COVID-19 Patients With Complete Recovery of Smell Function.

Subject	Smell Status at Presentation	Recovery Time, d	Ct Value
1	5	17	31.08
2	3	13	29.60
3	8	1	35.94
4	5	15	37.01
5	1	7	34.70
6	1	5	24.75
7	1	9	29.52
8	3	5	15.54
9	4	18	25.83
10	4	2	36.55
11	6	15	32.79
12	8	1	29.84
13	2	30	29.75
14	1	29	35.44
15	8	18	25.71
16	3	22	21.20
17	1	7	35.81
18	9	4	32.45
19	8	5	31.84
20	2	7	17.84
21	1	5	30.63
22	1	7	31.25
23	1	3	34.95
24	1	7	31.45
25	1	12	35.80
26	1	4	20.78

The recovery time was not correlated with the Ct value of nasopharyngeal and deep throat swab polymerase chain reaction (Pearson correlation coefficient: -0.008 , $P = .968$).

Ct = cycle threshold; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

TABLE IV.
Ct Values From SARS-CoV-2 Polymerase Chain Reaction Assays in COVID-19 Patients with Complete Recovery of Taste Function.

Subject	Taste Status at Presentation	Recovery Time, d	Ct Value
1	2	17	31.08
2	3	13	29.60
3	1	6	35.94
4	1	7	34.70
5	3	5	24.75
6	5	9	20.52
7	9	10	22.48
8	2	5	15.54
9	7	2	36.55
10	3	15	32.79
11	2	30	29.75
12	3	19	35.44
13	8	18	25.71
14	3	22	21.20
15	1	7	35.81
16	5	4	32.45
17	9	5	31.84
18	3	7	17.84
19	1	7	31.25
20	1	12	35.80
21	2	4	27.09
22	8	3	22.60
23	5	6	34.11
24	4	7	25.89
25	1	4	34.60
26	5	2	27.69
27	7	10	23.21

The recovery time was not correlated with the Ct value of nasopharyngeal and deep throat swab polymerase chain reaction (Pearson correlation coefficient: -0.015 , $P = .940$).

Ct = cycle threshold; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Among the COVID-19 patients who reported olfactory and gustatory loss, 28/39 (71.8%) and 30/36 (83.3%) had experienced complete recovery, respectively, at the time of writing. Two patients with olfactory loss and three with gustatory loss could not recall their recovery time. The mean recovery time was 10.3 ± 8.1 days (1–30 days) for the 26 patients with olfactory dysfunction, and 9.5 ± 6.8 days (2–30 days) for the 27 patients with gustatory loss. Finally, there were no correlations between the recovery time for olfactory or gustatory dysfunction and the Ct value of PCR from the nasopharyngeal and deep throat swabs, which indirectly reflected the viral load of SARS-CoV-2 (Pearson's correlation coefficient, olfactory: -0.008 , $P = .968$; gustatory: -0.015 , $P = .940$) (Tables III and IV).

DISCUSSION

In our cohort of COVID-19 patients in Hong Kong, the prevalence of olfactory and gustatory dysfunction was 47.0% and 43.4%, respectively, consistent with the symptom

reports of COVID-19 cases in Western populations.^{16–18} However, our findings demonstrate that olfactory and gustatory dysfunction are even more specific than other common symptoms widely adopted to screen COVID-19 infection, as none of the symptomatic patients with negative SARS-CoV-2 test results in our study complained of smell or taste impairment.

Based on evidence that the viral load of SARS-CoV-2 is higher in the nasopharynx than the oropharynx,¹⁹ we postulate a higher prevalence of olfactory than gustatory disturbance. We could not confirm the relationship between nasopharyngeal (oropharyngeal) load and olfactory (gustatory) disturbance in our study, as the PCR was performed in specimens taken from combined nasopharyngeal and oropharyngeal swabs. However, the prevalence of olfactory and gustatory disturbance in our local COVID-19 cohort is consistent with the results of a meta-analysis of 10 large cohort studies of smell impairment and nine large cohort studies of taste impairment, respectively, which showed a prevalence of 52.5% and 43.93% of olfactory and gustatory dysfunction.²⁰ However, some individual cohorts display the opposite trend, with a higher prevalence of gustatory than olfactory impairment,^{21,22} which cannot be explained solely by regional differences in viral load in the pharynx.

Real-time PCR yields a Ct value that is inversely proportional to the amount of the target virus in a sample. Consequently, the Ct level may indirectly represent the viral replication activity level and viral load of SARS-CoV-2 in a patient.¹⁴ Higher SARS-CoV-2 loads have been detected in the nose than in the throat.¹⁵ Moreover, the viral load in the pharynx typically grows during the first week after the onset of symptoms and remains high for another week.¹³ This was our reason for selecting the Ct value of PCR assays from nasopharyngeal and deep throat swabs on admission for our analysis. We postulated a correlation between the Ct value of PCR for the SARS-CoV-2 virus and the severity of olfactory and gustatory dysfunction. However, we found no correlation between the Ct values of PCR for individual patients and the presence or absence of olfactory and gustatory dysfunction. Furthermore, there was no correlation between the recovery time for either symptom in individual patients and their Ct values. This result suggests that the severity of olfactory or gustatory impairment and recovery may not be related to the viral load and activity. Our assumption of a positive correlation between viral load and the severity of smell and taste impairment in COVID-19 is not valid, and further studies are required to identify the risk factors that correlate with the severity of smell and taste disturbance in COVID-19.

Among the COVID-19 patients who reported olfactory and gustatory loss, 71.8% and 83.3%, respectively, had experienced complete recovery at the time of writing, which suggests that these dysfunctions are of short duration for the majority of patients. The mean recovery time was 10.3 days for the 26 patients with olfactory dysfunction, and 9.5 days for the 27 patients with gustatory dysfunction. Our finding is consistent with a report by Lechien et al. in a large multicenter European study with a cohort of 417 subjects, in which 72.6% of patients

recovered their olfactory function within the first 8 days.²³ Hopkins et al. also reported the overall recovery rate for a cohort of 382 subjects with olfactory and gustatory dysfunction to be 71% in 3 weeks or longer, and most of the recovery occurred in the first 2 weeks.²⁴

Anosmia has been well documented in coronavirus infections.^{25,26} However, the exact pathophysiological mechanism by which COVID-19 causes olfactory and gustatory dysfunction is still unknown.²⁷ Postviral olfactory disturbance can be caused by nasal obstruction blocking odors from reaching the olfactory cleft, a conductive impairment, or damage to the olfactory nerve, which is a sensorineural impairment.²⁸ In this study, most patients with olfactory dysfunction also suffered from nasal obstruction, and this effect was statistically significant, which may suggest at least a conductive component for the symptom. However, olfactory dysfunction can also occur in patients without subjective nasal obstruction, which may suggest neural damage. It has been postulated that SARS-CoV-2 can target the angiotensin-converting enzyme 2 receptors that are found on sustentacular and basal cells of the nasal epithelium, including the olfactory epithelium.^{29,30} The virus is also capable of invading the central nervous system through the olfactory bulb or causing peripheral neuropathy, which affect smell and taste functions.^{31,32} However, regardless of the mechanism by which the SARS-CoV-2 virus causes olfactory and gustatory dysfunction, our results do not indicate any association between the viral load and the severity of olfactory and gustatory impairment. Other studies have found that some asymptomatic patients infected with the virus had similar viral loads to symptomatic COVID-19 patients.¹⁵ This means that viral load alone is not a reliable predictor of disease outcome. Further research is needed to identify any predictive factors for the severity of these symptoms.

One limitation of our study is the lack of physical examinations of the nose and pharynx of patients to rule out other possible etiologies of olfactory disturbance that may have affected taste at the same time. Additionally, the symptoms related to smell and taste were determined via a questionnaire about symptoms, which may have introduced recall bias. Moreover, no objective tests were performed on the subjects to confirm and quantify the severity of these patient-reported abnormalities. Furthermore, the Ct readings in the PCR test for SARS-CoV-2 may have been erroneous if the nasopharyngeal and deep throat swabs were not performed correctly. The false negative rate of COVID-19 PCR test has been found to be highly variable in various studies, ranging between 100% to 20% depending on when the testing is performed in the course of the infection.³³ In this study, we could not obtain data from patients who were too ill to participate and required intensive care. However, the number of extremely sick patients with confirmed COVID-19 infection in our hospitals represented only a small proportion of the overall cohort, as the majority of cases were imported from overseas and were relatively young and generally free of chronic illnesses. Therefore, we are confident that the prevalence of olfactory and gustatory dysfunction, the severity of and recovery from symptoms, and

their correlation with the Ct values of the PCR test for SARS-CoV-2 reflect the true situation of the COVID-19 pandemic in Hong Kong.

CONCLUSION

In this study, olfactory and gustatory dysfunction were found to be more specific indicators for COVID-19 than fever, cough, and dyspnea. However, the severity of and recovery from olfactory and gustatory dysfunction were not shown to be correlated with the viral load of SARS-CoV-2. This finding may serve as a reference for further studies on the pathophysiology of olfactory and gustatory dysfunction in COVID-19 patients.

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