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Clinical Features of Parosmia Associated With COVID-19 Infection

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Objective: To characterize the clinical features, risk factors, symptom time-course, and quality of life implications for parosmia among coronavirus disease (COVID)-related olfactory dysfunction patients.

Methods: Individuals with olfactory dysfunction associated with laboratory-confirmed or clinically suspected COVID-19 infection were recruited from otolaryngology and primary care practices over a period from August 2020 to March 2021. Participants completed olfactory dysfunction and quality of life surveys.

Results: A total of 148 (64.1%) of 231 respondents reported parosmia at some point. Parosmia developed within 1 week of any COVID-19 symptom onset in 25.4% of respondents, but more than 1 month after symptom onset in 43.4% of respondents. Parosmia was associated with significantly better quantitative olfactory scores on Brief Smell Identification Test (8.7 vs. 7.5, $P = .006$), but demonstrated worse quality of life scores, including modified brief Questionnaire of Olfactory Dysfunction—Negative Statements and Sino-Nasal Outcome Test-22 scores (12.1 vs. 8.5, $P < .001$; 26.2 vs. 23.2, $P = .113$). Participants who developed parosmia at any point were significantly younger and less likely to have history of chronic sinusitis than those who did not develop parosmia (40.2 vs. 44.9 years, $P = .007$; 7.2% vs. 0.7%, $P = .006$).

Conclusion: COVID-19-associated olfactory dysfunction is frequently linked with development of parosmia, which often presents either at onset of smell loss or in a delayed fashion. Despite better quantitative olfactory scores, respondents with parosmia report decreased quality of life. A majority of respondents with persistent parosmia have sought treatment.

Key Words: Olfactory dysfunction, parosmia, anosmia, quality of life, COVID-19 infection.

Level of Evidence: 3

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INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) is frequently associated with development of new-onset olfactory dysfunction, often as the only presenting symptom.[1–10] Olfactory dysfunction can be either quantitative or qualitative.[10–12] Quantitative olfactory dysfunction includes both hyposmia and anosmia, rates of which have varied from 33.9% to 68% among symptomatic COVID-19 patients across several cross-sectional studies.[5,13–16] Parosmia, or a distorted sense of smell, is a less common qualitative form of olfactory dysfunction that has been linked to COVID-19 infection and may present in a delayed fashion.[6,7,10,17,18]

Parosmia is a condition that typically occurs idiopathically or in the postinfectious or posttraumatic setting.[11,12,19,20] The pathogenesis of parosmia is debated, with competing theories centering on either a central deficit within integrative centers of the brain or a peripheral process in which abnormal olfactory fibers convey an incomplete odorant picture.[11,12,21] Parosmia tends to occur after an injury or degenerative process affecting olfactory neurons, which lends support to the peripheral pathogenesis theory, although there is evidence supporting both hypotheses.[12,19–22]

Despite widespread publications on COVID-19 related olfactory dysfunction, most reports have focused on quantitative olfactory loss. Many studies have reported the occurrence of parosmia anecdotally and others have estimated the incidence of COVID-19 related parosmia ranging from 7.8% to 32.4% during disease course.[5,6,10,17] Previous studies lack granular detail regarding symptomatology, time-course, and implications for quality of life among those with parosmia relative to patients with quantitative olfactory dysfunction alone.

In our study, we evaluated risk factors for and clinical features associated with development of parosmia within the larger population of patients with COVID-19 related olfactory dysfunction. We also hope to provide clarity regarding time-course of parosmia symptomatology as well as implications of parosmia on quality of life.

MATERIALS AND METHODS

Study Design

Institutional review board approval was obtained for this study. This was a prospective cross-sectional cohort study of

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individuals with COVID-19 related olfactory dysfunction performed at a single tertiary care center. All subjects completed an olfactory dysfunction survey (Appendix S1) focused on identifying epidemiologic and clinical risk factors for and characterizing clinical features of COVID-19 related olfactory dysfunction.

In addition to the olfactory dysfunction survey, each subject completed a modified brief Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS, Table I), and Sino-Nasal Outcome Test (SNOT-22) survey to assess the impact on quality of life. The modified QOD-NS was derived from the brief QOD-NS, substituting a single question regarding enjoyment of dining at restaurants for the next most predictive survey question.[23] This change was made given that restaurant dining was not possible at many time points throughout the study period.

All subjects who reported any history of COVID-19 related parosmia during our study period were sent a follow-up survey (Appendix S2) in November 2020 or February 2021 depending on time of recruitment that addressed symptom time course, characteristics of distorted olfaction, and interventions sought.

All subjects were invited to take part in an additional therapeutic study. Interested patients received a Brief Smell Identification Test (BSIT) prior to enrollment as a baseline measurement. These baseline measurements are included in our analysis based on whether or not subjects reported active parosmia at time of BSIT completion.

Setting and Patient Population

Eligibility for this cohort study included all adults with laboratory-confirmed or clinically suspected COVID-19 infection and self-reported new-onset olfactory dysfunction from March 2020 to March 2021. Data were collected from August 2020 to March 2021. Subjects were recruited from otolaryngology and primary care practices across the Mount Sinai Health System as well as through a web-based symptom-tracking application. Otolaryngology and primary care practices were made aware of our research via e-mails and digital fliers. Otolaryngologists and primary care physicians referred all interested patients to our research team, who obtained consent and administered the study remotely. All patients who completed any portion of our study survey were included in final analysis. No patients were excluded for any reason.

Variables

In the olfactory dysfunction survey, patients provided responses on demographics, clinical risk factors, olfactory dysfunction symptomatology, and quality of life measures including the SNOT-22 and modified brief QOD-NS scores as previously outlined. All patients who endorsed any history of COVID-19 related parosmia during our study period were sent a follow-up survey, including responses on symptom time course, parosmia symptomatology, and interventions sought.

In the olfactory dysfunction study, subjects were asked whether they experienced distorted olfactory perception distinct from a change in smell intensity during the study time frame. Based on response to this question, subjects were categorized into those with and without history of COVID-19 related parosmia. Subjects were also asked whether they had persistent distorted olfactory perception at time of survey completion. Based on response to this question, subjects were also categorized as those with or without active COVID-19 related parosmia.

Study Outcomes and Statistical Analysis

The primary outcome was a comparison in time from any COVID-19 symptom onset to development of olfactory dysfunction in patients with or without parosmia. Secondary outcomes include comparison of clinical features between groups, including age, gender, smoking history, and current smoking status in addition to reported history of chronic sinusitis, sinonasal polyps, allergic rhinitis, head trauma, sinonasal surgery, and history of sinonasal symptoms. Given that we could not confirm prior diagnosis of chronic rhinosinusitis over survey, we also asked patients whether they had history of chronic nasal obstruction, facial pressure or pain, or postnasal drip.

Comparisons of continuous and discrete variables between subjects with and without parosmia were performed with unpaired *t*-tests and Fisher's exact test, respectively, using Prism version 9.0.2 (Graphpad Software Inc., La Jolla, CA). Separate comparisons were performed between participants with and without history of COVID-related parosmia as well as with and without current parosmia symptoms at the time of survey completion. Statistical significance was set prospectively with *P*-value less than .05.

RESULTS

Patient Population

A total of 231 subjects with olfactory dysfunction met study criteria and were included in analysis. No patients were excluded from analysis for any reason. Subjects responded to our olfactory dysfunction survey at a mean of 195.0 days (standard deviation 57.3 days) from symptom onset. The median number of days from symptom onset to survey response was 191 days with a

TABLE I.
Modified Brief Questionnaire of Olfactory Disorders—Negative Statements.

	Disagree (0)	Partly Disagree (1)	Partly Agree (2)	Agree (3)
The changes in my sense of smell makes me feel isolated	0	1	2	3
Because of the changes in my sense of smell, I have problems with taking part in activities of daily living	0	1	2	3
The changes in my sense of smell make me feel angry	0	1	2	3
Because of the changes in my sense of smell, I eat less than I use to or more than I use to	0	1	2	3
Because of the changes in my sense of smell, I do not enjoy drinks or food as much as I used to	0	1	2	3
Because of the changes in my sense of smell, I try harder to relax	0	1	2	3

TABLE II.
Characteristics of Patients With COVID-19 Related Olfactory Dysfunction With and Without Parosmia During Study Time Course.

	Any History Parosmia	No History Parosmia	*P*-Value
Patients	148	83	
% Positive COVID-19 PCR or antibody test	87.2% (129/148)	80.7% (67/83)	.251
Days from symptom onset to survey response	197.3	190.0	.217
Days from symptom onset to olfactory dysfunction	8.6	22.5	.006*
Age	40.2	44.9	.007*
% Male	30.4% (34/112)	29.0% (15/75)	.250
% Any smoking history	34.5% (51/148)	36.4% (28/77)	.771
% Current smoker	9.8% (5/51)	14.3% (4/28)	.713
% Sinonasal symptom history	0.7% (1/148)	7.2% (6/83)	.006*
% History of chronic sinusitis	0.7% (1/148)	7.2% (6/83)	.006*
% History of head trauma	3.4% (5/148)	1.2% (1/83)	.424
% History of nasal polyps	0% (0/148)	3.6% (3/83)	.045*
% History of allergic rhinitis	8.8% (13/148)	10.8% (9/83)	.644
% History of sinonasal surgery	4.1% (6/148)	7.2% (6/83)	.358

*Statistical significance at $P < .05$.
PCR = polymerase chain reaction.

standard deviation of 57.3 days. The range was 12 to 339 days with an interquartile range of 51.3 days. One hundred and eighty-seven (81.0%) participants responded to the survey question regarding gender identity, of which 138 (73.8%) identified as female.

Patients With COVID-19 Related Parosmia at Any Time

One hundred and forty-eight respondents reported parosmia symptoms during the study time frame, while 83 reported COVID-19 related olfactory dysfunction without parosmia. Respondents with any previous history of parosmia reported olfactory symptoms significantly earlier in their COVID-19 illness course, with an average of 8.6 days from any symptom onset to olfactory dysfunction compared to 22.5 days in participants who never experienced parosmia ($P = .006$).

We compared the date of COVID-19 symptom onset, using days from March 1, 2020, between patients who did or did not develop parosmia at any time. Patients who developed parosmia at any point on average had first COVID-19 symptom 55.4 days after March 1, 2020 (corresponding to April 25, 2020), compared to 35.9 days (April 5, 2020) among patients who did not develop parosmia at any time point ($P = .05$, median 22.5 vs. 20 days).

Respondents who developed parosmia at some point were significantly younger than those who did not develop parosmia (40.2 vs. 44.9 years, $P = .007$). There was also a significantly lower rate of both chronic sinusitis and sinonasal complaint history among respondents with parosmia compared to those with olfactory dysfunction without parosmia (both 0.7% vs. 7.2%, $P = .006$). Similarly, there was a significantly lower rate of history of sinonasal polyps among patients who developed parosmia at any point (0% vs. 3.6%, $P = .045$). There were no significant differences in gender, smoking history, current smoker status, or history of head trauma, allergic rhinitis, or sinonasal surgery between groups. Complete data for clinical and demographic comparison between respondents with and without any history of COVID-19 related parosmia are shown in Table II.

Long-Term Follow-Up for Patients With COVID-19 Related Parosmia at Any Point

For this portion of the analysis, we looked at the 148 participants with symptoms of parosmia at any point during the study. One hundred and five (70.9%) respondents who reported COVID-19 parosmia at any point during the study time frame completed a follow-up survey at a mean of 244.8 days and median of 237 days from symptom onset. The range was 89 to 369 days with a standard deviation of 40 days. The interquartile range was 15 days.

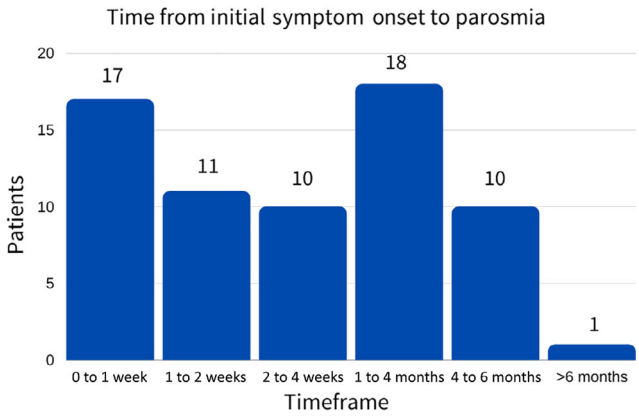

Fig. 1. Time from initial symptom onset to parosmia. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

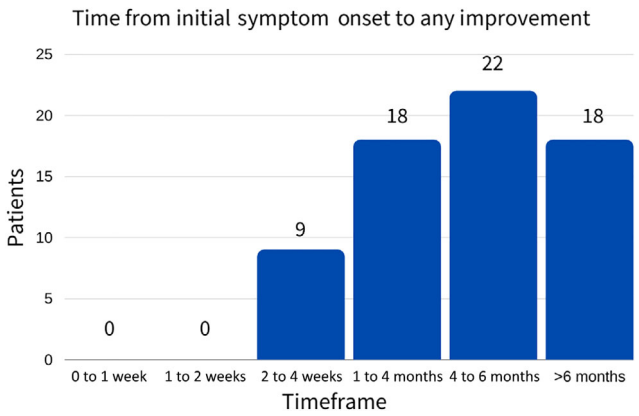

Fig. 2. Time from initial olfactory symptoms to any improvement. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Sixty-seven respondents (63.8%) reported any improvement in olfaction from symptom onset. When asked to rate current olfactory dysfunction severity from 0 to 100 with a score of 100 representing complete absence of normal olfactory function, respondents reported a current mean score of 63.6/100 (SD 13.4), compared to a mean maximal symptom severity score of 89.8/100 (SD 25.2). At time of follow-up survey, 77 respondents (73.3%) reported constant symptoms of distorted olfaction while 38 respondents (26.7%) reported intermittent symptoms.

Sixty-seven patients responded to both questions regarding time from onset of olfactory dysfunction to development of parosmia, as well as about time from onset of olfactory dysfunction to any form of improvement in symptoms. Figure 1 depicts the breakdown for time from olfactory dysfunction onset to development of parosmia. Figure 2 depicts the breakdown for time from olfactory dysfunction onset to any improvement in symptoms.

Respondents with distorted olfaction described their odor perceptions in a variety of ways, including chemicals (50.5%), cigarettes (27.6%), gasoline (17.1%), and other different or indescribable smells (27.6%). A majority (52.4%) of respondents reported seeking intervention to address their olfactory dysfunction, including over-the-counter supplements, smell retraining therapy, and intranasal steroids. Complete data for parosmia participant characteristics and interventions are shown in Table III.

TABLE III.
Parosmia Patient Characteristics and Interventions. Olfactory Dysfunction Scoring Self-Reported Between 0 and 100.

Characteristics	
Patients	105
Days from symptom onset to follow-up survey	244.8
Olfactory dysfunction score at worst	89.8
Olfactory dysfunction at score present	63.5
% Any improvement in olfactory dysfunction	63.8% (67/105)
Constant sensation of distorted olfaction	73.3% (77/105)
Phantosmia	41.0% (43/105)
Chemical smell	50.5% (53/105)
Cigarette smell	27.6% (29/105)
Gasoline smell	17.1% (18/105)
Other parosmia	27.6% (29/105)
Interventions	
Any therapeutic intervention	55/105 (52.38%)
Over-the-counter supplements	51/105 (48.57%)
Smell retraining therapy	34/105 (32.38%)
Intranasal steroids	23/105 (21.90%)

Patients With Active COVID-19 Related Parosmia at Evaluation

Two hundred and twenty-two of 231 (96.1%) subjects responded to a question regarding active parosmia at time of survey completion. Of these, 126 participants (56.7%) reported active parosmia present at time of survey completion compared to 96 subjects (43.2%) without parosmia at time of evaluation. Respondents with active parosmia symptoms were found to have a significantly greater time interval between COVID-19 symptom onset and survey response compared to those without current parosmia (208.5 vs. 175.0 days, $P < .001$). There was a significantly lower rate of both chronic sinusitis history and self-reported chronic sinonasal symptom history among respondents with persistent parosmia than among respondents without parosmia symptoms (both 6.3% vs. 0.8%, $P = .044$). Similarly, there were significantly fewer current smokers in the current parosmia cohort (4.6% vs. 22.6%, $P = .013$). There were no significant differences in age, gender, smoking history or history of head trauma, allergic rhinitis, nasal polyps, or sinonasal surgery between respondents with and without persistent parosmia.

Respondents with active parosmia had significantly better objective olfaction as measured by BSIT scores compared to respondents without parosmia (8.7 vs. 7.5, $P = .006$). Despite this, respondents with active parosmia had significantly decreased olfactory-related quality of life scores as measured by modified brief QOD-NS score compared to respondents without parosmia (12.1 vs. 8.5, SD 6.4 vs. 5.6, $P < .001$). Similarly, respondents with active parosmia tended to have higher SNOT-22 scores although this difference was not statistically significant (26.2 vs. 23.2, SD 14.1 vs. 14.3, $P = .113$). Complete data are shown in Table IV.

DISCUSSION

COVID-19 infection is linked to new-onset olfactory dysfunction with many patients experiencing parosmia during their clinical course.[1–3,5,8–10,24] Parosmia is a qualitative form of olfactory dysfunction that has been previously associated with upper respiratory infection, head trauma, and aging.[11,12,25] While the association between COVID-19 infection and development of parosmia has been widely reported, there has been inadequate

TABLE IV.
Characteristics of Patients With COVID-19 Related Olfactory Dysfunction With and Without Parosmia at Time of Evaluation.

	Active Parosmia	No Active Parosmia	*P*-Value
Patients	126	96	
% Positive COVID-19 PCR or antigen test	88.1% (111/126)	85.4% (82/96)	.555
Days from symptom onset to survey response	208.5	175.0	<.001*
Days from symptom onset to olfactory dysfunction	12.1	14.7	.594
Age	41.4	42.7	.474
% Male	23.8%	25.0%	.215
% Any smoking history	37.3% (47/126)	32.3% (31/96)	.441
% Current smoker	4.6% (2/47)	22.6% (7/31)	.013*
% History of chronic sinusitis	0.8% (1/126)	6.3% (6/96)	.004*
% Sinonasal symptom history	0.8% (1/126)	6.3% (6/96)	.004*
% History of head trauma	0.8% (1/126)	5.2% (5/96)	.087
% History of nasal polyps	0% (0/126)	3.1% (3/96)	.079
% History of allergic rhinitis	9.5% (12/126)	10.4% (10/96)	.825
% History of sinonasal surgery	3.2% (4/124)	8.3% (8/96)	.132
BSIT score	8.7 (93)	7.5 (50)	.006*
SNOT-22 score	26.2	23.2	.113
Modified brief QOD-NS score	12.1	8.5	<.001*

*Statistical significance at $P < .05$.
QOD-NS = Questionnaire of Olfactory Disorders—Negative Statements; SNOT-22 = Sinonasal Outcome Test Questionnaire.

characterization of parosmia as a distinct clinical entity from quantitative olfactory loss.[10]

In our study, we found that 148 (66.7%) of the 222 respondents reported parosmia at some point during COVID-19-related olfactory dysfunction. A total of 56.8% of subjects reported active parosmia at time of survey completion at a mean of 195 days since symptom onset, suggesting that parosmia symptoms often persist. Patients who developed parosmia experienced olfactory dysfunction significantly earlier in their COVID-19 illness course than patients with olfactory dysfunction without parosmia. While 25.4% of respondents who developed parosmia did so within 1 week of any COVID-19 symptom, 26.9% of patients reported parosmia onset more than 1 month from initial symptoms and 16.4% reported onset more than 4 months from initial symptoms. Our findings are consistent with earlier studies of non-COVID postinfectious olfactory dysfunction such as Bonfils et al, which demonstrate that onset of parosmia can occur alongside an initial olfactory insult as well as later as quantitative olfaction recovers.[10,11,25,26] The peripheral theory of parosmia pathogenesis suggests potential etiologies for parosmia onset at these time points: altered or ephaptic neuronal transmission for simultaneous parosmia and smell loss, and an "incomplete" odorant profile as olfactory neurons recover in the case of late-onset parosmia.[10–12,21,26,27]

Although there was no difference in gender between patients with and without history of parosmia or active parosmia at time of survey response, females comprised 73.8% of the overall study population of COVID-19 related olfactory dysfunction patients. Although this preponderance may reflect a bias of females presenting to our clinic for care, it may also point to a higher risk of olfactory dysfunction in females. Future cohort-based studies are warranted to provide further clarity.

Respondents who developed parosmia at some point were significantly younger and had a lower incidence of chronic sinusitis or sinonasal polyp history than did those who developed COVID-19 related olfactory dysfunction without parosmia. There was also a significant association between current smoking status and active parosmia at time of survey. Given the association between impaired olfaction and both older age and chronic sinusitis history with or without sinonasal polyps, previous olfactory insults may be associated with a decreased risk of developing parosmia at any point in the case of advanced age and chronic sinusitis history, as well as persistent parosmia in the case of chronic sinusitis history.[12,28–30] One possible explanation is that current smokers, older individuals, and individuals with history of chronic sinusitis with or without sinonasal polyps may have reduced quantitative olfaction that may result in an inability to perceive parosmia. For example, smoking has been linked to impaired olfaction, which may explain the relationship between current smoking and lower rates of persistent parosmia among patients with olfactory loss in our study.[31,32] In addition, patients with olfactory dysfunction without parosmia had lower objective olfaction scores on BSIT in our study, supporting the notion that those with more severely impaired quantitative olfaction are less likely to develop parosmia. Our finding of increased BSIT scores among parosmia patients supports previous evidence that parosmia is negatively correlated with self-reported reduced ability to smell as well as total smell loss.[10]

Although respondents with active parosmia demonstrated significantly better quantitative olfactory scores

as measured by BSIT, they also reported a significantly worse quality of life as measured by modified brief QOD-NS. Patients with active parosmia also had higher SNOT-22 scores, although this difference was not statistically significant. Hyposmia and parosmia have both been previously associated with poorer quality of life, but our study suggests that patients with parosmia may be even more affected than their counterparts with worse quantitative olfaction.[25,33,34] The negative impact of parosmia on quality of life may explain the finding that patients with active parosmia responded to our survey at a significantly longer time period from initial symptom onset than those without parosmia, reflecting a continued interest in seeking care.

Previous reports have shown that the majority of patients with COVID-19 related olfactory dysfunction exhibit early recovery.[5,35] However, our study demonstrates that there exists a large number of individuals with substantial symptom burden despite partial improvement. Self-reported symptom severity remained high among parosmia patients who responded to a follow-up survey at an average of 244.8 days after symptom onset. A majority of patients sought treatment for their olfactory dysfunction, which included over-the-counter supplements, intranasal steroids, and smell retraining. Within the non-COVID postinfectious olfactory dysfunction population, parosmia has been identified as a positive prognostic indicator for olfactory recovery after olfactory training.[36] Beyond observation and treatment of quantitative smell loss, there is no clearly effective therapy targeting parosmia, in particular, although gabapentin has been previously proposed as a medical therapy.[11,12,27]

Our study has several limitations. Given that our study is comprised of motivated patients seeking treatment from a primary care physician or otolaryngologist, patients in our study population are more likely to have severe, persistent symptoms relative to the COVID-19 olfactory dysfunction population at large. It is likely for this reason that the prevalence of parosmia in our study population is far higher than the 7.17% prevalence among 1,402 patients with laboratory-confirmed COVID-19 infection in a Parma et al. study.[10] Furthermore, our study is limited by its reliance on questionnaire survey responses. Subjects were provided with surveys upon enrollment and at time of study completion, limiting our ability to analyze clinical course for a single patient at set time points. Similarly, many patients completed only an initial survey but did not respond to a follow-up questionnaire or provided incomplete survey responses.

CONCLUSION

In our study, we evaluated clinical features of a large cohort of patients who developed parosmia within the larger COVID-19 related olfactory dysfunction population. We found that patients with COVID-19-associated olfactory dysfunction frequently develop parosmia, commonly in association with onset of quantitative smell loss or in a delayed fashion alongside partial olfactory recovery. Patients with parosmia exhibit significantly worse quality of life measures despite better quantitative olfaction scores relative to those without parosmia. Parosmia is a form of qualitative olfactory dysfunction distinct from quantitative olfactory loss that persists after COVID-19 infection in a substantial number of patients.

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