Prevalence and reversibility of smell dysfunction measured psychophysically in a cohort of COVID-19 patients

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Background: **Considerable evidence suggests that smell dysfunction is common in coronavirus disease-2019 (COVID-19). Unfortunately, extant data on prevalence and reversibility over time are highly variable, coming mainly from self-report surveys prone to multiple biases. Thus, validated psychophysical olfactory testing is sorely needed to establish such parameters.**

Methods: **One hundred severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2)-positive patients were administered the 40-item University of Pennsylvania Smell Identification Test (UPSIT) in the hospital near the end of the acute phase of the disease. Eighty-two were retested 1 or 4 weeks later at home. The data were analyzed using analysis of variance and mixed-effect regression models.**

Results: **Initial UPSIT scores were indicative of severe microsmia, with 96% exhibiting measurable dysfunction; 18% were anosmic. The scores improved upon retest (initial test: mean, 21.97; 95% confidence interval [CI], 20.84-23.09; retest: mean, 31.13; 95% CI, 30.16-32.10; $p < 0.0001$); no patient remained anosmic. After 5 weeks from COVID-19 symptom onset, the test scores of 63% of the retested patients were normal. However, the mean UPSIT score at that time continued to remain below that of age- and sex-matched healthy controls ($p < 0.001$). Such scores were related to time since symptom onset, sex, and age.**

Conclusion: **Smell loss was extremely common in the acute phase of a cohort of 100 COVID-19 patients when objectively measured. About one third of cases continued to exhibit dysfunction 6 to 8 weeks after symptom onset. These findings have direct implications for the use of olfactory testing in identifying SARS-CoV-2 carriers and for counseling such individuals with regard to their smell dysfunction and its reversibility.** © 2020 ARS-AAOA, LLC.

Key Words:
anosmia; hyposmia; COVID-19; SARS-CoV-2; UPSIT; odor identification; virus; olfaction

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There is strong evidence that many persons infected with severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) experience loss of smell function.[1] This has led the US Centers for Disease Control and other health organizations to recognize smell loss as a major sign of coronavirus disease-2019 (COVID-19), the disease caused by this virus.[2] Such loss has been suggested as a potential COVID-19 biomarker.[3] However, estimates of the prevalence of COVID-19–related smell dysfunction are highly variable, as are estimates of recovery of function, reflecting widespread reliance on self-report surveys. Such surveys are

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TABLE 1. Demographic characteristics of the COVID-19 and control subjects

	COVID-19 patients (test 1)	COVID-19 patients (test 2)	6- to 8-week COVID-19 retest group[a]	Normal controls
Sample size	100	82	51	51
Mean age, years (SD; range)	45.40 (11.80; 23-76)	45.53 (11.50; 24-76)	45.54 (10.95; 25-72)	45.41 (10.90; 25-72)
Gender	67 M/33 F	54 M/28 F	32 M/19 F	32 M/19 F
Current/never smoker	4/96	3/79	1/50	9/42
Education				
Grade school only	6%	4%	2%	0%
Middle school	15%	14%	12%	2%
High school	35%	39%	45%	20%
Associate degree	4%	4%	2%	4%
BA/BS	22%	21%	17%	27%
MS	6%	4%	6%	33%
MD/PhD	12%	14%	16%	14%

[a] These subjects were a subgroup of the 82 COVID-19 retest subjects. They were selected on the basis of having their second test 6 to 8 weeks after the onset of the disease symptoms.
BA = bachelor of arts; COVID-19 = coronavirus-2019; BS = bachelor of science; F = females; M = males; MD = doctor of medicine; MS = master of science; PhD = doctor of philosophy; SD = standard deviation.

susceptible to confounding by recall bias, sampling issues, and a lack of subject awareness, the latter being common when it comes to recognizing less-than-total smell or taste loss.[4,5] Thus, prevalence rates among such surveys range from 5%[6] to 85%,[7] with other rates found in between (eg, 15%,[8] 31%,[9] 39%,[10]41%,[11] 47%,[12] 50%,[13] 65%,[14] 72%,[15] and 74%[16]). Although based on fewer studies, extant information on reversibility of smell loss comes solely from self-report surveys showing nondefinitive findings, as seen with prevalence.[7,8,15] In most such studies, the majority of patients reported regaining normal function within 2 weeks.

In this study we employed a well-validated and sensitive psychophysical test to estimate the prevalence, magnitude, and reversibility of the olfactory dysfunction of a cohort of COVID-19 patients. It is the first to longitudinally test smell function in such a group over the course of 1 to 8 weeks after the onset of disease symptoms and the first to evaluate the influences of such variables as disease severity, sex, and age on the test scores. Its findings have direct implications for the use of olfactory tests in identifying SARS-CoV-2 carriers and for counseling patients with regard to their smell dysfunction and its likely course of return.

Patients and methods

Study design

The olfactory function of 100 SARS-CoV-2–positive patients, described in the next section, was tested during the late acute phase of their disease. Eighty-two of these subjects were retested a second time. The first test was performed at a tertiary referral hospital in Tehran, Iran, during the patients' inpatient recovery period. The second test was performed, on average, either 1 week (n = 35) or 4 weeks (n = 47) later in the patients' homes. To determine whether COVID-19 had a long-lasting adverse effect on smell function, the University of Pennsylvania Smell Identification Test (UPSIT) scores of 51 patients tested 6 to 8 weeks after disease symptom onset was compared with those of 51 age- and sex-matched normal controls.

Subjects

The 100 COVID-19 patients had been admitted to Masih Daneshvari University Hospital, Tehran, Iran, between March 21, 2020 and May 3, 2020. Of these, 2 declined to participate in the follow-up study, 3 were admitted to another hospital for other symptoms or comorbidities, and 13 were not available by phone, resulting in 82 subjects who underwent retesting. The 51 healthy controls were selected from a database of 141 subjects previously tested for an earlier study at the Institute for Research in Fundamental Sciences in Tehran, as described elsewhere.[3] The demographics of all patients and controls are presented in Table 1.

The patients were ready to be discharged from the hospital within 4 days; comorbidities are shown in Table 2. Inclusion criteria were: (a) having either a positive chest X-ray or computed tomography finding for COVID-19; (b) exhibiting a positive real-time reverse transcription–polymerase chain reaction (rRT-PCR) of SARS-CoV-2 infection in respiratory specimens collected from nasopharyngeal wash/aspirate or nasal aspirate; and (c) being healthy enough to take the olfactory test. The rRT-PCR assays for quantitative detection of SARS-CoV-2 RNA were performed using a nucleic acid reagent kit (2019-nCoV

TABLE 2. Clinical features and comorbidities of the 100 COVID-19 patients

Clinical features	Frequency (N = 100)
Symptoms	
Fever	78%
Cough	57%
Shortness of breath	48%
Headache	39%
Myalgia	5%
Shivering	3%
Sweating	2%
Gastrointestinal symptoms	3%
Malaise	1%
Tinnitus	1%
Bloody sputum	1%
COVID-19 clinical severity[a]	
Mild	58%
Moderate	30%
Severe	12%
Pretest self-reports of chemosensory dysfunction	
Smell loss	28%
Taste loss	22%
Both taste and smell loss	18%
Comorbidity	
Asthma	3%
Autoimmune disease[b]	5%
Benign prostatic hyperplasia	2%
Carcinoma[c]	2%
Chronic renal failure	2%
Congenital melanocytic nevi	1%
Diabetes	13%
Heart valve disease	2%
Hyperlipidemia	2%
Hypertension	10%
Hypothyroidism	7%
Sinusitis	2%

[a] Based on Massachusetts General Hospital COVID-19 guidance for treatment algorithm.[18]
[b] Autoimmune disease included Behcet disease in combination with Crohn disease (n = 1), multiple sclerosis (n = 2), and rheumatoid arthritis (n = 2).
[c] Prostate and cervical cancers.
COVID-19 = coronavirus disease-2019.

30-Minute Nucleic Acid Reagent Kits; Sansure Biotech, Inc, Development Zone, Changsha, China). The specimen collection, handling, and analyses were implemented according to World Health Organization recommendations.[17] Exclusion criteria were: age <18 years of age, pregnancy, dementia, invasive ventilation, and self-report of pre-existing chronic smell dysfunction before COVID-19. The clinical severity of the COVID-19 presentation was classified as mild, moderate, or severe according to the Massachusetts General Hospital COVID-19 treatment guidance algorithm.[18] All subjects provided informed consent and the study protocol was approved by the local ethics committee and the Iranian Ministry of Health (License No. IR.SBMU.NRITLD.REC.1399. 013).

Olfactory evaluation

Before psychophysical olfactory testing, the patients were asked 2 brief questions concerning their chemosensory perception: Do you suffer from smell or taste problems? (if yes, which one: smell, taste, or both). If the answer to the first question was yes, the next question was: When did your smell/taste problem start: before the onset of your COVID-19 symptoms or with/after the onset of COVID-19 symptoms?

A revised Persian version of the UPSIT (Sensonics International, Haddon Heights, NJ) was used to quantitatively test olfactory function.[3] This self-administered 40-odorant test is well-validated and reliable (test-retest, $r = 0.94$).[19] In addition to providing an overall quantitative score, this forced-choice test allows for the categorization of test scores into meaningful functional categories, including anosmia, severe microsmia, moderate microsmia, mild microsmia, normosmia, and malingering. The in-hospital olfactory testing was performed with the aid of a trained assistant.

After completion of the hospital testing, each patient was provided with an UPSIT to self-administer at home. The patients were subsequently recontacted by telephone to confirm their willingness to perform follow-up testing at the appropriate time for retest. If confirmed, a detailed instruction manual of the test was sent to them using the WhatsApp application to remind them of the administration procedures. Patients were asked not to have any food or beverage for 15 minutes before taking the smell test. Each patient sent back the photo of the choices made for each of the 40 odorants via WhatsApp.

Statistical analyses

All analyses were performed using MATLAB version R2019b (The MathWorks, Inc, Natick, MA). Comparisons between the initial test and retest UPSIT scores, as well as between the scores of the patients and their matched controls, were made using repeated-measures analyses of variance. To assess factors that impacted the COVID-19 olfactory deficit, linear mixed-effect regression models were developed. Independent variables, such as age, sex (female = 1, male = 0), clinical symptom severity, time since symptom onset, and education, were initially entered into the models. All independent variables were normalized using z-score transformations. Variables that did not meaningfully contribute to a model were sequentially removed. Our use of mixed-effect regression models, with maximum-likelihood estimation, allowed for the inclusion of all data, that is, that from subjects with and without follow-up scores. The model with the lowest Akaike information criterion (AIC), which optimizes model quality by providing a trade-off between goodness of fit and model simplicity, was chosen for the final model.[20]

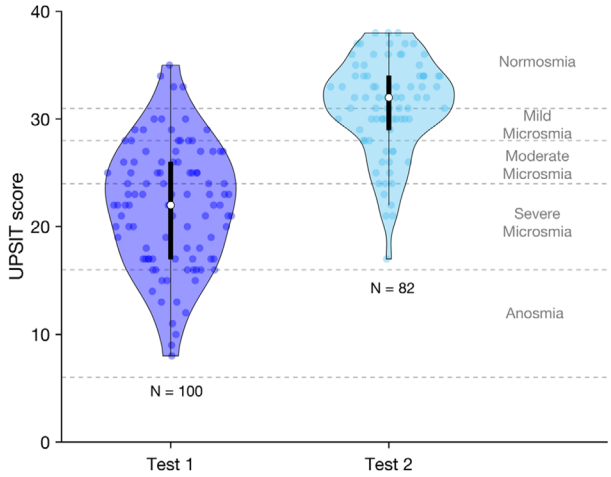

FIGURE 1. UPSIT scores of the COVID-19 patients for the initial (Test 1) and follow-up (Test 2) periods. The distribution of the subjects' scores in each group is depicted in a violin plot. White circles: medians; vertical dark lines: interquartile ranges. COVID-19 = coronavirus disease-2019; UPSIT = University of Pennsylvania Smell Identification Test.

Results

The initial (Test 1) and follow-up (Test 2) UPSIT scores are shown in Figure 1. Individual trajectories are presented in Figure 2, along with a bar graph showing that the amount of UPSIT change was greater for those with a 4-week test-retest interval than those with a 1-week test-retest interval [$F(1,80) = 8.16$, $p = 0.005$, $\eta^2 = 0.09$]. Interestingly, of the 100 patients included in the study, only 28 reported having a smell problem before psychophysical testing. None of the patients reported experiencing smell loss prior to the onset of disease symptoms.

The average Test 1 UPSIT scores were indicative of severe microsmia in the COVID-19 study group (mean, 21.97; 95% confidence interval [CI], 20.84-23.09), with 96% of the patients exhibiting measurable dysfunction; 18% were anosmic. The mean Test 2 UPSIT scores depicted in Figure 1 were higher than the Test 1 scores [$F(1,81) = 211.84$, $p < 0.0001$; $\eta^2 = 0.73$]. Despite the improvement over time, a significant number of patients continued to exhibit moderate to severe microsmia (Table 3). The proportion of subjects regaining normal smell function increased from 4%

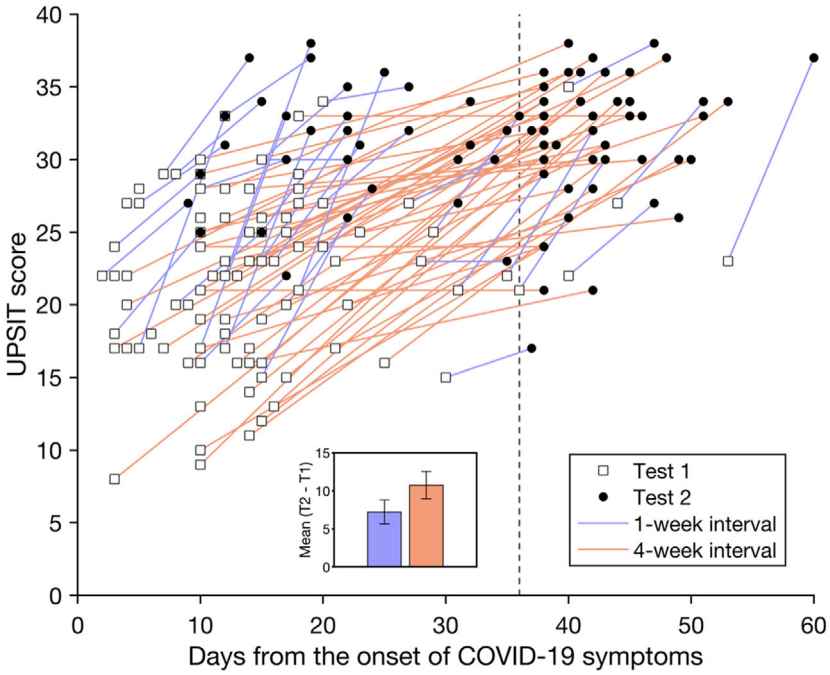

FIGURE 2. Test and retest UPSIT scores as a function of days from the onset of COVID-19 symptoms. The intertest intervals were 1 and 4 weeks. Repeat test scores to the right of the vertical dashed line represent the data that were compared with those of the healthy matched controls. The inset shows mean (95% confidence interval) differences between the initial and retest scores for the 1- and 4-week intervals. COVID-19 = coronavirus disease-2019; UPSIT = University of Pennsylvania Smell Identification Test.

(4 of 100) at the first test to 61% (50 of 82) in the follow-up period. It is remarkable that, of the 82 patients retested, only 5 (6%) failed to show improvement on retest, with their scores remaining the same.

Given reports that recovery of COVID-19–related olfactory dysfunction occurs within 1 month after disease onset, we compared UPSIT scores of those 51 patients who were retested after 5 weeks (i.e., those on the right side of the dashed vertical line in Fig. 2) with those of healthy age- and sex-matched normal controls (Fig. 3). Only 63% were normal, clearly indicating that smell dysfunction in many patients continues well beyond 1 month. The means of these 2 groups were significantly different (mean, 31.27; 95% CI, 29.97-32.57; mean, 34.39; 95% CI, 33.53-35.35, respectively) [$F(1,50) = 16.44$, $p < 0.001$; $\eta^2 = 0.32$].

Because variables such as age, sex, and time between assessments are amalgamated in the data in both Figures 1 and 2 and in the aforementioned analyses, we performed a series of linear mixed-effect regression models to identify the influences of such variables. The outcome variable was comprised of all of the UPSIT scores, which included both Test 1 and Test 2 scores. A number of independent variables served as fixed effects. Between-subject variability was considered a random effect. The initial regression model included age, sex, education, disease severity, and time from symptom onset. Smoking was not considered because only 4 of the 100 subjects were smokers. The final model with the lowest AIC (see Patients and methods) that accounted for the most variability in UPSIT scores included significant coeffiences for time from COVID-19 symptom onset

TABLE 3. Classification of olfactory function of UPSIT scores of COVID-19 patients with test and retest

UPSIT function category (score range)	Patients in initial testing (N = 100)	Patients in follow-up testing (N = 82)
Normosmia (31-40)	4%	61%
Mild microsmia (28-30)	13%	20%
Moderate microsmia (24-27)	24%	13%
Severe microsmia (17-23)	41%	6%
Anosmia (6-16)	18%	0%
Probable malingering (0-16)	0%	0%

COVID-19 = coronavirus disease-2019; UPSIT = University of Pennsylvania Smell Identification Test.

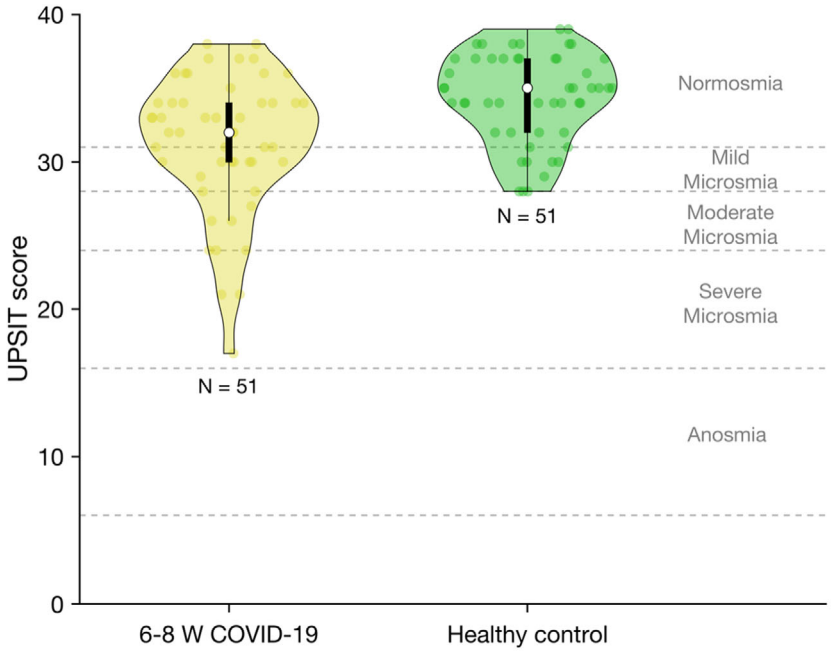

FIGURE 3. Comparison of UPSIT scores of patients tested 6 to 8 weeks after onset of initial COVID-19 symptoms (6-8 W COVID-19) vs those of healthy age- and sex-matched controls. White circles: medians; vertical dark lines: interquartile ranges. COVID-19 = coronavirus disease-2019.

(in days), sex, and age. In this model, the time from symptom onset was positively related to the UPSIT scores (coefficient = 4.25; 95% CI, 3.50–5.00; $p < 0.0001$), as was being female (0.98; 95% CI, 0.10–1.86; $p = 0.02$). Older age (−1.91; 95% CI, −2.79 to −1.04; $p < 0.0001$) negatively impacted the test scores. In other words, better scores were observed in women than in men, in younger than older subjects, and in those tested later with respect to the initial symptom onset. Including the intercept, this model explained over half of the UPSIT variance (26.09; 95% CI, 25.22–26.97; $p < 0.0001$) (adjusted $R^2 = 0.54$).

The proportion of patients regaining differing degrees of function over time is shown in Figure 4. It should be noted that all initial and follow-up scores are combined for the purpose of visualization. For the patients tested during the first 2 weeks after COVID-19 symptom onset, only 6% were normosmic; most had some degree of smell dysfunction, with over half exhibiting severe microsmia or anosmia. However, as time passed, these ratios changed toward improvement of function. In those tested during the third and fourth weeks, normosmia increased to 27% and anosmia and severe microsmia accounted for <30%. This normosmic proportion increased steadily over time so that, by 7 to 8 weeks from the onset of symptoms, >60% of the patients tested had normal olfactory function and those with severe microsmia or anosmia consisted only about 17% of the group. Overall, the test scores of 86% (71 of 82) of the patients improved by at least 1 clinical category, such as from mild microsmia to moderate microsmia. Among those who did not improve, 4 had normosmia, 4 had mild microsmia, and 3 had moderate to severe microsmia.

Discussion

By using a sensitive 40-odorant psychophysical smell test, we found some degree of smell loss in 96% of 100 COVID-19 patients tested during the late acute phase of their disease. Anosmia, however, was not the norm. Over the course of 8 post–symptom-onset weeks, 61% of those retested regained normal function. However, even by 6 weeks, the average UPSIT scores remained below those of age- and sex-matched normal controls, with a significant number of patients experiencing moderate to severe microsmia. Clearly, the time to recovery is highly variable.

Our finding that nearly all 100 COVID-19 patients tested in this study initially exhibited some degree of smell loss is remarkable, particularly in light of the fact that the initial testing of many of these patients was performed after the disease symptoms had been present for >2 weeks. This suggests that self-report surveys, with estimates of dysfunction commonly falling below 50%, greatly underestimate the prevalence of such loss. A lack of correspondence between awareness of olfactory dysfunction and objective testing is well established in the general population,[4] and this is paralleled by the present study's finding that only 28% of the COVID-19 patients were aware of their dysfunction until testing. Others have also seen significant discrepancies between self-report and psychophysical olfactory test measures.[21-23] Interestingly, the prevalence rate observed in self-report studies appears to be positively correlated with the amount of attention in the popular press paid to COVID-19's impact on the ability to smell.[24]

The present findings also contrast with prevalences reported in the few smaller studies in which olfactory tests

have been administered. Thus, using 16-item smell identification tests, Bocksberger et al[11] found olfactory dysfunction in 10 of 14 (71%) COVID-19 patients and Lechien et al[25] in 53 of 86 (62%) such patients. Vaira et al[16] found deficits in 62 of 72 COVID-19 patients (86%; 2 anosmic and 60 hyposmic) using a 10-odor identification test of household objects and ethyl alcohol and *n*-butanol threshold tests, whereas Tsivgoulis et al[26] found smell dysfunction in 17 of 22 (77%) such patients using a 3-odor smell test.

The basis for the higher initial prevalence of smell dysfunction in the present study is not clear, although several factors may be involved. First, the time of testing relative to disease onset appears to be longer in a number of studies than our mean of 14.75 (SD, 9.23) post-onset days, suggesting function may have returned in some cases.[16,25] Second, both threshold tests and shorter odor identification tests have been shown to be less reliable and sensitive to olfactory deficits than the 40-item UPSIT,[27] a test that provides a more nuanced assessment of different levels of dysfunction. Third, we used 31 of 40 (78%) as the normative UPSIT cutoff for defining abnormality for the Persian population based on healthy control group data obtained in Tehran. Because the 16-item test used in 2 of the aforementioned studies defined a smell problem as a score of ≤12 (75%), then conceivably a 3% difference in test scores would accrue. However, this difference would not completely explain our higher rate of dysfunction. Fourth, regional differences in the veracity of SARS-CoV-2 and susceptibility of local populations to infection, as well as differences in subject characteristics and recruitment strategies, could be involved. For example, in accord with most COVID-19 studies,[28] proportionately more men (67%) were present in our sample than in the other olfactory studies in which women predominated (eg, 30%,[29] 35%,[7] 37.5%,[16] and 57%[26]). Given that women generally outperform men on olfactory tests,[30] and are more likely to volunteer for studies than men,[31] these differences could reflect survey recruitment biases.

As clearly shown in Figure 2, the time course of return of olfactory function observed in our study varied considerably for individual patients. As we have shown, some of this variability relates to the sex and age of the subjects, as well as the time from the onset of COVID-19 symptoms. Our longitudinal cohort design overcame a number of limitations of self-report surveys, such as recall bias, overrepresentation of females, and the low awareness of smell loss observed in many individuals. Given the latter, our baseline metric for assessing change was the time of symptom onset. Although this metric has also been used in some self-report surveys,[11,16] others have employed the time since first noticing chemosensory dysfunction,[15,25,29] which seems questionable in light of the inaccuracy of awareness. All such studies, however, are in general agreement with ours in noting that many patients regain function over relatively brief periods of time.

Although SARS-CoV-2 viral load is significantly decreased by 2 weeks,[32] it is not clear whether viral load, per se, meaningfully impacts smell function or, if so, at what point in time such load is associated with enough cellular damage to induce smell deficits. There is evidence that

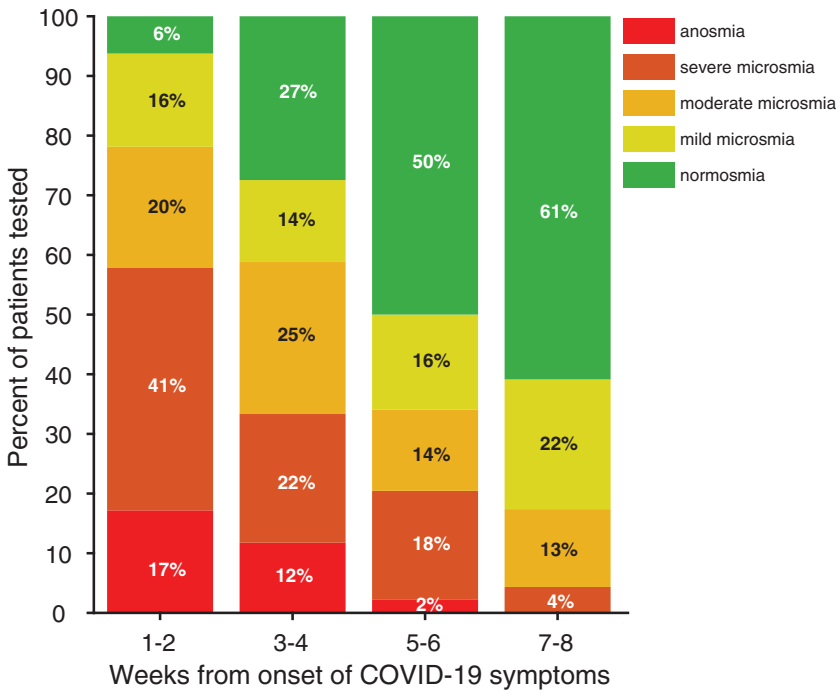

FIGURE 4. Proportion of patients with differing degrees of function relative to time since onset of COVID-19 symptoms. All initial and follow-up scores are combined for the purpose of visualization. COVID-19 = coronavirus disease-2019.

smell loss continues to be present in COVID-19 patients after rRT-PCR test findings have returned to normal.[13] Most likely, acute virus-related damage to the olfactory epithelium is the basis for the smell deficit of COVID-19, as seen in other viral infections.[33,34] The degree of return of function likely reflects the propensity of the olfactory neuroepithelium to regenerate and the amount of previous epithelial damage from cumulative xenobiotic insults.[35,36] The high rate of cell turnover and neurogenesis within the human olfactory neuroepithelium and the presence of immune system cells critical for epithelial homeostasis likely serve to mitigate the transport of viruses such as SARS-CoV-2 from the nasal cavity into the brain.[37] Animal models have shown angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 cell surface proteins are involved in the entry of SARS-CoV-2 into both supporting (sustentacular) and progenitor (horizontal and globose basal cells) cells within the olfactory neuroepithelium, thereby disrupting epithelial regeneration. Interestingly, TMPRSS2 expression is increased with older age.[38] This may explain the negative effect of older age on the recovery of sense of smell in the patients evaluated in this study.

Our study has both strengths and weaknesses. Among its strengths are: (a) the use of a well-validated sensitive test of olfactory function that allows for determining different degrees of olfactory function; (b) testing of a reasonably sized cohort of COVID-19 patients whose clinical severity was well documented; (c) longitudinal testing of patients over a period of time ranging, in individual cases, up to 8 weeks; and (d) an evaluation of the influences of multiple variables on the olfactory test scores. One limitation of the study is that no more than 2 time-points were assessed in individual subjects. Thus, it is not known whether improvement in those with a 4-week test-retest interval may have occurred earlier than that depicted in Figure 2. Another limitation is that longitudinal testing did not go beyond 8 weeks since symptom onset. In addition, although one may argue that self-administration of a smell test is a liability, the self-administered UPSIT is very reliable and its test scores have been shown not to vary between clinic and home administrations.[39] The patients of our study were proficient with computers and were able to use WhatsApp to provide their home test results.

In conclusion, we found, using well-validated psychophysical testing, some measurable degree of smell dysfunction near the end of the acute recovery period in most of the COVID-19 patients. However, complete loss of function occurred in only about one quarter of such patients, with severe microsmia occurring in about one third of them. In our study sample, only a minority of patients were aware of their dysfunction before testing, mirroring a phenomenon also present in the general population. Return to normal function was found in slightly over half of the patients by 5-6 weeks after symptom onset; by 7-8 weeks, this percentage rose to two thirds. However, even by this time the average olfactory test score was significantly lower than that of healthy age- and sex-matched normal controls. Factors significantly related to the extent of smell loss included time since disease symptom onset, age, and sex. Our findings support the view that olfactory testing, when performed early in the disease, may aid in the identification of patients infected with the SARS-CoV-2 virus. Future work is needed to determine whether otherwise asymptomatic persons carrying this virus can be detected by the presence of objectively measured smell dysfunction.

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