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CLINICAL LETTER

Risk factors and characteristics associated with persistent smell loss in coronavirus disease 2019 (COVID-19) patients

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Acute olfactory dysfunction (OD) is a well-documented symptom of coronavirus disease 2019 (COVID-19), yet risk factors for persistent OD remain poorly characterized, making it difficult to optimize clinical management. Prior studies addressing risk factors for persistent COVID-19 OD are limited by subjective OD measurements, delayed olfactory evaluation, or are specific to inpatient subjects.[1–3] In this longitudinal, multicenter, prospective assessment of the natural course of OD among polymerase chain reaction (PCR)-confirmed COVID-19 outpatient subjects, we aimed to determine the clinical risk factors, severity, and specific odorants associated with persistent OD.

Sixty-seven PCR-positive ambulatory COVID-19 subjects were prospectively recruited from the UC San Diego Health System and the Barts Health NHS Trust and underwent olfactory evaluation using the 12-item Brief Smell Identification Test (BSIT; Sensonics International, Haddon Heights, NJ, USA) and subjective visual analogue scale (VAS) olfactory assessments (0–10; 10 being normal baseline smell function). A BSIT score[4] of ≤8 at >30 days of OD symptoms was considered objective persistent smell loss based on findings from prior studies.[1,5] Risk factors were evaluated with a multivariable logistic regression model using a cutoff of $p < 0.15$ determined from the univariable logistic regression model (Table 1).

Of 67 (74.6%) patients, 50 demonstrated objective smell recovery whereas 17 (25.4%) had persistent smell loss with an average follow-up period of 60 days (range, 30–189 days) for the persistent smell loss group. The average ± standard deviation (SD) VAS score at last follow-up was 8.1 ± 2.0 for the smell recovery group and 4.8 ± 3.6 for the persistent smell loss group ($p < 0.001$). Multivariable logistic regression analysis demonstrated muscle/joint pain and female gender as potential risk factors for persistent OD (odds ratio [OR] 0.16; 95% confidence interval [CI], 0.026 to 0.95; $p = 0.044$, and OR 0.25; 95% CI, 0.06 to 1.06; $p = 0.06$, respectively). Although the effect of gender in this study did not reach statistical significance, perhaps due to underpowering, this association likely remains of clinical significance as previously suggested.[3,6]

TABLE 1 Univariable and multivariable logistic regression models of baseline demographic, clinical, and disease factors associated with objective recovery of smell loss

Variable	Univariable regression *p*	Univariable regression OR (95% CI)	Multivariable regression *p*	Multivariable regression OR (95% CI)
Age (years)	0.63	0.99 (0.95-1.03)		
Gender (female)	0.01	0.21 (0.06-0.68)	0.060	0.25 (0.06-1.06)
History of tobacco use	0.33	2.26 (0.52-15.87)		
DM	0.6	2.66 (0.27-36.24)		
Hypertension	0.65	1.46 (0.32-10.43)		
Cancer	0.76	0.68 (0.06-15.22)		
Sinus disease	0.17	0.30 (0.05-1.80)		
Cough	0.14	2.42 (0.75-8.10)	0.027	5.98 (1.23-29.23)
Fever	0.53	1.45 (0.45–4.75)		
Fatigue	0.47	1.56 (0.45–5.13)		
Shortness of breath	0.3	0.53 (0.16-1.83)		
Diarrhea	0.38	0.58 (0.18–2.02)		
Nasal congestion	0.13	0.35 (0.07–1.25)	0.250	0.356 (0.06-2.07)
Sore throat	0.74	1.23 (0.37–4.44)		
Muscle or joint pain	0.03	0.18 (0.03–0.74)	0.044	0.156 (0.03-0.95)
Nausea/vomiting	0.83	0.87 (0.24–3.58)		
Loss of taste	0.94	1.06 (0.26–3.71)		

Abbreviations: CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

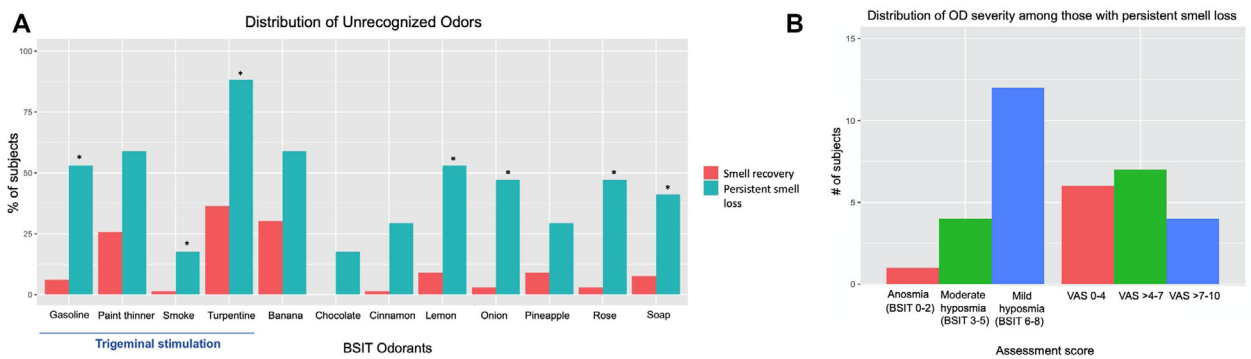

FIGURE 1 (A) Specific odorants associated with persistent smell loss. *Indicates $p < 0.05$ between the objectively recovered and persistent smell loss groups using ANOVA. (B) Distribution of the severity of olfactory dysfunction among COVID-19 subjects with persistent smell loss. Those with persistent OD, defined as having a BSIT score of ≤8 after at least 30 days from initial reported COVID-19–associated OD, are subcategorized into anosmia (BSIT 0–2), moderate hyposmia (BSIT 3–5), mild hyposmia (BSIT 6–8), VAS 0 to 4, VAS >4 to 7, and VAS >7 to 10.[6] Abbreviations: ANOVA, analysis of variance; BSIT, Brief Smell Identification Test; COVID-19, coronavirus disease 2019; OD, olfactory dysfunction; VAS, visual analogue scale

Muscle/joint pain has not previously been reported as a risk factor for persistent COVID-19–associated OD. However, recent literature suggests that COVID-19–associated myalgias may be the result of direct viral attack on skeletal muscle and that muscle pain may reflect a higher viral load,[7] which has been associated with persistent OD.[2] Curiously, the presence of cough during COVID-19 was protective against persistent OD (OR 5.98; 95% CI, 1.23 to 29.2; $p = 0.027$). Although this association is potentially due to sampling error, it may also reflect an exposure-specific viral tropism based on particle size with the smallest particles distributing in the olfactory epithelium leading to OD versus the lower airway leading to cough.[8]

Specific BSIT odorants associated with persistent OD were identified (Figure 1A). Of all odorants, smoke was the easiest to identify for those with persistent OD, which

may reflect its relationship with trigeminal stimulation.[6] A statistical difference in scent recognition by recovered and persistent OD subjects was seen with most odorants, with the greatest difference noted for rose (OR 21.3; 95% CI, 3.88 to 117.4; $p < 0.001$) and onion (OR 21.3; 95% CI, 3.88 to 117.4; $p < 0.001$). Interestingly, rose is a common odorant utilized in olfactory training, but this therapy was not mandated in this cohort. Further studies might assess if there are benefits in using odorants most associated with persistent OD for olfactory training.

Though characterized as persistent OD, most subjects demonstrated some level of improvement and were subcharacterized as having mild hyposmia (12/17, 70.6%), moderate hyposmia (4/17, 23.5%), and anosmia (1/17, 5.9%) (Figure 1B). Although those with persistent OD significantly improved quantifiably, their self-rated level of improvement was not as high: VAS > 7 (4/17, 23.5%); VAS > 4 to 7 (7/17, 41.2%); and VAS 0 to 4: (6/17, 35.3%). Only one of 17 subjects with persistent measured OD reported a subjective full recovery (VAS = 10/10).

Because individuals with subjective OD may be more likely to seek continued care, our study may reflect a sample bias with 25.4% overestimating the true percentage of COVID-19 patients with persistent OD. In prior studies, persistent OD occurred in 5% to 37% of subjects, depending on length of follow-up.[1,6] Long-term follow-up is more favorable in assessing persistent OD because individuals may demonstrate delayed recovery extending beyond the first few months of symptom onset. OD following other postinfectious etiologies demonstrates spontaneous recovery up to 2 years later. Nonetheless, our findings support the observation that a significant proportion of COVID-19–associated OD will continue to persist beyond a 2-month period. Thus, we highlight the importance of identifying risk factors and notable features of persistent OD that can be leveraged in clinical care to optimize smell recovery and therapeutic options like olfactory training.

Future studies with larger cohorts and continued long-term follow-up are recommended to further strengthen our findings, which will be important to inform future trials for early intervention in patients with OD.

CONFLICTS OF INTEREST

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