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RESEARCH NOTE

Population differences between COVID-19 and other postviral olfactory dysfunction: Results from a large case–control study

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KEYWORDS
olfaction, olfactory disorders, postviral olfactory dysfunction, SARS-CoV-2 (COVID-19), TDI testing

INTRODUCTION

Persistent olfactory dysfunction (OD) can occur following SARS-CoV2 infection but is not necessarily unique given that postviral olfactory dysfunction (PVOD) is a well-established phenomenon.[1,2] Differences between COVID-associated OD and other etiologies of PVOD remain unclear and are actively under investigation, with recent evidence indicating that they may have a similar pathophysiologic mechanism.[3] In this study, we sought to compare the time course, clinical characteristics, and objective olfactory testing between patients with post-COVID OD and PVOD.

METHODS

This is a case–control study of 230 patients presenting with associated hyposmia and hypogeusia to a large regional healthcare system. All consecutive patients were evaluated at the specialized Vanderbilt Smell and Taste Center clinic for post-non-COVID upper respiratory infection (URI) or COVID-19-specific hyposmia between October 2017 and July 2021. Only adult patients over 18 years of age were included in our study. Patients with post-traumatic or other etiologies for OD were excluded. Demographic data and clinical factors were examined, and threshold, discrimination, identification (TDI) testing was performed.

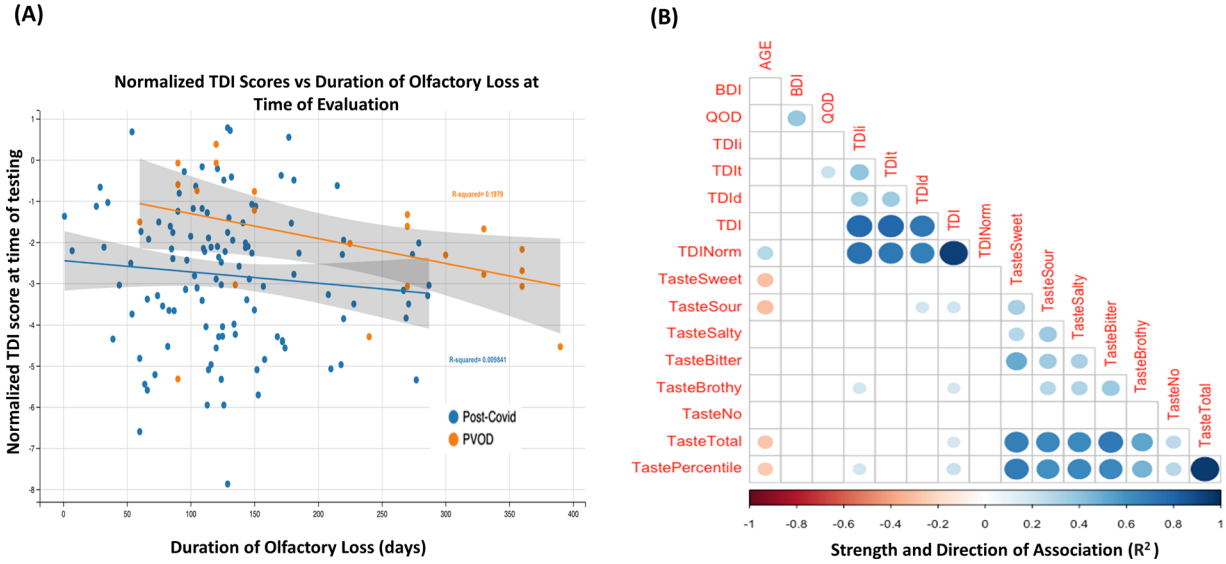

FIGURE 1 (A) Time-based analysis scatterplot of normalized threshold, discrimination, identification (TDI) scores (for age and sex) as a function of duration of olfactory dysfunction (OD) at the time of evaluation (in days) for both the post-COVID and postviral olfactory dysfunction (PVOD) groups. R^2 values for each model: PVOD group = 0.1979, post-COVID = 0.0098. (B) Pearson correlation heat plot for statistically significant ($p < 0.05$) associations for all tested patients. Positive correlations are shown in blue, negative in red with the associated strength represented by both size and shade of the subunit

We also performed olfactory and gustatory testing using the Sniffin' Sticks Test and the Waterless Empirical Taste Test, respectively.[4] The Questionnaire of Olfactory Disorders (QOD) and Beck's Depression Inventory (BDI) were also administered to patients at the time of evaluation. TDI scores were normalized to adjust for age and gender differences as previously described in the literature by Oleszkiewicz et al.[5] Pearson correlations, chi-square, and *t*-tests were performed in R Studio statistical software (R Core Team 2021) and used to identify differences between the groups (Table 1) and significant associations between covariates (Figure 1B).

RESULTS

A total of 230 patients were enrolled in the study, with 122 post-COVID patients and 108 PVOD patients. An overview of our results for clinical, demographic, and chemosensory testing outcomes between PVOD and post-COVID patients are outlined in Table 1. Patients in the post-COVID group were significantly younger (mean age of 39.3 vs. 60.8) and more likely to be female (67.2% vs. 52.8%, $p = 0.011$) than in the PVOD group. Post-COVID patients had substantial olfactory dysfunction, with average adjusted TDI scores of −2.81 standard deviations below the mean score for each age/sex group's normal values. Taste function was negatively correlated with age, with females being more likely to have higher taste function (mean: 36.1% vs. 60.3%). The duration of OD symptoms at the time of testing was 18.03 months for the PVOD group and 4.26 months in the post-COVID group ($p < 0.001$). Time-based analysis scatterplot of our data demonstrated that patients with greater duration of OD at the time of presentation tended to have worse normalized TDI scores (Figure 1A). BDI scores were positively correlated with QOD scores ($R^2 = 0.381$, $p = 0.0001$) (Figure 1B). There were no significant differences between normalized TDI ($p = 0.216$), QOD ($p = 0.158$), or BDI ($p = 0.398$) scores between post-COVID and PVOD patients in aggregate analysis. However, comparing only patients with prolonged OD, defined as ≥2 months, we did observe that COVID patients tended to have lower normalized TDI scores (−2.8 vs. −2.07, $p = 0.0238$) and thus have somewhat more severe OD. This overall trend was also seen in our time-based analysis (Figure 1A), but that association was weak and was not statistically significant except for patients with prolonged OD of ≥2 months. We did not observe any other differences in taste metrics or quality-of-life scores in in the prolonged OD subset of patients.

DISCUSSION

This study is the largest in the published literature with objective testing data of patient with post-COVID and other post-URI olfactory loss. Based on our results, it appears that there are notable demographic differences between patients presenting with either post-COVID and other PVOD, with post-COVID patients being more likely to be younger and female. These findings are in line with

TABLE 1 Clinical, demographic and chemosensory testing outcomes between postviral olfactory dysfunction (PVOD) and post-COVID patients

	All patients with OD			Patients with prolonged OD (≥ 2 months)		
Demographics	**Non-COVID PVOD**	**Post-COVID**	***p* value**	**Non-COVID PVOD**	**Post-COVID**	***p* value**
N = (number of patients)	108	122		92	108	
Mean age	60.75	39.27	<0.0001	60.00	38.84	<0.0001
% Female	52.78	67.18	0.0111	52.17	68.47	0.0260
Duration of symptoms at the time of testing (days)	540.98	128.73	<0.0005	540.98	138.12	<0.0006
Quality-of-life scores						
Mean QOD score	24.63	27.65	0.1577	25.11	27.16	0.3396
Mean BDI score	7.85	8.86	0.3977	8.27	8.63	0.7775
Olfactory testing						
Mean TDI threshold	3.19	3.80	0.3014	3.16	3.81	0.3047
Mean TDI discrimination	10.33	9.33	0.0604	10.21	9.26	0.1002
Mean TDI identification	9.78	9.50	0.6467	9.63	9.28	0.607
Mean total TDI score	21.18	22.63	0.3608	21.89	22.35	0.7663
TDI normalized mean	−2.33	−2.81	0.2159	−2.07	−2.89	0.0238
Gustatory testing mean scores						
Sweet	2.00	4.40	0.0240	1.75	4.28	0.0543
Sour	5.20	5.35	0.8172	4.75	5.42	0.2668
Salty	4.40	5.10	0.5188	3.50	5.10	0.0392
Bitter	3.60	3.72	0.8951	3.25	3.70	0.6769
Brothy	2.00	1.55	0.6224	1.25	1.54	0.601
No taste mean	8.20	11.82	0.0507	7.00	11.72	0.0040
Taste total mean	29.17	31.66	0.6284	26.80	31.46	0.4175
Taste mean percentile	47.50	52.99	0.7364	39.00	52.22	0.446

Abbreviations: BDI, Beck's Depression Inventory; OD, olfactory dysfunction; PVOD, postviral olfactory dysfunction; QOD, Questionnaire of Olfactory Disorders; TDI, threshold, discrimination, identification.

the epidemiological data from recent literature.[6,7] Post-COVID patients showed severe olfactory disfunction, as expected, with average adjusted TDI scores −2.81 standard deviations below the mean score for each age/sex normalized group. For patients with prolonged OD defined as ≥2 months of symptoms, the OD was even more severe (−2.89). On a percentile basis, this places these patients within the bottom 0.25% percentile of healthy individuals. There was no statistical difference in age/sex-normalized TDI scores between post-COVID and PVOD patients ($p = 0.216$). Interestingly, both groups appeared to have a similar degree of hyposmia and TDI scores. When comparing only the patients with prolonged OD, defined as ≥2 months, we do see that COVID patients have lower normalized TDI scores (−2.8 vs. −2.07, $p = 0.0238$) and thus have somewhat more severe OD. This trend was consistent when controlling for duration of symptoms (Figure 1A), but we did not observe any other notable differences between the groups in taste outcomes or quality-of-life metric. Time-based analysis scatterplot of our data demonstrates that patients with greater duration of OD at the time of presentation tended to have worse TDI scores (Figure 1A), but this may be due to patient selection bias rather than representation of disease trajectory. Additional statistically significant correlations from our Pearson model are shown in Figure 1B and may be helpful in guiding future research studies.

A unique aspect of our work involved inclusion of quality-of-life metrics. Our results indicate that, on average, post-COVID and PVOD patients reported BDI scores of 7.85 and 8.86 ($p = 0.398$), respectively, indicating no differences between groups and no significant mood disturbance. Patients did however report a statistically significant impact on olfactory quality-of-life scores (mean of 24.6 in post-COVID patients vs. 27.6 in PVOD, $p = 0.1577$). Interestingly, the BDI scores were positively correlated with QOD scores ($R^2 = 0.381$, $p = 0.0001$), suggesting an association between poor olfactory quality-of-life scores and depressive symptoms (Figure 1B). These results are congruent with the body of literature supporting a link between olfaction and depressive symptoms.[8,9]

Prior work indicated that COVID-19 may lead to hypogeusia, but interestingly, objective testing data from our cohort revealed mean overall taste score percentiles to be 52% for the post-COVID and 48% for the post-URI groups at the time of evaluation. These scores are relatively normal and do not seem to correlate with the severe OD seen based on TDI testing. More research is needed to expand and validate these findings.

There are notable limitations to our study, including its exploratory design. Patients were only tested once, and such testing may not fully describe the entire disease trajectory. Specifically, it appears that while there are notable demographic differences between patients presenting with post-COVID and PVOD, there were no significant differences in normalized TDI, BDI, and QOD testing between these groups. Post-COVID patients with prolonged OD, however, did demonstrate decreased normalized TDI scores, indicating more severe hyposmia. These results provide initial insights into chemosensory dysfunction in both groups and can guide future research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope*. 2018;128:10-15.
2. Fornazieri MA, Borges BBP, Bezerra TFP, Pinna FR, Voegels RL. Main causes and diagnostic evaluation in patients with primary complaint of olfactory disturbances. *Braz J Otorhinolaryngol*. 2014;80:202-207.
3. Imam SA, Lao WP, Reddy P, Nguyen SA, Schlosser RJ. Is SARS-CoV-2 (COVID-19) postviral olfactory dysfunction (PVOD) different from other PVOD?. *World J Otorhinolaryngol Head Neck Surg*. 2020;6(Suppl 1):S26-S32.
4. Doty RL. Psychophysical testing of smell and taste function. *Handb Clin Neurol*. 2019;164:229-246.
5. Oleszkiewicz A, Schriever VA, Croy I, Hähner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur Arch Otorhinolaryngol*. 2019;276(3):719-728.
6. Wong C, Kit D, Gendeh H, et al. A review of smell and taste dysfunction in COVID-19 patients. *Med J Malaysia*. 2020;75(5):574-581.
7. Chapurin N, Totten DJ, Chaballout B, et al. Differential olfactory outcomes in COVID-19: a large healthcare system population study. *Int Forum Allergy Rhinol*. 2022;12(1):108-111.
8. Kohli P, Soler ZM, Nguyen SA, Muus JS, Schlosser RJ. The association between olfaction and depression: a systematic review. *Chem Senses*. 2016;41(6):479-486.
9. Simopoulos E, Katotomichelakis M, Gouveris H, Tripsianis G, Livaditis M, Danielides V. Olfaction-associated quality of life in chronic rhinosinusitis: adaptation and validation of an olfaction-specific questionnaire. *Laryngoscope*. 2012;122:1450-1454.

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