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

Nikita Chapurin MD, MHS1,2 | Spencer Dennis1 | Naweed I. Chowdhury MD1,2 | Timothy Trone MD1,2 | Basil Chaballout BA3 | Elizabeth Longino MD1 | Justin H. Turner MD, PhD1,2 | Rakesh K. Chandra MD, MMHC1,2

1 Division of Rhinology/Skull Base Surgery, Department of Otolaryngology-Head and Neck Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA
2 Vanderbilt University Medical Center Smell and Taste Center, Nashville, USA
3 University of South Carolina School of Medicine, Greenville, South Carolina, USA

Correspondence
Nikita Chapurin, MD, MHS, Vanderbilt University Medical Center, Department of Otolaryngology-Head and Neck Surgery, Division of Rhinology/Skull Base Surgery, 1215 21st Avenue South, Suite 7209, Nashville, TN 37232-8605, USA.
Email: nikita.chapurin@vumc.org

Nikita Chapurin and Spencer Dennis denote equal contribution

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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.
We also performed olfactory and gustatory testing using the Sniffin’ Sticks Test and the Waterless Empirical Taste Test, respectively. 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. 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 (R² = 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

| Demographics                                      | All patients with OD | Patients with prolonged OD (≥ 2 months) |
|---------------------------------------------------|----------------------|----------------------------------------|
|                                                   | 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      | 0.011   | 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.\textsuperscript{5,7} Post-COVID patients showed severe olfactory dysfunction, 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 $\geq 2$ 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 $\geq 2$ 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.\textsuperscript{8,9}

Prior work indicated that COVID-19 may lead to hypoguesia, 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.

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