Olfactory Dysfunction in Patients With Mild COVID-19 During Gamma, Delta, and Omicron Waves in Rio de Janeiro, Brazil

Olfactory dysfunction is a common symptom of COVID-19, with reported rates as high as 70%. This symptom can be associated with mild COVID-19, mostly occurs within 5 days after symptom onset, and can persist for a few days to several months after infection resolution. The mechanism of SARS-CoV-2–related olfactory dysfunction is not completely understood.

Host genetics, acute inflammation in the olfactory epithelium, local ACE2 expression, and downregulation of olfactory receptors seem to play a role; however, the viral contribution remains to be explored. We conducted a retrospective analysis of individuals with mild COVID-19 during different SARS-CoV-2 variant waves to assess the prevalence of self-reported olfactory dysfunction.

Methods | Individuals with SARS-CoV-2 infection confirmed by quantitative reverse transcriptase–polymerase chain reaction were enrolled at the Center for COVID-19 Diagnosis at the Federal University of Rio de Janeiro between March 16, 2020, and March 28, 2022. Participants were aged 18 years or older and presented with mild symptoms at the time of sample collection for diagnosis. The study was approved by the Brazilian national commission of ethics in research and written informed consent was obtained from all participants.

Clinical and demographic data were obtained through an updated version of the Brazilian National Health System Questionnaire for COVID-19 that was administered by qualified specialists. Participants could answer “yes” or “no” to the question: “Have you experienced olfactory/smell loss since the date of symptoms onset?”

Viral lineages were attributed to each participant using genomic surveillance data from the state of Rio de Janeiro. A lineage was considered predominant when it was detected in more than 90% of the individuals diagnosed during a given period. Individuals were recruited when the original lineages (B.1.1.28 and B.1.1.33) were circulating in Rio de Janeiro between March 16 and December 22, 2020, when Gamma was circulating between March 1 and June 30, 2021, when Delta was circulating between August 2 and November 10, 2021, and when Omicron was circulating between January 4 and March 28, 2022. The study did not include individuals diagnosed during periods when 2 or more lineages co-circulated at a high frequency.

Association analyses were conducted using logistic regression models with the original lineage period as the reference group. Age, sex, viral load, time since symptom onset, hypertension, diabetes, and smoking status were evaluated as potential confounders. A sensitivity analysis including only individuals diagnosed when COVID-19 vaccines were available (after February 2021) also was performed, adding vaccination status as an additional variable in the logistic regression models. Because no vaccines were available during the period of the original lineages, the Gamma period was used as the reference group.

The analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing). A 2-sided P value <.05 was considered statistically significant.

Results | Of the 6053 participants with mild COVID-19 in the cohort, 2650 reported olfactory dysfunction (Table 1) and 3403 did not report this symptom. Olfactory dysfunction was reported by 2223 of the 4227 participants (52.6% [95% CI, 51.1%-54.1%]) diagnosed during the period of the original lineages (Table 2). The prevalence decreased to 27.5% (95% CI, 24.3%-30.8%) during Gamma, 42.1% (95% CI, 37.4%-47.0%) during Delta, and 5.8% (95% CI, 4.4%-8.5%) during Omicron.

### Table 1. Characteristics of Participants With Mild COVID-19 Who Reported Olfactory Dysfunction

<table>
<thead>
<tr>
<th>SARS-CoV-2 lineage</th>
<th>Original lineages (n = 2223)</th>
<th>Gamma (n = 211)</th>
<th>Delta (n = 179)</th>
<th>Omicron (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>38.6 (11.5)</td>
<td>38.4 (13.8)</td>
<td>37.6 (15.0)</td>
<td>38.2 (13.9)</td>
</tr>
<tr>
<td>Time since symptom onset, mean (SD), d</td>
<td>7.5 (5.6)</td>
<td>6.5 (3.9)</td>
<td>6.3 (4.5)</td>
<td>3.6 (2.2)</td>
</tr>
<tr>
<td>Threshold cycle value for SARS-CoV-2 target N1, mean (SD)</td>
<td>25.6 (5.9)</td>
<td>22.6 (5.6)</td>
<td>22.1 (5.5)</td>
<td>21.5 (5.4)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>778 (35.0)</td>
<td>99 (46.9)</td>
<td>76 (42.5)</td>
<td>17 (45.9)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>427 (19.2)</td>
<td>49 (23.2)</td>
<td>26 (14.5)</td>
<td>9 (24.3)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>134 (6.0)</td>
<td>14 (6.6)</td>
<td>13 (7.3)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Smokers, No. (%)</td>
<td>151 (6.8)</td>
<td>18 (8.5)</td>
<td>14 (7.8)</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>Vaccinated individuals, No. (%)</td>
<td>0 (1)</td>
<td>66 (31.3)</td>
<td>154 (86.0)</td>
<td>37 (100)</td>
</tr>
</tbody>
</table>

a The study did not include individuals diagnosed during periods when 2 or more lineages co-circulated at a high frequency.

b Indicates the interval between symptom onset and the date of the clinical interview and sample collection.

c Percentages do not sum to 100% by row.

d The COVID-19 vaccine was not yet available in Brazil.

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The odds of olfactory dysfunction were lower for those infected during Gamma (adjusted odds ratio [OR], 0.48 [95% CI, 0.39-0.59]; P < .001) and Omicron (adjusted OR, 0.07 [95% CI, 0.05-0.10]; P < .001) compared with the original lineages (Table 2). No association was observed during Delta (adjusted OR, 0.90 [95% CI, 0.71-1.15]; P = .41). The sensitivity analysis found an adjusted OR of 0.95 (95% CI, 0.86-0.15; P < .001) for olfactory dysfunction during Omicron vs Gamma after additional adjustment for vaccination status.

Discussion | This study found that individuals with mild COVID-19 infected during the Gamma and Omicron waves had lower odds of reporting olfactory dysfunction than individuals infected during the period of the original lineages. These results suggest that the type of SARS-CoV-2 variant might be a risk factor for olfactory dysfunction, along with host genetic susceptibility. The association with Omicron also was observed after controlling for vaccination status, supporting its independence of host immunologic factors.

Limitations of this study include self-reported outcome, variant attribution according to epidemiological surveillance data, and possible unmeasured confounding. The present findings highlight the importance of considering SARS-CoV-2 variants when modeling olfactory outcomes and suggest that olfactory dysfunction might not be a hallmark of COVID-19 with certain variants.

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