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COVID-19 Status Differentially Affects Olfaction: A Prospective Case-Control Study

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Abstract

Objective. The symptoms and long-term sequelae of SARS-CoV-2 infection have yet to be determined, and evaluating possible early signs is critical to determine which patients should be tested and treated. The objective of this ongoing study is to evaluate initial and short-term rhinologic symptoms, olfactory ability, and general quality of life in patients undergoing SARS-CoV-2 testing.

Study Design. Prospective case-control.

Setting. Academic institute.

Methods. Adult patients tested for SARS-CoV-2 were prospectively enrolled and separated into positive and negative groups. Each participant completed 4 validated patient-reported outcome measures. The UPSIT (University of Pennsylvania Smell Identification Test) was distributed to patients who were SARS-CoV-2 positive.

Results. The positive group reported significantly decreased sense of smell and taste on the 22-item Sinonasal Outcome Test (SNOT-22) as compared with the negative group (mean $\pm$ SD: 3.4 $\pm$ 1.7 vs 1.2 $\pm$ 1.4, $P < .001$). The positive group had a much higher probability of reporting a decrease in smell/taste as "severe" or "as bad as it can be" (63.3% vs 5.8%) with an odds ratio of 27.6 (95% CI, 5.9-128.8). There were no differences between groups for overall SNOT-22 domain scores, PHQ-4 depression/anxiety (Patient Health Questionnaire−4), and 5-Level EQ-5D quality-of-life scores. Mean Self-MOQ (Self-reported Mini Olfactory Questionnaire) scores were 7.0 $\pm$ 5.6 for the positive group and 1.8 $\pm$ 4.0 for the negative group ($P < .001$). The mean UPSIT score was 28.8 $\pm$ 7.2 in the positive group.

Conclusion. Symptomatic patients who are SARS-CoV-2 positive report severe olfactory and gustatory dysfunction via the Self-MOQ and SNOT-22 as compared with symptomatic patients testing negative.

Keywords

COVID-19, anosmia, rhinosinusitis, rhinitis, dysgeusia, coronavirus, SARS-CoV-2, PHQ-4, EQ-5D

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The novel coronavirus disease 2019 (COVID-19) has spread exponentially throughout the world causing a significant threat to the health of the global population. High viral loads of the causative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are harbored in the upper respiratory tract, and the primary mode of transmission is thought to occur through the spread of respiratory droplets.[1,2] Up to 56% of patients remain asymptomatic or have very minor symptoms similar to common upper respiratory illnesses, including anosmia and nasal congestion.[3]

Several articles recently revealed that >50% of patients with COVID-19 have smell and taste impairment.[4-20] In patients reported to have chemosensory dysfunction, 73.0% noted anosmia prior to diagnosis, and it was the initial symptom in 26.6%.[4] A study in Iran utilizing objective validated testing found that 98% of inpatients with COVID-19 exhibited smell dysfunction.[5] A recent systematic review of 10 studies reported a 52.7% and 43.9% prevalence of

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olfactory and gustatory dysfunction, respectively.[6] However, most studies utilized self-reported surveys and did not have a control group for comparison. Nonetheless, the growing evidence has led the US Centers for Disease Control and Prevention and the World Health Organization to add loss of smell and taste to the list of common symptoms that may appear 2 to 14 days after viral exposure.

Though smell and taste dysfunction are now recognized presentations of COVID-19, the onset, duration, and possible long-term consequences remain unknown. It is critical to characterize the early signs of infection to determine which patients should be tested, quarantined, and potentially treated. Additionally, there is still much unknown about the effect that the virus has on the mental well-being of patients and on overall quality of life. The purpose of this prospective case-control study is to evaluate rhinologic symptoms, self-reported and objective olfactory ability, anxiety and depression, and health-related quality of life in symptomatic patients undergoing SARS-CoV-2 testing.

Materials and Methods

This study was approved by the Indiana University institutional review board. Patients who obtained a nasopharyngeal swab for SARS-CoV-2 and underwent molecular testing for symptoms concerning for COVID-19 (ie, fever, fatigue, cough, shortness of breath pharyngitis, nasal congestion) at Indiana University Health facilities across 9 Indiana counties were identified. Each patient's electronic health record was reviewed for contact information and demographic data, which included age, race, gender, and medical history. The following patients were excluded from the study: (1) <18 years of age; (2) non-English speaking; (3) diagnosed with a chronic debilitating medical condition that would preclude participation, such as dementia; (4) admitted to an intensive care unit or unstable at the time of chart review; (5) no documented phone number or email address; and (6) negative test result for SARS-CoV-2 and no viral symptoms.

Patients who met the inclusion criteria were recruited by phone call or email. If recruited by phone, email addresses were obtained from each participant. Consent, HIPAA authorization (Health Insurance Portability and Accountability Act), and patient-reported outcome measures were completed in REDCap, a secure and HIPAA-compliant web application for building and managing online surveys. Patients were separated into positive and negative groups based on the results of their SARS-CoV-2 testing. For patients who tested negative, it was confirmed that they reported symptoms concerning for COVID-19 at the time of testing. After consenting, participants rated their senses of smell at baseline and while sick (0, no sense of smell; 10, normal sense of smell). They then completed 4 validated surveys electronically.

The Sinonasal Outcomes Test (SNOT-22) comprises 22 symptoms, each scored by severity (0, no problem; 5, as bad as it can be), with scores ranging from 0 to 110.[21] There are also 5 subdomain scores. The Self-reported Mini Olfactory Questionnaire (Self-MOQ) consists of 14 true-false items about olfactory problems in daily life, with scores ranging from 0 to 14.[22] The Patient Health Questionnaire 4 (PHQ-4) asks about 4 core depression and anxiety symptoms, each scored 0 (not at all) to 3 (nearly every days), with the total ranging from 0 to 12.[23] The 5-Level EQ-5D (EQ-5D-5L) has patients rate overall health status (0, worst health you can imagine; 100, best health you can imagine) plus 5 dimensions: mobility, self-care, usual activities, pain, and anxiety/depression (0, no problem; 4, extreme problem).[24] The overall health status score and the mean scores from the 5 dimensions were reported. Patients with smell or taste dysfunction were mailed the University of Pennsylvania Smell Identification Test (UPSIT), and the results were collected through email or mail. If patients were enrolled during an active hospitalization, the test was delivered to the hospital room. Data analysis was performed with Microsoft Excel version 2004 and included the Student's *t* test and the Pearson correlation coefficient. Simultaneous 95% CI for multinomial proportions were constructed in SAS version 9.4 (SAS Institute Inc) via the Goodman method.

Table 1. Demographics of Survey Respondents.

	SARS-CoV-2		
	Positive	Negative	*P* value
Total, No.	49	34	
Age, y, mean ± SD	43.1 ± 15.3	46.2 ± 10.5	.27
Gender, %			.46
Male	34.7	20.6	
Female	65.3	76.5	
Other	0.0	2.9	
Race, %			.50
White	77.6	85.3	
Black	16.3	8.8	
Asian	2.0	0.0	
Multiple	4.1	5.9	

Results

Surveys were completed by 49 patients who tested positive for SARS-CoV-2 and by 34 who tested negative between April 12 and May 4, 2020. Outpatients represented 87.8% of the positive group and 97.1% of the negative group. Demographics for each group are summarized in **Table 1**. There were no significant differences between positive and negative groups in age ($P = .27$), gender ($P = .46$), and race ($P = .50$). Surveys were completed at a mean ± SD 7.9 ± 3.4 days after testing for the positive group and 8.4 ± 4.4 days for the negative group ($P = .57$).

Patients rated their subjective senses of smell on a scale of 0 to 10 at baseline and while exhibiting symptoms concerning for COVID-19. There was no difference in baseline sense of smell between the positive and negative groups (9.1 ± 2.1 vs 9.2 ± 2.1, $P = .87$), but the positive group had a highly significant lower mean sense of smell while

Table 2. SNOT-22 Responses for Severity of Decreased Sense of Smell and Taste.

	SARS-CoV-2 prevalence, % (95% CI)	
	Positive	Negative
None	10.2 (3.4-26.9)	47.1 (27.0-68.1)
Very mild	6.1 (1.5-21.6)	14.7 (4.9-36.5)
Mild or slight	12.2 (4.5-29.4)	17.6 (6.5-39.8)
Moderate	8.2 (2.4-24.3)	14.7 (4.9-36.5)
Severe	30.6 (16.6-49.5)	2.9 (0.3-21.5)
As bad as it can be	32.7 (18.1-51.5)	2.9 (0.3-21.5)

Abbreviation: SNOT-22, 22-item Sinonasal Outcome Test.

Table 3. SNOT-22 Scores for Positive and Negative Cases of SARS-CoV-2.

	Score, mean ± SD		
SNOT-22	Positive	Negative	*P* value
Rhinologic	9.4 ± 5.9	8.1 ± 6.3	.34
Extranasal rhinologic	4.2 ± 3.0	5.1 ± 4.0	.26
Ear/facial	5.5 ± 4.7	6.6 ± 6.0	.38
Psychological	13.8 ± 7.8	13.7 ± 9.2	.93
Sleep dysfunction	10.8 ± 7.1	11.1 ± 7.3	.85
Total	36.7 ± 18.9	37.2 ± 24.4	.92

Abbreviation: SNOT-22, 22-item Sinonasal Outcome Test.

symptomatic as compared with the negative group (2.6 ± 3.7 vs 7.1 ± 2.7, $P < .001$). The positive group also reported significantly higher scores for decreased sense of smell/taste on the SNOT-22 (3.4 ± 1.7 vs 1.2 ± 1.4, $P < .001$; **Table 2**). The positive group had a much higher probability of reporting its decrease in smell/taste as ''severe'' or ''as bad as it can be'' (63.3% vs 5.8%) with an odds ratio of 27.6 (95% CI, 5.9-128.8). There were no significant differences between male and female scores for decreased sense of smell/taste on the SNOT-22 for the positive group (3.6 ± 1.4 vs 3.3 ± 1.8, $P = .43$) or the negative group (1.1 ± 1.7 vs 1.3 ± 1.4, $P = .86$). In addition, no differences were noted between the groups in overall SNOT-22 scores or the 5 symptom domains (**Table 3**). Mean Self-MOQ scores were 7.0 ± 5.6 for the positive group and 1.8 ± 4.0 for the negative group ($P < .001$). Based on Self-MOQ scores, 6.1% of the positive group was considered hyposmic (Self-MOQ score >3.5) and 55.1% anosmic (>4.5), while no patients in the negative group were hyposmic and 14.7% were anosmic. There were no significant differences between male and female Self-MOQ scores for the positive group (8.4 ± 5.6 vs 6.3 ± 5.5, $P = .22$) or the negative group (1.9 ± 4.1 vs 1.9 ± 4.1, $P = .99$).

Eighteen individuals from the positive group completed the UPSIT, with a mean score of 28.8 ± 7.2 out of 40 possible total points. Hyposmia (UPSIT score, 20-31) was identified in 44.4% and anosmia (8-19) in 11.1%. Bivariate analysis with Pearson correlation of the UPSIT and Self-MOQ scores demonstrated a medium-strength negative linear relationship ($r = -0.45$). This relationship is negative, as a lower score on the UPSIT and a higher score on the Self-MOQ indicate hyposmia/anosmia.

Mean PHQ-4 scores were 3.3 ± 3.1 for the positive group and 3.2 ± 3.1 for the negative group ($P = .92$). The positive group rated overall health status as 67.3 ± 19.6, as compared with 67.1 ± 23.2 for the negative group ($P = .97$). For the positive and negative groups, responses to additional EQ-5D-5L questions averaged 0.3 ± 0.7 vs 0.5 ± 0.8 for mobility ($P = .24$), 0.2 ± 0.5 vs 0.2 ± 0.5 for self-care ($P = .85$), 1.1 ± 1.0 vs 0.8 ± 1.0 for usual activities ($P = .231$), 1.0 ± 0.9 vs 1.4 ± 1.0 for pain/discomfort ($P = .09$), and 0.8 ±0.9 vs 0.9 ± 0.9 for anxiety/depression ($P = .60$), respectively.

Discussion

As more data have been published on COVID-19, anosmia continues to prove a common and early symptom displayed by patients who contract the disease.[6,7] Loss of smell and taste has been found to strongly correlate with positive SARS-CoV-2 testing in ambulatory patients presenting with influenza-like symptoms.[13-17] Two studies have also reported a correlation between internet searches for smell-related information and the incidence of SARS-CoV-2 infection, showing that patients recognize anosmia as a symptom and that its attention in the media is increasing public knowledge on the condition.[12,13] Strikingly, a recent meta-analysis by Tong showed that 52.7% of patients with COVID-19 demonstrated olfactory dysfunction, and additional studies have shown that up to 86% of outpatients who tested positive for SARS-CoV-2 have self-reported olfactory dysfunction.[6,14,15,19] All of these findings underscore the need for physicians to remain vigilant when dealing with patients who present with viral illnesses and/or anosmia and for there to be standardized methods to evaluate these patients to determine if they need testing.

This prospective case-control study utilized cohorts of patients who tested positive and negative for SARS-CoV-2 and evaluated them via questionnaires on subjective smell ability, the SNOT-22, the Self-MOQ, the PHQ-4, and the EQ-5D-5L in an attempt to better understand the ways in which the virus can affect patients and to set up a method in which symptoms can be tracked over time. Our results demonstrate that during the symptomatic phase of the illness, patients with SARS-CoV-2 had a significantly diminished subjective sense of smell as compared with patients testing negative. This correlated with the findings from the validated patient-reported outcome measures, as the positive cohort reported higher scores for decreased sense of smell and taste on the SNOT-22 and the Self-MOQ.

This certainly seems to verify previously published data that patients with COVID-19 have a similar viral prodrome when compared with other common viruses but with smell

seemingly affected to a greater degree. Viruses that give rise to the common cold are well known to cause postinfectious olfactory loss. In fact, postviral anosmia accounts for approximately 18% to 45% of cases of anosmia, and the natural history of viral-associated olfactory loss generally includes some degree of spontaneous recovery.[8] In the years following initial diagnosis, 40% to 60% of patients with postviral olfactory loss will have a measurable spontaneous improvement, with 46% of anosmic and 35% of hyposmic populations exhibiting significant improvement.[10,11] However, only 15% of those with anosmia and 25% of those with hyposmia will eventually recover normal olfaction.[10] Several studies have looked into this relationship between COVID-19 and olfactory dysfunction as a predictor for clinical outcomes of the disease. Yan et al found that anosmia strongly and independently correlated with outpatient management, while intact sense of smell and taste correlated with hospital admission.[20] This relationship was contradicted by Moein et al, who found that 58% of inpatients had either anosmia (25%) or hyposmia (33%), and Vaira et al, who found no significant correlation between the extent of smell and taste loss and the severity of the illness.[5,25] Contradictory findings like these underline the need for additional prospective data to evaluate the natural history of anosmia after SARS-CoV2 infection.

As more studies are performed, it is critical that steps be taken to collect long-term data with the initial presentation of these patients. In looking at time course, Klopfenstein et al reported that anosmia begins approximately 4 days after exposure and that the mean duration of anosmia was 9 days, with 98% of patients completely recovered within 28 days.[26] Interestingly, Hopkins et al evaluated 382 patients with a positive COVID-19 diagnosis via survey and found that 80.1% reported subjective improvement in loss of smell and that recovery appeared to plateau after 3 weeks.[11] However, these studies did not use validated tools to measure these outcomes. To evaluate symptoms at the time of diagnosis and at scheduled intervals in the future, we combined the SNOT-22 questionnaire with the Self-MOQ. In addition, the UPSIT was used to objectively evaluate patients with a positive COVID-19 diagnosis and self-reported olfactory dysfunction. These tests provide information on subjective and objective olfactory ability and can be repeated to track severity over time and evaluate patients for anosmia/hyposmia recovery.

The validated SNOT-22 questionnaire is a widely adopted instrument to evaluate chronic rhinosinusitis treatment outcomes, and the associated questions can be subcategorized into 5 distinct clinical domains.[21,27] To our knowledge, our study is the first to utilize the SNOT-22 questionnaire for comparison of positive and negative cases of SARS-CoV-2 . When we considered the SNOT-22 question regarding the single symptom of decreased sense of smell and taste in our study, there was again a significant difference between the positive and negative groups. However, the overall SNOT-22 scores and rhinologic, extranasal rhinologic, ear/facial, psychological, and sleep dysfunction domain scores between the cohorts were not significantly different, suggesting that the overall symptoms represented by each domain are no different for patients with common viral symptoms who test either positive or negative for SARS-CoV-2.

In an attempt to evaluate subjective olfactory dysfunction with a validated survey tool, we used the Self-MOQ. This simple and reliable questionnaire used for screening olfactory dysfunction was developed to reduce the time and expense involved with other tests of quantitative olfactory dysfunction.[22] We found that patients who were SARS-CoV-2 positive had clinically significant diminished olfaction as compared with the negative cohort. Unfortunately, the prevalence of short-term olfactory loss caused by upper respiratory illnesses has not been well studied. On the basis of the Self-MOQ, we report a 61.2% prevalence of self-reported olfactory loss (6.1% hyposmia, 55.1% anosmia) in patients who were SARS-CoV-2, which is >4 times higher relative to those who were negative. To our knowledge, our study is the first to evaluate the differences in olfaction between the positive and negative groups utilizing any validated questionnaire specific to olfactory dysfunction.

Similar to the Self-MOQ, the UPSIT revealed a 55.5% overall prevalence of olfactory loss in patients who were SARS-CoV-2 positive, but hyposmia instead predominated at 44.4%. This suggests that patients with COVID-19 are able to accurately self-report severe olfactory dysfunction, but there may be some overestimation of the actual degree of severity as compared with objective testing. In addition, a Pearson correlation for the Self-MOQ and the UPSIT demonstrated a nearly significant medium-strength negative linear relationship ($r = -0.45$). The Self-MOQ could easily be included when screening patients with a concern for COVID-19 in a setting where the UPSIT is difficult to obtain, as a result showing hyposmia or anosmia should raise suspicion and potentially lead to further testing.

As the COVID-19 health crisis deepens, it is important to evaluate how infection with the virus, quarantining, and social distancing affect the mental health and general quality of life of patients. The PHQ-4 was used to evaluate for anxiety and depression, and the EQ-5D-5L was used to evaluate the general health dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[24,28,29] Our results did not show a significant difference between the cohorts with regard to anxiety, depression, or general well-being. However, this is a preliminary report, and continued follow-up is necessary to understand potential long-term sequelae.

The strengths of this study include utilizing multiple validated patient-reported outcome measures, an objective olfactory test, a well-matched control group of patients with negative SARS-CoV-2 status. It also demonstrates the correlation of the Self-MOQ, suggesting a role for this test in the screening of patients. Several limitations to this study warrant discussion. Recall bias may influence patients answering the 2 subjective olfactory questions. In particular, the use of self-reported olfactory dysfunction can be influenced by extraneous factors, especially in those who report symptoms after being informed of positive or negative diagnosis.

Furthermore, the study sample represented those with a predominantly ambulatory clinical course, and these data may not be generalizable to patients ill enough to require prolonged hospitalization. The cross-sectional nature of these data would be strengthened by longitudinal data. Finally, our small sample of UPSITs from the positive cohort (n = 18) makes our objective findings regarding olfactory dysfunction preliminary.

Conclusion

Our data demonstrate a significant difference in self-reported olfactory ability based on the Self-MOQ and no difference in self-reported anxiety/depression scores or general quality of life via the PHQ-4 and ED-5D-5L, respectively. We believe our study to be the first to directly evaluate positive and negative cohorts where each presented with viral symptoms, utilizing the SNOT-22 and the Self-MOQ. Further research must be done to understand long-term sequela of the virus

Author Contributions

Kolin Rubel, concept, design, interpretation, drafting, revising, final approval; **Dhruv Sharma**, concept, design, interpretation, drafting, revising, final approval; **Vincent Campiti**, design, interpretation, drafting, revising, final approval; **Grace Yedlicka**, design, interpretation, drafting, revising, final approval; **Sarah J. Burgin**, design, interpretation, drafting, revising, final approval; **Elisa A. Illing**, design, interpretation, drafting, revising, final approval; **Kurt Kroenke**, design, interpretation, drafting, revising, final approval; **Jonathan Y. Ting**, concept, design, interpretation, drafting, revising, final approval.

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