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ORIGINAL ARTICLE

# Assessment of Olfactory Dysfunction in COVID-19 Patients with Validated Quantitative Test: Sniffin' Sticks Test

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## Abstract

**Introduction:** The SARS-CoV-2 virus can cause a high rate of olfactory disorders. Although some patients report subjective improvement, quantitative olfactory tests may not reflect an actual improvement in olfactory function. The aim of our study was to assess the olfactory dysfunction caused by SARS-CoV-2 using the Sniffin' Sticks test and to determine whether there is a significant difference in the results of olfactory tests between patients with olfactory recovery and those without.

**Methods:** The study included 54 patients with olfactory disorders after a COVID-19 diagnosis and 27 healthy controls. COVID-19 patients were divided into two groups: Group 1 (n=27) with recovered complaints and Group 2 (n=27) with persistent complaints. Olfactory functions were tested using the Sniffin' Sticks test and compared with those of the healthy controls (Group 3, n=27).

**Results:** Threshold (T), Discrimination (D), Identification (I), and TDI scores significantly decreased ($p<0.01$) between the olfactory dysfunction groups (Groups 1 and 2) and the healthy controls. Comparison between Groups 1 and 2 showed significant decreases in D, I, and TDI scores ($p<0.01$), while T scores did not differ significantly ($p>0.05$). In Group 1, the mean recovery time for olfactory dysfunction was recorded as 11.7 days.

**Discussion and Conclusion:** In the subjective evaluation of COVID-19 patients who reported improvement in their sense of smell, the validated olfactory test revealed that their olfactory impairment persisted. According to the results of the Sniffin' Sticks test, lower TDI values were observed compared to healthy controls.

**Keywords:** Anosmia; COVID-19; Olfactory disorders.

Coronaviruses can cause a wide spectrum of respiratory infectious diseases. The SARS-CoV-2 that caused the pandemic may also be a causative agent in the olfactory disorders seen with this disease. Recently, strong relationships between COVID-19 and gustatory and olfactory impairments have been reported[1–4].

It has been suggested that in patients with COVID-19, SARS-CoV-2 causes obstructive inflammation of olfactory clefts or targets and damages stem cells, impairing olfactory epithelial support and causing olfactory disorders[5]. Following inhalation, however, some types of coronavirus have been shown to spread from the nasal epithelium after

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passing through the cribriform plate to infect the olfactory bulb and downstream regions such as the piriform cortex and brainstem[6,7]. There is no evidence suggesting SARS-CoV-2 affects the central olfactory system in this way. Unaware of the possibility of recovery, a sudden loss of smell can lead to an anxious situation and adversely affect a patient's quality of life, especially during the current COVID-19 pandemic.

The aim of our study was to assess the olfactory dysfunction in COVID-19 patients with the Sniffin' Sticks test. We also aimed to determine whether there was a comparable difference in the results of olfactory tests in patients with olfactory recovery.

## Materials and Methods

### Patients

This study was approved by the Local Ethics Committee of İstanbul Haydarpaşa Numune Training and Research Hospital (2020/142). This study was conducted in accordance with the Declaration of Helsinki. In this prospective study, we collected 350 polymerase chain reaction (PCR) results from combined nasopharyngeal and oropharyngeal swab test (+) patients. These patients were admitted to İstanbul Haydarpaşa Numune Training and Research Hospital between April 1, 2020 and June 30, 2020. Upon admission, these patients were questioned about any anosmia symptoms.

The study included patients who had olfactory loss during the active phase of the infection, were between the ages of 18 and 65, had a normal nasal endoscopic examination, had no other diseases, and had at least one negative SARS-CoV-2 PCR test after their infection. Patients with active infections and those who had previously experienced olfactory symptoms were excluded.

### Study Design

The study included 54 patients in total, including 36 female patients. Informed consent was obtained from all patients. The patients with a coronavirus infection were screened by a questionnaire and were classified into two groups according to recovery from olfactory dysfunction. Group 1 consisted of 27 patients who reported that their olfactory disruption complaints had completely recovered. The examination was performed on patients at least 1 month after the positive result. Group 2 also consisted of 27 patients who reported that their complaints had not recovered. These two groups were compared first among themselves and then with a control group (Group 3), which included healthy adults. Healthy adults were selected from health professionals who did not have problems with their sense of smell.

Patients' data, including age, sex, previous surgical history, allergies, and smoking history, were collected. The patients were also questioned about the symptom onset dates and duration, whether they were hospitalized due to COVID-19, and whether the anosmia symptoms fully regressed.

The Sniffin' Sticks test was compared with smell disorders. The extended "Sniffin' Sticks" test battery (Burghart GmbH, Wedel, Germany) based on odor-containing felt tips was used to assess orthonasal olfactory function[8]. Threshold detection (T), discrimination (D), and identification (I) were the three olfactory tasks that were carried out.

### Statistical Analysis

For statistical analysis, the Number Cruncher Statistical System (NCSS) program was employed. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used to analyze the study data. With the help of the Shapiro-Wilk test and graphical analyses, it was determined whether quantitative data fit the normal distribution. Mann-Whitney U tests were used to compare quantitative variables between the two groups that did not exhibit a normal distribution. More than two groups of quantitative variables with a normal distribution were compared using one-way analysis of variance (ANOVA) and Bonferroni-corrected pairwise comparisons. Fisher-Freeman-Halton exact tests were employed to compare qualitative data. The accepted cutoff for statistical significance was $p<0.05$.

## Results

There was no significant difference in values such as age, sex, smoking, or length of hospitalization among the three groups (Table 1).

Between the threshold measurements of the cases according to the groups, a statistically significant difference was discovered ($p=0.001$; $p<0.01$). The threshold value was significantly lower in Group 1 cases compared to the

**Table 1.** Comparison of characteristics between groups 1 and 2, patients with COVID-19

| | Group 1 | Group 2 |
|---|---|---|
| Age | 33.04 | 33.20 |
| Gender | | |
| Male | 9 | 9 |
| Female | 18 | 18 |
| Smoking, n (%) | 5/27 (18.5) | 4/27 (14.8) |
| Need for hospitalization, n (%) | 9/27 (33.3) | 9/27 (33.3) |
| Hospitalization time (days) | 7.5 | 7.4 |

**Table 2.** The Sniffin' Sticks test comparisons between groups

| | Group 1 | Group 2 | Group 3 | p | Post Hoc |
|---|---|---|---|---|---|
| Threshold, min-max(med) (mean±SD) | 1.5-16 (6.5) | 1.5-7 (4) | 5.5-11 (8.5) | [a]0.001** | 2<1-3 |
| | 6.98±3.97 | 4.22±1.29 | 8.44±1.44 | | |
| Discrimination, min-max(med) (mean±SD) | 7-15 (11) | 6-14 (10) | 9-15 (14) | [a]0.001** | 2<1<3 |
| | 11.48±2.05 | 10.04±2.33 | 13.04±1.72 | | |
| Identification, min-max(med) (mean±SD) | 8-13 (12) | 6-13 (10) | 11-15 (13) | [a]0.001** | 2<1<3 |
| | 11.26±1.43 | 10.07±1.59 | 12.93±1.14 | | |
| TDI score, min-max (med) (mean±SD) | 18-42 (30) | 15-31 (24) | 25.5-40 (35) | [a]0.001** | 2<1<3 |
| | 29.72±5.66 | 24.33±3.84 | 34.41±3.01 | | |

[a]: Oneway ANOVA; **: p<0.01. SD: Standard deviation; TDI: Treshold + Discrimination + Identification; ANOVA: Analysis of variance.

control group cases, as shown by the results of the paired comparison used to ascertain the difference (p=0.005, p=0.001, and p<0.01; Table 2).

The discrimination measurements according to the groups showed a statistically significant difference (p=0.001; p<0.01). The discrimination value in Group 2 was significantly lower than in Group 1 and the control group, according to the results of the paired comparison to ascertain the difference (p=0.034, p=0.001, and p<0.05). Likewise, the discrimination value was significantly lower in Group 1 compared to the control group (p=0.020; p<0.05; Table 2).

The identification measurements of the cases according to the groups showed a statistically significant difference (p=0.001; p<0.01). The identification value in Group 2 was significantly lower compared to Group 1 and the control group, as shown by the results of the paired comparison to ascertain the difference (p=0.008, p=0.001, and p<0.01). Similarly, it was discovered that Group 1's identification value was significantly lower than that of the control group (p=0.001; p<0.01; Table 2).

According to the groups, there was a statistically significant difference between the total TDI measurements (p=0.001; p<0.01). The TDI value was discovered to be significantly lower in Group 2 when compared to Group 1 and the control group, according to the results of paired comparisons to ascertain the difference (p=0.001, p=0.001, and p<0.01). Likewise, it was discovered that Group 1's TDI value was significantly lower than that of the control group (p=0.001; p<0.01; Table 2).

The average recovery period in Group 1, which had previously experienced olfactory dysfunction, was estimated to be 11.7 days. There was no discernible difference between the distribution of the onset of complaints in the patients according to the presence of anosmia (p>0.05).

A total of 18 hospitalized patients included 1 anosmic patient, 12 hyposmic patients, and 5 normosmic patients. Additionally, the requirement for hospitalization had no impact on the TDI scores.

## Discussion

Sniffin' Sticks is a method used in olfactory disorders and shows specifically which fraction is lost. In this study, we have shown that although this loss of smell improves subjectively in COVID-19 patients, it may not improve in almost any fraction as much as in healthy patients.

The disease brought on by SARS-CoV-2 was given the COVID-19 designation by the World Health Organization[9]. The most typical signs and symptoms are myalgia, a dry cough, fever, and shortness of breath. Additionally, COVID-19 patients may also experience upper respiratory tract symptoms like nasal congestion, runny nose, sore throat, and hyposmia/anosmia[10]. Additionally, it has been noted that COVID-19 can cause a lone, unexpected case of hyposmia or anosmia[11]. Anosmia may be a patient's first complaint or it may appear after other symptoms as a result of the SARS-CoV-2 virus's effects. A loss of taste may also occur in some patients.

Another known potential cause of this post-viral olfactory disorder is coronaviruses[12]. However, the odor and taste disturbances associated with COVID-19 appear to differ significantly from those of other post-viral olfactory disorders in a number of ways. As an illustration, symptoms like smell loss that have been linked to trauma may appear suddenly. Post-infectious olfactory disorders typically appear within a few days and progress rather slowly. Despite a generally positive prognosis, post-infection smell loss can last a lifetime as opposed to a conductive loss of smell during acute rhinitis.

Despite the fact that viruses and other xenobiotics are known to harm the olfactory neuroepithelium, it is

unknown what causes SARS-CoV-2-related smell loss. The main cause of chronic olfactory dysfunction is acute upper respiratory viral infections that damage this epithelium, and several viruses are known to harm the brain via cellular and pericellular transport through this epithelium[13].

By directly attaching to the angiotensin-converting enzyme 2 (ACE2) protein on the cell surface, SARS-CoV-2 can enter epithelial cells[14]. Contrary to epithelial sustentacular and stem cells, olfactory receptor cells do not express ACE2 or another gene (TMPRSS2) involved in SARS-CoV-2 input[5]. Damage to olfactory receptors and the spread of SARS-CoV-2 to other cells necessary for preserving the population of olfactory receptor cells can both indirectly contribute to this. One potential location for an ACE2-independent viral transfer to olfactory neurons via exosomes is the olfactory filament surrounding olfactory receptor cell axons. According to one theory, olfactory receptor neurons may at this point trigger a quick immune response in the host, leading to olfactory dysfunction. However, the olfactory neuroepithelium tends to significantly regenerate if the root layer cell is not significantly damaged[15,16]. This is probably related to spontaneous recovery over time.

In order to interview the patients, either a questionnaire or a phone call was typically used because there was a risk of transmission in the early stages of the pandemic. By calling 3,191 patients, Lee et al.[17] prospectively gathered information on anosmia cases beginning on March 8, 2020. 15.3% (488/3,191) of the patients showed acute anosmia, and the majority of patients recovered within three weeks, with a mean recovery time of roughly seven days. Lechien et al.[4] looked at 417 mild-to-moderate COVID-19 patients. According to results from a condensed version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS), 85.6% and 88.0% of the patients in this group reported having olfactory and gustatory dysfunctions, respectively. Both disorders had a significant correlation ($p<0.001$) with one another. In 11.8% of cases, olfactory dysfunction (OD) presented before the other symptoms. Patients with anosmia had significantly lower sQOD-NS scores than normosmic or hyposmic people.

Studies have recently been published in the literature that emphasize the importance of validated olfactory tests. Among these, olfactory dysfunction was frequently assessed subjectively by looking for anosmia. One of the first studies to make use of a certified smell test, this team employed the quantitative University of Pennsylvania Smell Identification Test (UPSIT) and discovered that 59 (98%) of the 60 patients had some sort of smell dysfunction[18].

**Table 3.** The comparison of olfactory dysfunction between the groups

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Anosmia, n (%) | 0 | 2 (7.41) | 0 |
| Hyposmia, n (%) | 15 (55.56) | 23 (85.18) | 0 |
| Normosmia, n (%) | 12 (44.44) | 2 (7.41) | 27 (100) |

Otte et al.[19] divided the patients into normosmic and hyposmic groups and questioned each group about their perception of smell. 15 (32.61%) participants in the normosmic group (n=46) reported subjectively persistent olfactory issues, compared to 31 (67.39%) participants who did not. In the hyposmic group (n=37), 19 (51.35%) participants felt recovered, while 18 (48.65%) participants continued to complain (no data for 7 patients). Nine patients were normosmic and two patients were hyposmic out of the 11 olfactory recovered patients, who did not experience a sudden olfactory loss during the course of their disease and who did not report the olfactory loss at the time of testing. The findings of this study revealed a poor correlation between patients' subjective assessments of their olfactory disorder and the estimated TDI values. When the validated olfactory test, which has been used to classify patients, was looked at in our study, similar values were found (Table 3).

The T, D, I, and TDI scores between the groups showed a significant difference, according to the findings of our study. Gozen et al.[20], who conducted a study that is similar to ours, discovered a significant difference in the T, D, I, and TDI scores between groups. Olfactory dysfunction was present in 52.5% of COVID-19 patients who completed a questionnaire, but 83% of those who underwent a validated test had it. To quantitatively assess the olfactory dysfunction in 16 patients with COVID-19 and anosmia symptoms, Lechien et al.[21] used the Sniffin' Sticks identification test. Sniffin' Sticks scores ranged from 4.6 to 1.7 on average.

Le Bon et al.[22] used the Sniffin' Sticks test to assess smell loss in COVID-19 patients and reported that compound tests that evaluate threshold, discrimination, and identification scores may be more accurate than screening tests that only focus on smell identification.

The study's strength lies in the fact that anosmia patients underwent an objective test, with a significant outcome. The study's weakness is its inability to assess the long-term outcomes.

Studies conducted so far generally include acute and subacute olfactory dysfunction. Further investigations are needed to determine whether there is another underlying cause in patients with long-term, unresolved olfactory dysfunction.

## Conclusion

In a subjective evaluation of COVID-19 patients who reported their smell had improved, we observed their smell impairments continued, as measured with a validated olfactory test.

**Ethics Committee Approval:** The study was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (no: 2020/142, date: 27/07/2020).

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**Conflict of Interest:** None declared.

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