Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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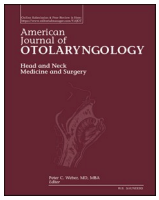

Objective evaluation of odor loss in COVID-19 and other suspected cases

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ABSTRACT

Introduction: COVID-19 is a pandemic disease known with one of the symptoms is sudden onset anosmia. This symptom sometimes may be the only sign of the disease, therefore it must be research widely.
Objective: We aim to evaluate odor dysfunction in COVID-19 patients objectively and safely without any risk of transmitting the disease.
Methods: The odor threshold test was performed on 105 patients hospitalized at the XXXX Training and Research Hospital on the COVID-19 pandemic service before any treatment began. Odor threshold was tested using a modification of the Connecticut Chemosensory Clinical Research Center olfactory function test. COVID-19 signs and symptoms, PCR test results, thorax computed tomography (CT) findings, and length of hospital stay were recorded. Odor tests were scored between 0–8, 0–1 anosmia, 2–3 severely hyposmia, 4 moderate hyposmia, 5 mild hyposmia, 6 and above normosmia.
Results: Forty-one (39%) of the 105 patients were diagnosed with COVID-19 after the PCR results. Patients with an odor threshold score < 5 were classified as "Smell-Impaired Group", patients with an odor threshold score ≥ 5 were placed in "Smell Intact Group". The incidence of female patients in smell-impaired group was significantly higher ($p < 0.05$). The proportion of patients who were PCR-positive for COVID-19 in smell-impaired group was significantly higher ($p < 0.05$) than in smell intact group. Among patients with an odor threshold score from 0 to 1 (anosmic; $n = 15$), 12 (80%) demonstrated PCR positivity ($p < 0.0001$).
Conclusion: Anosmia can be predictive for coronavirus disease. Odor threshold test can be helpful for diagnosis.

1. Introduction

A novel coronavirus pandemic is currently affecting the globe in many ways. The sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused 267.291 new cases of coronavirus disease (COVID-19) infection per day and more than 5985 deaths per day in 2020 worldwide [1]. Some scientists also predict that the world needs to be prepared for a second wave [2].

The importance of rapid testing, diagnosis, and isolation against COVID-19 spread is emphasized. Sudden onset hyposmia/anosmia has received increasing attention as a symptom of COVID-19 as the number of cases has risen worldwide. Due to the efforts of the American Academy of Otolaryngology-Head and Neck Surgery and the British Association of Otorhinolaryngology-Head and Neck Surgery, sudden onset hyposmia and anosmia were accepted as symptoms of COVID-19 by the Centers for Disease Control and Prevention (CDC) and the World Health Organization on 17 April 2020 and 4 May 2020, respectively [3–6].

Many studies have been published on COVID-19 and odor disorders since the beginning of the pandemic [7–14]. The vast majority are subjective reports based on questionnaires or self-report [9–11]. Only three published studies have performed objective smell tests in SARS-CoV-2-positive patients thus far [12–14]. In these studies, Moein et al. administered the University of Pennsylvania Smell Identification test (UPSIT) [12], Vaira et al. performed the Connecticut Chemosensory Clinical Research Center (CCCRC) test [13], and Lechien et al. used the Sniffin' Sticks method [14]; all three found significant olfactory dysfunction in patients with COVID-19. However, in these three studies, all patients with confirmed SARS-CoV-2 positivity, and they were presented with the same test bottles, catalogs, or sticks. This is a risky practice for the novel coronavirus, which is reported to be highly infectious. If a patient who has not been confirmed as being SARS-CoV-2-positive, there is a risk of virus transmission from the previous patient who was tested using the same materials. Therefore, before the disease status is confirmed, odor test cannot be performed in patients with a suspicious diagnosis before the definitive diagnosis.

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1.1. Objective

We aimed to objectively evaluate the odor dysfunctions of COVID-19 patients before starting any treatment and we wanted to compare these patients results with other diseases that can be confused with COVID-19 in the emergency room. In our method, we aimed to prevent virus transmission between patients during the test with a single-use odor threshold test so we could test both SARS-CoV-2-positive patients and suspected patients.

2. Methods

2.1. Study design and patient selection

Ethics committee approval was granted from our Local Ethical Committee of Istanbul Training and Research Hospital (approval number:2384). The odor threshold test was performed on 105 patients hospitalized at the Istanbul Training and Research Hospital on the COVID-19 pandemic service before any treatment began.

We performed the odor threshold test for all COVID-19-suspected patients who were hospitalized, on day 1 of their hospitalization before any treatment had been performed. Thus, we were able to examine the possible differences between patients with symptoms that may interfere with COVID-19 in the ED (such as another virus-induced upper respiratory infection, fever, other viral factor pneumonia, etc.) and definitive COVID-19 patients.

Patients older than 18 years of age who were suspected of having a COVID-19 infection. We excluded patients with psychiatric or neurological disorders, those who were non-cooperative, patients who had undergone previous surgical or radiotherapy to the oral or nasal cavity, and those with a history of previous head trauma, allergic rhinitis, chronic rhinosinusitis, or a pre-existing odor disorder.

All patients provided informed consent for participation in the study. Their general information, including their age, gender, and clinical history, were recorded. COVID-19 signs and symptoms, PCR test results, thorax computed tomography (CT) findings, and length of hospital stay were also recorded. All the PCR specimen collection was done by both nasopharynx and oropharynx swabbing.

The butanol threshold test described in the CCCRC orthonasal olfactory test was used [15]. The strongest butanol concentration (Bottle 0) was prepared as 4% butanol in deionized water. Each subsequent dilution (Bottles 1–8) was diluted at a ratio of 1:3 with deionized water. The N-Butanol solutions were placed in dropper bottles. Then, 0.75 ml of butanol solution were dropped from the same numbered bottles on filter papers numbered from 1 to 8 (7 cm diameter, circular, high suction rate laboratory filter papers, ISOLAB®). Finally, only deionized water was dropped onto a control paper and served as number 9. A separate filter paper set was used for each patient to prevent the risk of contamination.

For each trial, the patient was presented with two filter papers: one with water and the other with a diluted butanol solution. The second filter paper was then sampled in a similar way, and patients were asked to choose the one that contained something other than water. If the selection was wrong, the next stronger butanol concentration was presented along with a filter paper containing water only. When the patient correctly identified the butanol filter paper at the same threshold five times in a row, the threshold value was recorded for that nostril. The other nostril was then individually tested, and both nostril scores were averaged. Possible scores ranged from 0 to 8, with scores $\geq$7 recorded as 7. Since the average CCCRC value was between 6.00 and 7.00 in a report that previously investigated normosmic values in a Turkish society, we also accepted these ranges [16]. In the current study, odor threshold scores from 6.00–7.00 were considered to be normosmic. Scores between 5.00 and 5.75 were classified as mildly hyposmic. Scores from 4.00–4.75 were labeled as moderately hyposmic, while participants were classified as severely hyposmic for scores ranging from 2.00–3.75. Finally, patients with scores between 0 and 1.75 were considered anosmic.

All tests were carried out by the same operators. These operators entered the rooms of patients in isolated single rooms and wore N95 masks, face protection, protective overalls, and shoe covers. Papers with varying concentrations of butanol solutions to be presented to the patients were prepared outside the patients' rooms, at the nurses' bench, just before entering each patients room. After the test, we placed all the papers in the trash before leaving the patient's room. Gloves were changed in between each patient. The same test was also applied to 20 healthy volunteers who served as a control group. Threshold testing was performed with these volunteers both directly from the bottles containing butanol with their numbered dilutions and also by dropping the solutions onto filter paper from the same concentrations. No threshold difference was detected between the bottles and the paper.

2.2. Statistical analysis

The statistical analysis was carried out using the Statistical Package for the Social Sciences, version 26.0 (IBM, Armonk, New York). The mean $\pm$ standard deviation, median (minimum-maximum), frequency, and ratio values were used to report the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. A Mann-Whitney *U* test was used in the analysis of the quantitative independent data. A Chi-square test was carried out to analyze the qualitative independent data. The statistical significance level of the obtained data was interpreted with the value of "p." p values <0.05 were considered statistically significant.

3. Results

Following the exclusion criteria, 105 patients (56 women and 49 men) who were hospitalized with the suspicion of COVID-19 on the pandemic service of the XXXX Training and Research Hospital were included in the study. The mean age was 56.1 $\pm$ 15.6 years (range: 9–21). Forty-one (39%) of the 105 patients were diagnosed with COVID-19 after the PCR results were positive for SARS-CoV-2. The general and clinical features of the patients are shown in Table 1.

We selected 5 as the threshold value and then divided the patients into two groups according to their smell scores. Patients with an odor threshold score $<$ 5 were classified as 'Smell-Impaired' group, while patients with an odor threshold score $\geq$ 5 were placed in 'Smell Intact' group. There were no significant differences between the groups in terms of age, taste complaints, cough, dyspnea, headache, and asthenia. The incidence of female patients in the 'Smell-Impaired' group was significantly higher ($p < 0.05$) than 'Smell Intact' group. The proportion of patients who were PCR-positive for COVID-19 in 'Smell-Impaired' group was significantly higher ($p < 0.05$) than in 'Smell Intact' group. In the smell-impaired group, the rate of abdominal complaints and sore

Table 1
General and clinical features of patients.

Age(years)	56,1 $\pm$ 15,6 (range 21–91)
Hospital stay(day)	8.4 $\pm$ 5 (range 0–24)
Olfactory threshold score	4,3 $\pm$ 2,3 (range 0–7)
Female	56 (53,3%)
Male	49 (46,7%)
PCR positive	41 (39,0%)
Viral pneumonia Finding in CT	93 (88,6%)
Olfactory complaint	14 (13,3%)
Taste complaint	15 (14,3%)
Fever	34 (32,4%)
Cough	46 (43,8%)
Dyspnoea	41 (39,0%)
Abdominal symptoms	17 (16,2%)
Headache	18 (17,1%)
Sore throat	17 (16,2%)
Asthenia	38 (36,2%)

throats was also significantly higher than that seen in smell intact group ($p < 0.05$) (Table 2).

Among patients with an odor threshold score from 0 to 1 (anosmic; n = 15), 12 (80%) demonstrated PCR positivity. This finding was statistically significant when compared to the rest of the patients ($p < 0.0001$). Other results according to olfactory scores are listed in Table 3.

There was no significant difference between the two groups in regards to their length of hospital stay ($p = 0.629$). While the average length of hospital stay was 7.98 days in smell-impaired group, the average length of hospitalization was 8.08 days in normal smell threshold group. We therefore concluded that a loss of smell had no effect on the patient's prognosis after hospitalization.

None of our authors who performed the tests were infected with SARS-CoV-2.

4. Discussion

COVID-19 is a disease with a severity ranging from a mild upper respiratory disease to severe interstitial pneumonia and acute respiratory distress syndrome [17–19].According to the CDC, frequently recorded symptoms of COVID-19 include fever, chills, cough, shortness of breath, muscle pain, headache, sore throat, and sudden onset of the loss of taste and smell [5].

In a multicenter European study, a total of 357 patients (85.6%) had olfactory dysfunction related to COVID-19 infection. Among them, 284 (79.6%) patients were anosmic, and 73 (20.4%) were hyposmic. Phantosmia and parosmia were noted in 12.6% and 32.4% of the patients during the disease course, respectively. That report was a survey study that was only conducted among certain patients diagnosed with COVID-19 [9].

Speth et al. also only included patients who were COVID-19-positive and reported that their olfactory dysfunction prevalence was 61.2%. They also found that age was negatively associated with a report of olfactory dysfunction, while female sex was positively associated with reporting olfactory dysfunction [10]. We found no relation among different ages, but there was a female predominance in our anosmia/hyposmia group compared to the normosmic group.

In their study, Yan et al. contacted participants via email. As in our study, Yan et al. included all patients with COVID-19-like symptoms who were both PCR-positive and negative, and groups from two similar clinics were compared among themselves. A smell disorder was detected in 68% of SARS-CoV-2-positive patients and in 16% of negative patients [11].

Moein evaluated odor function with the UPSIT method in 60 SARS-CoV-2-positive patients and found odor dysfunction in 98% of patients: 25% of patients were anosmic, 33% were severely hyposmic, 27% were moderately hyposmic, 13% were mildly hyposmic, and 2% were normosmic [12].

In Vaira et al.'s objective evaluations, they used the CCCRC test only in patients with confirmed COVID-19 infection. Complete anosmia was detected in 2.8% of their participants. Most patients presented with variable degrees of hyposmia (80.6%), while 16.7% demonstrated normal olfactory function [13].

A third objective test report was recently published by Lechien et al. They used the Sniffin' Stick method but only included the odor discrimination component. These researchers also only tested patients with confirmed COVID-19. They found that 48% were anosmic and 14% were hyposmic, while 38% of patients who reported a loss of smell were objectively normosmic [14].

In our study, 64 participants were PCR-negative, and 41 were PCR-positive. We found that among the 41 COVID-19 patients, only 7 (17%) had olfactory complaints, although 60% of them demonstrated several degrees of hyposmia.

Post-viral anosmia is a common cause of smell loss in adults and is known to be associated with many human viral strains, including other coronaviruses that cause the common cold [20]. The pathophysiological mechanisms leading to olfactory and gustatory dysfunctions in COVID-19 infection are still unknown. Early studies that have evaluated the mechanisms of SARS-CoV-2-mediated loss of smell have suggested neurotrophic targeting of olfactory neurons versus infection of non-neural olfactory epithelial cells as a possible mechanism [8].

The UPSIT, CCCRC test, Sniffin' Sticks, and OSIT methods are previously developed and accepted odor tests. The UPSIT has four "scratch and sniff" booklets that each contain 10 microcapsule fragrances. After people open the capsule, they smell the page in the booklet [21,22]. In the CCCRC test, fragrances are offered in bottles that are not transparent [15]. Sniffin' Sticks are felt tip pens impregnated with scents that are handed to the patient to smell [23]. In the OSIT test, the researcher folds a piece of fragrant paraffin paper in half to crush the microcapsule and then offers it to the participant. The participant then opens and smells the paper [24]. For the Sniffin' Sticks and CCCRC tests, the odor threshold is considered along with the ability for odor discrimination, while discrimination alone is assessed in the UPSIT and OSIT.

We thought it was more important to determine the threshold level because patients were complaining about not being able to smell at all rather than simply being unable to distinguish between odors. In their study, Vaira et al. performed the CCCRC test on COVID-19 patients and found that the threshold scores were lower than the discrimination scores [13].

We set out to develop a quick, easy-to-apply test without the risk of transmission between patients. We chose the butanol threshold test defined in the CCCRC test; instead of using the bottles, we distributed the scent using absorbent, disposable, cheap filter papers. The idea for the paper use came from other techniques commonly used for odor discrimination, especially OSIT. We didn't use OSIT instead of the technique we developed for a few reasons. First, we didn't have enough time to order and provide the fragrances; second, as we mentioned above wouldn't be able to test thresholds by using the OSIT.

In order to modify the threshold step of the CCCRC test to the method where the solution was dropped onto the filter paper, we performed the threshold test on 20 volunteers. These participants both smelled from the bottle and sniffed the filter paper, and it was found that both scores were the same. Therefore, our ratings remained the same.

When the CCCRC test was first identified, it was not designed to give the degree of olfaction loss by evaluating only the threshold test [15]. Thus, we accepted the threshold values from an article where the CCCRC test was performed in a Turkish society and normative data were presented [16].

Of patients with COVID-19-like symptoms, those who demonstrated an odor threshold of ≤4 were significantly more likely to be SARS-CoV-

Table 2
Comparison of the two groups.

	Smell-impaired group		Smell intact group		p value
	N		N		
Age	43	54,1 ± 16,1	62	57,4 ± 15,3	0,180
Female	29	67,4%	27	43,5%	***0,016***
Male	14	32,6%	35	56,5%	
Positive swab	23	53,5%	18	29,0%	***0,012***
Viral pneumonia	39	90,7%	54	87,1%	0,568
Finding in CT					
Olfactory complaint	11	25,6%	3	4,8%	***0,002***
Taste complaint	9	20,9%	6	9,7%	0,113
Fever	13	30,2%	21	33,9%	0,695
Cough	23	53,5%	23	37,1%	0,096
Dyspnoea	16	37,2%	25	40,3%	0,748
Abdominal symptoms	3	7,0%	14	22,6%	***0,033***
Headache	10	23,3%	8	12,9%	0,166
Sore throat	11	25,6%	6	9,7%	***0,030***
Asthenia	14	32,6%	24	38,7%	0,519
Hospital stay (day)	7.98 ± 5.5		8.08 ± 4.6		0,629

[m] Mann-Whitney U test/[X2] Ki-square test.
Bold and italic p values means statistically difference.

Table 3
Number of patients according to their Olfactory scores.

Olfactory threshold score	0–1 Anosmia	2–3 Severe hyposmia	4 Moderate hyposmia	5 Mild hyposmia	6–7 Normosmia
Total	15	22	6	21	42
Female	13	12	4	9	18
Male	2	10	2	12	23
PCR positive	12	8	3	2	16
Viral pneumonia	12	16	5	16	35
Finding in CT					
Pneumonia	12	16	5	16	35
Olfactory complaint	6	4	1	2	1
Taste complaint	6	2	1	2	4
Fever	5	6	2	7	14
Cough	7	13	3	12	12
Dyspnoea	6	8	2	9	16
Abdominal symptoms	0	2	1	5	9
Headache	0	6	4	4	4
Sore throat	6	5	0	2	4
Asthenia	3	8	3	5	19

2-positive. More interestingly, among patients with an odor threshold score from 0 to 1 (anosmic; n = 15), 12 of them (80%) demonstrated PCR positivity, and this difference was statistically significant when compared to the rest of the patients ($p < 0.0001$).

We also did not detect any effect of the degree of odor loss on the course of the disease. There was no difference in terms of the length of hospital stay of the patients and their inability to identify odors. However, this result may have occurred because we only tested patients with relatively mild and moderate disease severities. Further studies will be needed to determine if the loss of smell is associated with the disease course or length of hospitalization.

We did have the chance to compare PCR-positive patients with PCR-negative patients across every parameter because of the method we developed. Thus, we did not face the risk of transmitting COVID-19 to patients who were not positive for SARS-CoV-2.

This study has several limitations. Firstly, Odor Test was performed on patients with mild or moderate symptoms. We did not perform olfactory threshold testing on severe patients who were in the intensive care unit, which means we cannot find an objective result between the loss of smell and the course of the disease. Second, and may be the most important, limitation is the need for validation of this modified test method. In the future we hope to validate our method before the second wave hits the world. Lastly, we accepted only PCR positivity for COVID-19; more than one PCR test was performed on most of the strongly suspicious patients and it was enough for us to get one positive results in any of them.

5. Conclusion

Anosmia can be predictive for coronavirus disease. Olfaction threshold test can be helpful for pre-diagnosis, and can be used all the patients safely in the era of the pandemic.

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CRediT authorship contribution statement

Nihal Seden: Setting, Study design, Data collection, Writing, Editing.
Enes Yiğit: Study design, Data collection, Writing, Editing.
Özgür Yiğit: Study design, Data collection, Writing, Editing.
İsmail Kaygısız: Study design, Data collection, Writing.

Declaration of competing interest

None.

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