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Original article

Assessment of anosmia/hyposmia in post-COVID-19 patients: a cross-sectional study in an eastern province of Saudi Arabia

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Abstract. *Background and aim*: It has been shown that olfactory dysfunction is one of Coronavirus disease-2019 (COVID-19) common and puzzling symptoms that may persist weeks after the infection. This study aimed for the objective assessment of persisting olfactory dysfunction in post-COVID-19 patients. It also investigated the factors associated with the development of such symptoms in the Eastern Province of Saudi Arabia. *Methods:* A cross-sectional study that was conducted in the Department of Physiology, College of Medicine, Imam Abdulrahman bin Faisal University, Khobar, Saudi Arabia. One hundred and forty-seven participants were included in this study, and sixty of them agreed to participate in the objective testing using the Connecticut Chemosensory Clinical Research Center (CCCRC) olfaction test. *Results:* There was a significant correlation between the following factors: (a) Persistence of anosmia/hyposmia and the time of onset of anosmia/hyposmia (P=0.015). (b) Persistence of anosmia/hyposmia and the duration of anosmia/hyposmia (P=0.012). (c) Duration of anosmia/hyposmia and the duration of COVID-19 symptoms (P=0.010). Interestingly, there was a significant association between the subjective participants' claim of anosmia/hyposmia and the score of their objective assessment (P=0.026). *Conclusion:* The current study demonstrated that post-COVID-19 participants with delayed onset of anosmia/hyposmia and/or longer duration of either anosmia/hyposmia or COVID-19 symptoms were prone to have persistent olfactory dysfunction. Further studies are necessary to uncover the underlying pathophysiology and management of this olfactory dysfunction in COVID-19 patients. (www.actabiomedica.it)

Key words: COVID-19, olfactory dysfunction, anosmia, hyposmia, Saudi Arabia

Introduction

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2. It was discovered and traced in Wuhan, China, in December 2019, spreading globally and leading to the COVID-19 pandemic (1). By September 2022, over 620 million cases of COVID-19 have been reported, including 6.5 million deaths worldwide (2). The first case of COVID-19 in Saudi Arabia was reported in March 2020 (3). Managing COVID-19 is challenging because of the variety of symptoms, severities, and complications. Patients report a range of mild-to-severe symptoms. However, in previous studies, the most commonly reported symptoms were fever, dyspnea, cough, myalgia, and fatigue (3,4). Additionally, changes in smell or taste have been reported in approximately 60–64% of patients with COVID-19 (5).

Studies have shown that the olfactory dysfunction (OD) caused by COVID-19 resolves within the first

weeks of infection. However, it may persist for months, and recovery may take longer in up to 60% of patients (6). According to the World Health Organization (WHO), post-COVID-19 condition is defined as symptoms that persist for at least two months and cannot be explained by other etiologies (7). One of these persistent symptoms is OD, which can range from a reduced ability to smell (hyposmia) to a complete loss of smell (anosmia) (8).

The prevalence and risk factors associated with post-COVID-19 anosmia were assessed in many studies worldwide (9-12). In Saudi Arabia, few studies evaluated anosmia and hyposmia in post-COVID-19 patients using self-reported data. They showed that anosmia is one of the most reported persistent symptoms in post-COVID-19 patients (13-17). All published studies have reported that COVID-19 can cause OD. However, most studies conducted in Saudi Arabia reached conclusions based on subjective reporting of OD in affected patients. Therefore, this study aimed to objectively assess the olfactory function of post-COVID-19 patients using a standardized testing method. Different tests can be used to objectively assess OD, such as the University of Pennsylvania Smell Identification Test (UPSIT) and the Connecticut Chemosensory Clinical Research Center (CCCRC) olfaction test (18,19). The CCCRC olfactory test was adopted for the objective assessment of this study because it is sensitive, valid, easy to perform, and cost-effective (19). In the literature, few studies have used the CCCRC olfactory test to assess olfaction in COVID-19 patients (20-23).

We believe that the findings of this study will contribute to our understanding of the epidemiology and pathophysiology of COVID-19-related OD. This is because only a few studies have been conducted in this regard in Saudi Arabia. Most previous studies have subjectively assessed anosmia. To the best of our knowledge, only one study has evaluated post-COVID-19 anosmia objectively using the CCCRC test in Abha, Saudi Arabia (23). Accordingly, this study is the first to objectively assess the persistence of anosmia in post-COVID-19 patients and to investigate the factors associated with its development in the Eastern Province of Saudi Arabia.

Patients and methods

This cross-sectional study was conducted between September 2022 and April 2023 in the Department of Physiology, College of Medicine, Imam Abdulrahman bin Faisal University (IAU), Khobar, Saudi Arabia. This study covered four cities in the Eastern Province: Dammam, Dhahran, Khobar, and Qatif. This study aimed to objectively assess participants who complained of a reduced ability to smell (hyposmia) or a complete loss of smell (anosmia) after COVID-19 infection between January and August 2022 (8). The Connecticut Chemosensory Clinical Research Center (CCCRC) olfaction test was used as an objective assessment tool to evaluate study participants.

Post-COVID-19 condition is defined by the WHO as symptoms that persist for at least two months and cannot be explained by other etiologies (7). Therefore, since data collection started in October 2022, we included all participants with positive swabs between January 2022 and August 2022 who reported persistent post-COVID-19 anosmia/hyposmia. During the COVID-19 pandemic, the Ministry of Health (MOH) in Saudi Arabia declared daily local statistics, including the number of new cases, active cases, recoveries, and mortalities in each city. According to the King Abdullah Petroleum Studies and Research Center in collaboration with the MOH, the number of confirmed COVID-19 cases in Dammam, Dhahran, Khobar, and Qatif between January 1, 2022, and August 31, 2022, was 486, 465, 462, and 431, respectively, with a total of 1844 cases. Using the Epi Info Software application, the required sample size was estimated to be 366 participants (24), based on a predicted confidence level of 95%, acceptable margin of error of 4%, and expected frequency of 25.5% in previous studies, which stated that the prevalence of anosmia and hyposmia was 15.5% and 10%, respectively (25).

The study included all males and females aged >18 years old with post-COVID-19 anosmia/hyposmia in the eastern provincial cities of Dammam, Khobar, Dhahran, and Qatif. Informed consent was obtained from all participants. A major criterion for inclusion was a formal record in Tawakkalna that confirmed a positive oropharyngeal or nasal swab for COVID-19 between January 2022 and August 2022. Tawakkalna

is an official COVID-19 application in Saudi Arabia that prevents the spread of the COVID-19 virus. It was developed by the Saudi Authority for Data and Artificial Intelligence. The study excluded all participants with known allergies, previous nasal cavity surgery or radiotherapy, current smokers, pre-existing smell dysfunction before COVID-19 infection, participants with a history of head trauma, or those with current or previous history of allergic rhinitis, chronic rhinosinusitis, or psychotic or neurodegenerative disorders. After applying the inclusion and exclusion criteria to the total number of participants who claimed to have post-COVID-19 anosmia/hyposmia (n=1254), 147 participants were eligible for this study and 60 agreed to be objectively evaluated, representing approximately 40% and 16.4% of the estimated sample size (n=366), respectively (Figure 1).

The data collection included two steps; in the first step the data was collected using an online self-administered questionnaire distributed through social media platforms. The questionnaire was designed on the basis of a validated questionnaire used in an observational study conducted in Jeddah, Saudi Arabia (3). In the second step of data collection, participants who fulfilled the inclusion criteria were contacted to participate in the objective assessment using the CCCRC olfaction test. The CCCRC olfaction test comprised two steps: the first step assessed the olfaction threshold, and the second step assessed the olfaction identification ability of different smells (19).

Procedures

1. Olfactory threshold assessment

Preparation of Butanol concentrations for olfactory threshold assessment

The olfactory threshold assessment used diluted butanol (n-butyl alcohol) at seven different concentrations, which were prepared using 99% butanol

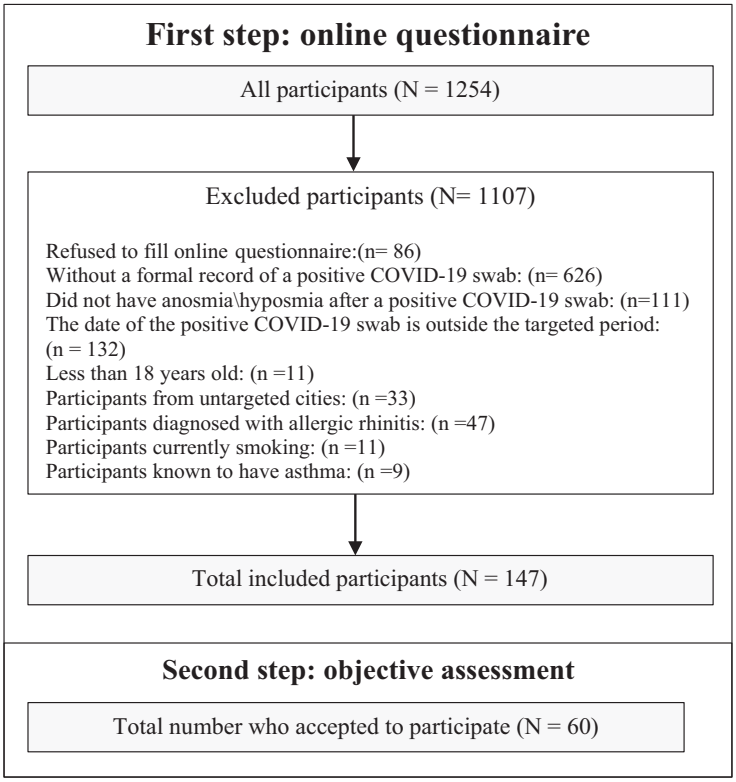

Figure 1. Inclusion and exclusion criteria flow chart.

obtained from a Saudi overseas marketing and trading company (SOMATCO, KSA) and distilled water obtained from Drop Supply Trading Company (DSTC, KSA). Diluted butanol (n-butyl alcohol) was placed in seven different amber flasks, each with a total solution volume of 60 mL, numbered from one to seven based on its concentration in a descending fashion as follows: 4%, 1%, 0.4%, 0.1%, 0.05%, 0.01%, and 0.005%. As a control, a flask containing odorless distilled water was labeled flask eight. All the flasks were colorless and identical in shape to maintain test accuracy.

Method of application of olfactory threshold assessment

The olfactory threshold test was conducted by a single examiner in a noiseless room. Before starting the test, the participants were instructed not to use any perfume to minimize fragrance interference. The participants were positioned with both eyes closed, occluding one of the nostrils, and using the other patent nostril. Subsequently, two identical 60 mL-amber flasks were displayed alternately, one with distilled water, and the other with a butanol solution. Starting with the lowest butanol concentration (0.005%), the participants were instructed to inhale gently and detect the presence or absence of an odor. If the participant was not able to detect the odor, another 60-mL amber flask with a higher concentration solution of butanol was presented while maintaining the alternation with the control flask (number 8). The repetition of any step was permitted upon request by the participant. The same steps were repeated for other nostrils.

Scoring of the olfactory threshold test

The participants required at least two correct identifications of the flask to obtain a score. The scores ranged from zero to seven points for each nostril. The olfactory threshold score was obtained by calculating the average score for both nostrils. Each score has a composite score that is used in the final score calculation, as shown in Table 1.

Table 1. Scoring criteria of olfactory threshold assessment.

Detected concentration	Olfactory thresholds score out of 7	Olfactory threshold corresponding composite score
Participants with ability to detect the lowest concentration of (0.005%)	7	50
Participants with ability to detect the concentration of (0.01%)	6	40
Participants with ability to detect the concentration of (0.05%)	5	30
Participants with ability to detect the concentration of (0.1%)	4	20
Participants with ability to detect the concentration of (0.4%)	3	10
Participants with ability to detect the concentration of (1%)	2	
Participants with ability to detect the highest concentration of (4%)	1	0
Participants who could not detect any concentration after repetition of the test.	0	

2. Olfactory identification test

Preparation of the olfactory identification test

The identification test aimed to test the participants' ability to identify 10 odorants that are well known to the population. The containers were identical, closely sealed with a lid, and covered with a black label to avoid identification by sight rather than smell. Each container had an equivalent proportion of 10 g/flask. The containers were labeled with numbers from 1–10. The test also contained other 10 distracting substances that were randomly presented to the participants between the original 10 substances. No specific distracting

agents were administered. A familiar odor was commonly recommended for each culture. A study conducted in Italy used substances familiar to the Italian population, such as sardines and spoiled meat. Thus, to adapt this test to the Saudi culture, we added cardamom powder and dried mint as distracting substances, as they are more locally recognized products (20). The identification test items are presented in Table 2.

Method of application of the olfactory identification test

The identification test was performed in the same noiseless room by the same examiner who performed the olfactory threshold test. In this test, a list of names for the 10 test items, in addition to the 10 distracting substances, was given to the participants beforehand. To enhance monorhinic olfaction testing, the other nostrils must be closed. Additionally, the participants had to close their eyes, while the examiner positioned the flask near the patient's nostrils. The examiner gently shook the container to homogenize odorous substances before opening each container. With each container opened to the participants, they were asked to identify the substance using only the names of the substances on the list given previously. If incorrect, the participants received corrective feedback. Each container was presented again to participants who were in doubt. When all the testing was completed, all the 10 substances were tested in one nostril, the same steps were repeated on the other side. The examiner must present the containers randomly to reduce the chances of memorizing the order.

Scoring of the olfactory identification test

Scores for this test were calculated by taking the number of odors that the participant could identify out of ten for each nostril, and the average of both nostrils was calculated. Each score had a composite score that was used in the final score calculation.

3. Final scoring (Combined olfactory threshold and olfactory identification test scores)

The final scores of both tests, the olfaction threshold and identification tests, were calculated by first taking the olfactory threshold test score and its corresponding composite score, then taking olfactory identification test score and its corresponding composite score (Table 3).

Next, the olfactory threshold test composite score was added to the olfactory identification test composite score to obtain a final score out of 100. Finally, the

Table 3. CCCRC test composite scores.

Olfactory threshold score	Olfactory threshold composite score	Olfactory identification score	Olfactory identification composite score
7	50	8-10	50
6	40	6-7	40
5	30	4-5	30
4	20	3	20
2-3	10	1-2	10
0-1	0	0	0

Table 2. Identification test: test items and distractors list.

Test items		Distractors	
Johnson's® Baby powder (JOHNSON & JOHNSON CONSUMER INC., Thailand)	Fruit-flavoured gum (Mentos, Perfetti Van Melle Inc., USA)	Potato chips (Lay's, PepsiCo, KSA)	Tobacco (Marlboro Red, Philip Morris, USA)
Nutella® Chocolate (FERRERO INDUSTRIAL CO, Italy)	Tomato Ketchup (Heinz, Heinz Foods, UK)	Leather	Cardamom powder
Coffee (Nescafe, Nestle CO, Swaziland)	Black pepper	Wood shavings	Garlic
Ammonia	(Dove, Binzagr Unilever Limited, KSA)	Cinnamon	Rubber
Vicks-VapoRub. (Procter & Gamble GmbH, Germany)	Orange	Burnt paper	Dried mint

participants were categorized into five groups based on their final scores, as shown in Table 4.

Ethical considerations

This study was approved by the Institutional Review Board (IRB) of Imam Abdulrahman bin Faisal University (IRB reference number, IRB – UGS – 2022 – 01 - 469; date, November 21, 2022). The approved study duration was eight months.

Statistical analysis

Analysis was done using IBM SPSS software (Version 26). Using Chi-square and Fisher's exact tests, the associations between categorical variables were studied. The statistical significance for all analyses was set at $P < 0.05$ and 95% confidence interval.

Results

After collecting all the data from both the online questionnaire and objective assessment, analysis was performed using IBM SPSS software (Version 26). One hundred and forty-seven participants were included; 394 were excluded because they did not meet the inclusion criteria (Figure 1). The sociodemographic data and clinical characteristics of the target population are shown in (Table 5).

Regarding the pattern of COVID-19 symptoms, the majority had positive COVID-19 oropharyngeal/nasal swabs in January (n=31, 21.1%) and July (n=30, 20.4%) 2022. Regarding the duration of COVID-19 symptoms, 133 (90.5%) participants had symptoms for <2 weeks, whereas 14 (9.5%) participants had symptoms for >2 weeks. Regarding the severity of COVID-19 infection, 122 (83%) patients had mild symptoms and were treated at home with analgesia, eight (5.4%) had moderate symptoms, needed nebulizers, and were treated as outpatients, whereas 17 (11.6%) had severe symptoms and required either emergency room or intensive care unit (ICU) admission. Among the included participants, only one (0.7%) did not receive COVID-19 vaccination. The patterns of anosmia and hyposmia are described in (Table 6).

Sixty participants underwent the second step, which is the CCCRC olfaction test. The sociodemographic and clinical characteristics of the participants in the objective assessment are listed in (Table 7). The majority of participants had positive COVID-19 swabs in June (n=13, 21.7%) and January (n=12, 20%) 2022. Additionally, 57 (95%) participants had COVID-19

Table 4. Participants overall composite score and the corresponding level of smell dysfunction.

Participants final score	Level of smell dysfunction
0-10	Anosmia
20-40	Severe hyposmia
50-60	Moderate hyposmia
70-80	Mild hyposmia
90-100	Normal

Table 5. Sociodemographic and clinical characteristics of targeted population (n=147, from online survey).

Variables	N (%)
Age (Years)	
From 18-30	108 (73.5%)
From 31-45	30 (20.4%)
More than 45	9 (6.1%)
Sex	
Male	19 (12.9%)
Female	128 (87.1%)
Nationality	
Saudi	138 (93.9%)
Non-Saudi	9 (6.1%)
Medical condition	
Obesity	20 (13.6%)
Diabetes	3 (2%)
Hypertension	3 (2%)
Cardiovascular disease	1 (0.7%)
No medical condition	(1.7%)
City of residence	
Khobar	29 (19.7%)
Dammam	63 (42.9%)
Dhahran	22 (15%)
Qatif	33 (22.4%)
BMI	
Underweight	15 (10.2%)
Normal	70 (47.6%)
Overweight	42 (28.6%)
Obese	20 (13.6%)
Exposure to chemicals at work	
Yes	16 (10.9%)
No	131(89.1%)

symptoms for <2 weeks. Moreover, 53 (88.3%) participants had three doses of the COVID-19 vaccine. Regarding the severity of COVID-19 symptoms, 53 (88.3%) participants had mild symptoms, three (5%) had moderate, and only four (6.7%) participants suffered from severe symptoms. Regarding the pattern of anosmia/hyposmia, the onset of anosmia/hyposmia started within 1–7 days in 55 (91.7%) participants, within 8–14 days in four (6.7%), and after 14 days of COVID-19 infection in one (1.7%). The duration of anosmia/hyposmia varied from <1 month, 1–6 months, and > 6 months, representing (n=56, 93.3%), (n=3, 5%), and (n=1, 1.7%), respectively. Persistence of anosmia/hyposmia was observed in eight (13.3%) participants only.

In this study, several factors were assessed to determine the association between persistent anosmia and hyposmia after recovery from COVID-19. Remarkably, four significant associations were observed. First, statistical analysis revealed that the onset of anosmia and hyposmia had a significant relationship with persistent anosmia/hyposmia (P = 0.015). This validated that those who had anosmia and hyposmia eight days after having a positive COVID-19 oropharyngeal/nasal swab were more likely to have persistent anosmia/hyposmia. Second, the relationship between persistent anosmia/hyposmia and the duration of anosmia/hyposmia was statistically significant (P= 0.012). It was demonstrated that having anosmia/hyposmia for >1 month increased the likelihood of developing persistent anosmia/hyposmia. Third, the relationship between the duration of anosmia/hyposmia and COVID-19 symptoms was statistically significant (P= 0.010). This confirmed that those who had COVID-19 symptoms for >2 weeks were more likely

Table 6. The pattern of anosmia/hyposmia of targeted population (n=147, from online survey).

Variables	N (%)
Onset of anosmia/hyposmia	
1-7 days	129 (87.8%)
8-14 days	15 (10.2%)
>14 days	3 (2%)
Severity of anosmia/hyposmia	
Mild (smell all kinds of odors but to a lesser degree than before)	45 (30.6%)
Moderate (only smell strong odors)	41 (27.9%)
Severe (can't smell any odors)	61 (41.5%)
Duration of anosmia/hyposmia	
< 1 month	137 (93.2%)
1-6 months	6 (4.1%)
> 6 months	4 (2.7%)
Persistent anosmia/hyposmia	
Yes	36 (24.5%)
No	111 (75.5%)
If yes specify the level of anosmia/hyposmia:	
Mild (smell all kinds of odors but to a lesser degree than before)	19 (52.8%)
Moderate (only smell strong odors)	17 (47.2%)
Severe (can't smell any odors)	0 (0%)
Any family member develops the same problem.	
Yes	93 (63.3%)
No	54 (36.7%)

Table 7. Sociodemographic and clinical characteristics of participants in the objective assessment (n=60).

Variables	N (%)
Age (Years)	
From 18-30	53 (88.3%)
From 31-45	6 (10%)
More than 45	1 (1.7%)
Medical condition	
Obesity	9 (15%)
Diabetes	0 (0%)
Hypertension	1 (1.7%)
Cardiovascular disease	1 (1.7%)
No medical condition	49 (81.6%)
Nationality	
Saudi	55 (91.7%)
Non-Saudi	5 (8.3%)
City of residence	
Khobar	15 (25%)
Dammam	33 (55%)
Dhahran	6 (10%)
Qatif	6 (10%)
Sex	
Male	10 (16.7%)
female	50 (83.3%)
BMI	
Underweight	8 (13.3%)
Normal	32 (53.3%)
Overweight	11 (18.3%)
Obese	9 (15%)
Exposure to chemicals at work	
Yes	7 (11.7%)
No	53 (88.3%)

to have anosmia/hyposmia for > 1 month. Fourth, a significant relationship was found between the final total score on the objective assessment and subjective claim of persistent anosmia/hyposmia by the participants (P= 0.026). Accordingly, participants who reported persistent anosmia/hyposmia subjectively showed a score indicating persistent anosmia/hyposmia when objectively evaluated using the CCCRC olfaction test (Table 8).

Discussion

This study revealed a significant correlation between the persistence of anosmia/hyposmia and the time of onset, duration of OD, and duration of COVID-19 symptoms. The study also confirmed a significant association between the participants' subjective claims of anosmia/hyposmia and the final score of their objective assessment. This demonstrates that post-COVID-19 participants with delayed onset of anosmia/hyposmia and/or longer duration of anosmia/hyposmia or COVID-19 symptoms were prone to persistent OD.

Our results showed a significant correlation between the time of onset of anosmia/hyposmia and persistence of anosmia/hyposmia (P=0.015). This suggests that the delayed onset of OD (after eight days of a positive COVID-19 swab) may be associated with a greater chance of developing persistent dysfunction. However, Algahtani et al. reported that this correlation was insignificant (14). Besides, a study by Vaira et al. suggested that OD typically has an early onset within the first five days of COVID-19 infection and is temporary in most cases. However, the correlation between symptom onset and persistence has not been investigated (20). Our study also showed that the duration of anosmia/hyposmia was positively correlated with the persistence of these symptoms (P=0.012). This confirms that the longer the duration of anosmia/hyposmia, the higher the chance of developing persistent symptoms. In contrast, Algahtani et al. reported an insignificant association between anosmia duration and persistence among study participants (14). Additionally, the current study reported a significant association between the duration of COVID-19 symptoms and that of anosmia/hyposmia (P=0.010). More precisely, the study showed that participants who had COVID-19 symptoms for >2 weeks were more likely to have anosmia/hyposmia for >1 month. Paranhos et al. reached a similar conclusion (21). Future research is needed to explore the pathophysiology of post-COVID-19 anosmia and hyposmia.

Our data showed that the age and sex of the participants, their body mass indices, and/or the co-occurrence of any chronic diseases were not associated with the development of persistent anosmia/hyposmia. Although our study showed no difference between males and females in the persistence of anosmia/hyposmia symptoms, a few studies have shown that females are significantly more susceptible to developing persistent anosmia/hyposmia (3,11,14,26). This could be attributed to the fact that males comprised only 12.9% of the sample, making the comparison between males and females in that regard difficult. Our results were not in agreement with those of Mahmoud et al. (16) and Alkwai et al. (17), since they reported that chronic diseases increased the chances of persistent anosmia/hyposmia. This is in contrast to the results of our study, which showed no significant correlation. This could be explained by the fact that 81.6% of the participants did not have any concurrent chronic diseases.

The current study reported no significant association between the severity of COVID-19 and the

Table 8. The associations of persistent anosmia/hyposmia, duration of anosmia/hyposmia and final score with the studied factors of targeted population.

Variable 1	Variable 2	Chi-square (x^2) value 95% CI	p-value
Persistent anosmia/hyposmia	Onset of anosmia/hyposmia	9.570[a]	.015 **
	Duration of anosmia/hyposmia	8.128[a]	.012 **
Duration of anosmia/hyposmia	Duration of Covid-19 symptoms	12.339[a]	.010 **
Final score of objective assessment	Persistent anosmia/hyposmia	6.061[a]	.026 **

persistence of anosmia/hyposmia among the participants. However, the literature has reported controversial results. Some studies reported a significant association between COVID-19 severity and the development of persistent anosmia/hyposmia (15,16,27). By contrast, Lechien et al. (9) and Mariani et al. (10) showed that most patients who developed persistent anosmia/hyposmia had a history of mild infection.

During the objective assessment using the CCCRC olfaction test, we found that 26.7% (n=16) of the participants were truly affected. In particular, 18.3% (n=11), 6.7% (n=4), and 1.7% (n=1) of the patients had mild, moderate, and severe hyposmia, respectively. This suggests that a relatively high percentage of patients with COVID-19 developed post-COVID-19 persistent anosmia/hyposmia. Many studies have shown similar results but with higher reported percentages. This difference may be attributed to the sample size, as not all the participants agreed to participate in the objective assessment. A study conducted in the Saudi city of Abha showed that 42% of the participants had low CCCRC scores when objectively evaluated (23). Moreover, a study conducted in Brazil using the same method of assessment reported that approximately 63.5% of the participants had some form of OD (21). Another Turkish study used the CCCRC test to evaluate patients. They found that 80% of participants showed some degree of smell dysfunction. Of these, 31 had mild hyposmia, 26 had moderate anosmia, and 17 had severe anosmia (22). Furthermore, a European case series, which was the first to objectively assess olfaction using the CCCRC test, reported OD in 61.1% of participants (20).

The current study showed that the results of participants who subjectively affirmed persistent anosmia/hyposmia were significantly correlated with the results of objective evaluation using the CCCRC olfaction test. In contrast, those who reported no persistent anosmia/hyposmia had normal results. This could be attributed to the use of a validated, detailed questionnaire and an accurate assessment method. Other studies have compared the results of objective olfaction tests with participants' self-reports. In 2020, a study was conducted on 86 patients who self-reported OD and compared their subjective reporting with the results of objective assessment using Sniffin's sticks test. Interestingly, smell dysfunction was observed in only 62% of the patients (28). In contrast, another study mentioned that although 52.5% of their patients self-reported OD, the rate was found to be higher, with up to 83% using the objective testing (29). Similarly, another study supports this result. It stated that 51 of 70 patients who did not complain of smell loss were found to have OD when evaluated using the CCCRC test (22). This variation between the previously mentioned studies may be due to differences in the level of patients' awareness of smell loss and/or the presence of some kind of chronic genetic alteration in their sense of smell.

From a physiological perspective, olfaction is a chemosensory process mediated by the olfactory nerve (cranial nerve I). Olfactory neurons are located in the olfactory neuroepithelium, and they project across the cribriform plate at the roof of the nasal cavity, forming synapses with neurons in the central olfactory nervous system for modulation and interpretation (30). Olfaction in humans can include an odorant's association with experiencing emotions and memory formation due to its direct relationship with the limbic system and cerebral cortex (31). Many theories have been discussed as possible explanations for OD in patients with COVID-19. First, viral infections can cause nasal blockage, thereby preventing access of odor to the sensory epithelium and impeding its binding to olfactory receptors. However, many studies have ruled out this theory because of the large proportion of patients with anosmia without nasal obstruction. Second, olfactory neuronal loss is considered a potential cause of anosmia. Third, the possibility of the virus infiltrating the brain and affecting the centers of olfaction has been studied by many investigators. Nevertheless, the two aforementioned scenarios have many inconsistencies, such as the absence of viral entry protein expression and unavailability of the virus within olfactory neurons. Fourth, researchers have described another mechanism by which the virus enters the olfactory epithelium and damages support cells. This hypothesis is supported by the existence of two entry proteins (angiotensin-converting enzyme 2 and trans-membrane protease serine 2) in the olfactory epithelium of the sustentacular cells, where the virus is primarily present. Taken

together, the latter mechanism is the most likely explanation for anosmia and hyposmia in patients with COVID-19 (32).

Conclusion

In this study, we showed that a significant proportion of patients with COVID-19 may develop post-COVID-19 persistent anosmia/hyposmia. The results revealed that post-COVID-19 patients with late onset of anosmia/hyposmia, longer duration of COVID-19 symptoms, and longer duration of anosmia/hyposmia were prone to persistent anosmia/hyposmia. Moreover, there was a significant correlation between the final score of the objective assessment and subjective claim of persistent anosmia/hyposmia. One of the strengths of this study is that it used a standardized objective method for the assessment of persistent anosmia/hyposmia in post-COVID-19 patients. This can help in obtaining the most accurate results. Additionally, our sample size was based on the defined inclusion and exclusion criteria, which reduced the impact of the confounding factors. However, this limited the number of participants and decreased the chances of achieving an optimal sample size. Another potential limitation of our study is the high female-to-male ratio, which may not represent the general population. Therefore, future similar studies with larger sample sizes are needed to study this new clinical entity and uncover the underlying pathophysiology of this chemosensitive disorder in patients with COVID-19.

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Ethics Committee: This study was approved by the Institutional Review Board (IRB) of Imam Abdulrahman bin Faisal University (IRB reference number, IRB – UGS – 2022 – 01 - 469; date, November 21, 2022).

Conflict of Interest: All authors declare that they have no commercial associations that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: RQ, RA conceived and designed the study, conducted research, provided research materials, and organized data. LA, NA conceived the idea, conducted research, organized data, and wrote draft of the manuscript. LI, SA, HA conceived the idea, conducted research, analyzed, and interpreted data. SS conducted research and revised the draft of the manuscript. KA conducted research, supervised it, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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