Prospective Clinical Research Report

Testing for anosmia and ageusia in patients presenting to the emergency department with suspected coronavirus disease 2019 in Saudi Arabia

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Abstract

Objective: This study investigated the role of objective olfactory dysfunction (OD) and gustatory dysfunction (GD) testing among patients with suspected coronavirus disease 2019 (COVID-19) who presented with respiratory symptoms.

Methods: A prospective, blinded, observational study was conducted in the emergency units of two tertiary hospitals. Participants were asked to identify scents in the pocket smell test (PST) and flavors in four different solutions in the gustatory dysfunction test (GDT). We assessed the level of agreement between objective findings and self-reported symptoms. We evaluated the diagnostic accuracy of chemosensory dysfunction for diagnosing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Results: Of 250 participants, 74 (29.6%) were SARS-CoV-2-positive. There was slight agreement between self-reported symptoms and objective findings (kappa = 0.13 and 0.10 for OD and GD, respectively). OD assessed by the PST was independently associated with COVID-19

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(adjusted odds ratio $= 1.89$, 95% confidence interval, 1.04–3.46). This association was stronger when OD was combined with objective GD, cough, and fever (adjusted odds ratio $= 7.33$, 95% confidence interval, 1.17–45.84).

**Conclusions:** Neither the PST nor GDT alone are useful screening tools for COVID-19. However, a diagnostic scale based on objective OD, GD, fever, and cough may help triage patients with suspected COVID-19.

**Keywords**
Coronavirus disease 2019, olfactory disorder, taste, diagnostic accuracy, anosmia, ageusia

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**Introduction**

The health consequences of coronavirus disease (COVID-19) are unprecedented, and this health crisis has posed unique challenges in the public health sector. Early reports from China showed that these patients had symptoms of a lower respiratory tract infection, including cough, fever, and shortness of breath. However, these observations were regarding hospitalized patients who experienced the worst forms of infection.\(^1\),\(^2\) Subsequently, with the substantial spread of this disease, official reports indicated other prevalent symptoms of the upper respiratory tract, such as a sore throat, nasal congestion, and rhinorrhea, in addition to headache, fatigue, and myalgia.\(^3\),\(^4\) Importantly, accumulated evidence has suggested that smell and/or taste dysfunction are also frequent symptoms, ranging from a reduction in the perceived odor and/or flavor intensity (hyposmia/hyposmia) to a complete loss of chemosensory function (anosmia/ageusia).\(^5\),\(^6\) These symptoms are usually characterized by a sudden onset and rapid recovery, and they usually present in the early stage of infection.\(^7\) Therefore, the World Health Organization and the Centers for Disease Control and Prevention have included olfactory dysfunction (OD) and gustatory dysfunction (GD) as COVID-19 symptoms.\(^3\),\(^4\)

Although symptomatic patients with respiratory viral infections, such as rhinovirus, parainfluenza, and Epstein–Barr virus, may exhibit smell and/or taste disorders,\(^8\) the prevalence of chemosensory dysfunction may be higher among patients with COVID-19. More specifically, recent data from COVID-19 studies estimated that the prevalence of smell disorders was 53.7% to 85.6% in European countries,\(^9\) 11.4% to 47.0% in China,\(^10\) and 75.2% in Saudi Arabia.\(^11\) Additionally, the prevalence of taste loss was 52.9% to 61.4% in North America and 5.1% to 43.4% in Asia.\(^12\) No relevant corresponding study has been conducted in Saudi Arabia to date. The global discrepancies in chemosensory symptomatology may be due to differences in participants’ recruitment, disease severity, and methods of olfactory/gustative assessment. Furthermore, there are two main types of data collection techniques, namely subjective and objective methods. Subjective reporting of chemosensory alteration has been frequently used in recent epidemiological studies of patients with COVID-19.\(^13\),\(^14\) However, subjective reports may over or underestimate the true prevalence and may not agree with the outcomes of
objective tests.\textsuperscript{15,16} Therefore, reliable objective tests need to be identified for detecting OD and GD as early symptoms to augment the diagnosis and prediction of SARS-CoV-2 test positivity. However, little is known about the diagnostic accuracy of objective tests for OD and GD and their applicability as screening tools among patients with suspected COVID-19 infection.

In this study, within the context of unique infection control measures, we aimed to objectively assess OD and/or GD in patients presenting with respiratory symptoms, and to examine the agreement between the outcomes of objective testing and self-reported disrupted smell/taste. We also assessed the diagnostic accuracy of OD and GD testing for the diagnosis of COVID-19.

**Methods**

**Study design and setting**

A prospective, blinded, and multicenter study was carried out from June 2020 to March 2021. Patients were concurrently recruited at two hospitals in Riyadh, Saudi Arabia, one of which was a Ministry of Health hospital designated for managing patients with COVID-19. The study protocol was approved by the Institutional Review Board of King Abdullah Bin Abdulaziz University Hospital (KAAUH), Princess Nourah Bint Abdulrahman University (PNU) and registered in the ClinicalTrials.gov database (identifier #: NCT04388618).

**Selection of participants**

Eligible participants were patients of both sexes who fulfilled the surveillance definitions of suspected COVID-19 cases in accordance with the guidelines of the Saudi Center for Disease Prevention and Control (Saudi CDC).\textsuperscript{17} These included patients presenting with the following: acute respiratory illness (fever, cough, or shortness of breath); sudden onset of headache, sore throat, nausea, rhinorrhea, dysgeusia, or dysosmia; and previous intimate contact with confirmed COVID-19 cases. Children aged \(<12\) years, adults aged \(>65\) years, and pregnant and lactating women were not considered for the study. Additionally, patients with the following conditions were excluded: congenital anomalies interfering with normal olfactory and taste, including Kallmann syndrome, indifference to pain syndrome, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities syndrome, and ciliopathy disorders; trigeminal nerve disease; blindness and deafness; and suspected malingering.

**Sample size calculations**

The OpenEpi online calculator (Version 3; https://www.openepi.com/SampleSize/SSCohort.htm) was used to estimate the sample size for frequency in a population. At the time of the study, the number of patients with COVID-19 in Saudi Arabia was 1920. We estimated the sample size on the basis of a prevalence of 24.82% for ageusia/anosmia, as indicated in the literature.\textsuperscript{18} Therefore, based on a confidence level (CI) of 95% and a design effect of 1, the required sample was estimated at 250 patients. The patients were selected using a probability sampling technique, and eligible patients were enrolled until the required sample size was reached (\(N = 250\)).

**Data collection**

Each potential study participant was isolated in a single, negative-pressure room to meet the infection control requirements at the institutions. A research assistant collected the patients’ demographic data,
including age, sex, nationality, smoking status, and occupation, as well as clinical information, including a medical history of hypertension, diabetes, and asthma. The patients’ self-reported symptoms of OD and GD were also recorded. Subsequently, each participant was tested for OD and GD using validated objective tests as described below.

**Measurements and outcomes**

An odor identification test was performed using the eight-item pocket smell test ([PST] Sensonics, Inc., Haddon Heights, NJ, USA). The PST is a rapid screening tool based on the gold standard of OD detection, namely the University of Pennsylvania smell identification test.\(^{19}\) The PST was validated in the National Health and Nutrition Examination Survey, which was carried out on a large, nationally representative sample in the USA.\(^{20}\) The test tool comprises two test cards, with four scent strips at the bottom of each card.

Taste function was assessed using a standardized, validated taste measure.\(^{21,22}\) In the gustatory dysfunction test (GDT), four solutions were used to assess gustatory function. These solutions comprised a salted solution (30 g of table salt in 1 L of deionized water), a sweet solution (30 g of refined sugar in 1 L of deionized water), a sour solution (90 mL of lemon juice in 1 L of deionized water), and deionized water (control) (Figure 1a).\(^{22,23}\) A research assistant was assigned to each isolation room with the potential study participant. The room contained an envelope containing a copy of the consent form, a pen for signing the form, two PST smell cards, four bottles for testing taste, a stylus for scratching the cards, and a plastic bag (Figure 1b).

The objectives of the study were discussed with each patient before participation, and written informed consent was obtained upon enrollment. Neither the participant nor the research assistant knew the different pieces of equipment used for the tests. The envelope and its content complied with the required infection control measures to prevent disease transmission. Each envelope could be used only once. After opening the envelope, the participants were asked to smell the scents and select one response out of four possible choices indicated above each strip. To conduct the GDT, the patients were asked to pour the contents of a color-coded 1-mL container onto the middle of their tongue and indicate whether the flavor was bitter, salty, acid, or neutral. The correct answers for both the scent and flavor tests were only made available to the assigned study investigator.

The research assistant recorded the answers of the PST and GDT on a specifically designated online form using a tablet placed in the isolation room and submitted the patient’s answers to the system. Following data collection, each patient was asked to place the smell cards and the taste test bottles in the plastic bag, which was then placed within the envelope. Subsequently, the envelope was sealed and disinfected. Finally, the same research assistant took a nasopharyngeal swab for SARS-CoV-2 testing. The samples were sent to Riyadh National Laboratory to test for SARS-CoV-2 using a real-time reverse transcription polymerase chain reaction (RT-PCR) test in accordance with the Saudi CDC guidelines.\(^{17}\)

The numbers of correct answers were summed up to calculate the PST scores, which ranged between 0 and 8. OD was defined as an olfactory function score on a scale of 0 to 5 (when a patient provided three or more incorrect answers).\(^{24,25}\) The correct answers of the GDT were used to calculate a taste score on a scale of 0 to 4. A taste score of ≤3 indicated hypogeusia/ageusia.\(^{23}\) The reporting of this study conforms to the STROBE Guidelines.\(^{26}\)
Statistical analysis

Statistical analysis was carried out using IBM SPSS v 26.0 (IBM Corp., Armonk, NY, USA). Two-sided p values <0.05 were considered statistically significant. Continuous data are reported as the mean ± standard deviation, and categorical data are reported as the frequency and percentage.

Method agreement analysis was applied to assess the agreement between self-reported OD and/or GD (no or yes) and the objective results via the PST and GDT (no disorder versus the existence of a disorder), respectively. The method agreement analysis comprised the following three assessment approaches: 1) testing the systematic difference in the proportion of positive results between the self-reported and objective tests by performing McNemar’s test; 2) testing the degree of agreement by calculating Cohen’s kappa (κ); and 3) testing the diagnostic accuracy of the PST and GDT for detecting patients with COVID-19 by computing the sensitivity, specificity, likelihood ratios, and test accuracy, as well as the area under the receiver operating characteristic curve (AUC). Cohen’s κ values were interpreted as poor agreement (κ ≤ 0), slight agreement
Univariate associations between SARS-CoV-2 test positivity and the clinical variables (presenting symptoms), and those between the objective PST and GDT categorical outcomes were tested using the chi-square test. A multivariable logistic regression analysis was performed to assess the predictors of SARS-CoV-2 test positivity. The presenting symptoms significantly associated with SARS-CoV-2 test positivity (from the univariate analyses), as well as the variables of objective olfactory and gustatory outcomes (PST and GDT), were included as potential predictors. The confirmed COVID-19 status (based on the SARS-CoV-2 real-time RT-PCR test result) was the dependent variable. The analyses were adjusted for the demographic characteristics of the participants, namely age, sex, nationality, and employment status. The results are expressed as adjusted odds ratios (aORs) and the respective 95% CIs.

### Results

#### Characteristics of the study participants

We enrolled 250 participants in the study. The participants’ demographic and clinical characteristics are shown in Table 1. Among them, 74 (29.6%) were SARS-CoV-2-positive. The median (interquartile range) age of the study participants was 32.0 years (25.0–44.3). More than half of the study participants were men (56.4%), non-Saudi (64.8%), and employed (64.0%). The most prevalent symptoms

| Parameter | Category |
|-----------|----------|
| Age, years (median [IQR]) | 32.0 (25.0–44.3) |
| Hospital, n (%) | KAAUH 65 (26.0) |
| | PMAH 185 (74.0) |
| Sex, n (%) | Male 141 (56.4) |
| | Female 109 (43.6) |
| Nationality, n (%) | Saudi 88 (35.2) |
| | Non-Saudi 162 (64.8) |
| Employment status,* n (%) | Student 39 (15.6) |
| | Employed – healthcare 67 (26.8) |
| | Employed – other 93 (37.2) |
| | Retired/not working 48 (19.2) |
| Medical history, n (%) | Hypertension 28 (11.2) |
| | Diabetes 33 (13.2) |
| | Asthma 17 (6.8) |
| | Chronic sinusitis 7 (2.8) |
| | Multiple sclerosis 0 |
| | Smoking 30 (12.0) |
| SARS-CoV-2 real-time RT-PCR result, n (%) | Positive 74 (29.6) |
| | Negative 176 (70.4) |

*Missing data (N = 247).

IQR, interquartile range; KAAUH, King Abdullah Bin Abdulaziz University Hospital; PMAH, Prince Mohammed Bin Abdulaziz Hospital; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction.
were a cough (61.2%), fever (44.0%), and shortness of breath (44.0%) (Table 2).

**OD assessment**

The correct responses of patients regarding perceived smells and flavors, and the frequency distributions of the PST and GDT scores are shown in Figure 2. Sixteen (6.4%) patients reported OD. However, based on the objective PST results, 113 (45.2%) patients had OD. Although self-reported symptom data showed no significant association between SARS-CoV-2 test positivity and smell disorder, the PST results indicated that the prevalence of OD was significantly higher in patients with SARS-CoV-2 than in those without SARS-CoV-2 ($p = 0.001$). Among the patients with SARS-CoV-2, the agreement between self-reported smell impairment and objective OD (as indicated by the PST results) was 48.6%, with a $\kappa$ value of 0.13 ($p = 0.026$), which indicated slight agreement (Table 3). This result was confirmed by a significant systematic disagreement between the symptomatic and objective evaluation methods ($p < 0.001$, McNemar’s test).

**GD assessment**

Ten (4.0%) participants reported hypogeusia, and 27 (10.8%) suffered from GD according to the objective GDT. Self-reported GD was significantly higher in participants with SARS-CoV-2 than in those without SARS-CoV-2 ($p = 0.004$). Among participants with SARS-CoV-2, there was slight agreement between self-reported dysgeusia and dysgeusia detected using the GDT test (agreement = 79.7%, $\kappa = 0.10$, $p = 0.351$). However, there was no systematic difference in the positive outcomes ($p = 0.302$, McNemar’s test).

**Diagnostic accuracy of the PST and GDT in patients with COVID-19**

As screening tests for the detection of patients with COVID-19, the PST and GDT showed a sensitivity of 60.8% and 16.2%, specificity of 61.4% and 91.5%, test accuracy of 61.2% and 69.2%, and an area under the curve of 0.611 and 0.538, respectively (Table 4).

**Predictive model for SARS-CoV-2 test positivity**

The potential predictors of SARS-CoV-2-positive test results were assessed using the symptoms that were significantly associated in the univariate analysis (fever, cough, and self-reported GD), as well as the outcomes of chemosensory functions (using the PST and GDT). All of the significantly associated presenting symptoms in the univariate analysis were independently

### Table 2. Participants’ symptoms according to their SARS-CoV-2 real-time reverse transcription polymerase chain reaction test result.

| Parameter                  | All participants (N = 250) | SARS-CoV-2-positive (N = 74) | SARS-CoV-2-negative (N = 176) | p    |
|----------------------------|---------------------------|-------------------------------|-------------------------------|------|
| Fever                      | 110 (44.0)                | 51 (68.9)                     | 59 (33.5)                     | <0.001|
| Cough                      | 153 (61.2)                | 54 (73.0)                     | 99 (56.3)                     | 0.013 |
| Shortness of breath        | 110 (44.0)                | 36 (48.6)                     | 74 (42.0)                     | 0.337 |
| Vomiting and/or diarrhea   | 60 (24.0)                 | 17 (23)                       | 43 (24.4)                     | 0.805 |
| Rash                       | 4 (1.6)                   | 1 (1.4)                       | 3 (1.7)                       | 0.839 |
| Runny nose/sore throat     | 97 (38.8)                 | 27 (36.5)                     | 70 (39.8)                     | 0.626 |

Data are n (%).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Figure 2. Correct patient responses regarding perceived smells and flavors, and the frequency distributions of (a) PST and (b) GDT scores. GDT, gustatory dysfunction test; PST, pocket smell test.
Self-reported GD had the strongest association (aOR = 5.62; 95% CI, 1.18–26.71; p = 0.030), followed by fever (aOR = 4.91; 95% CI, 2.55–9.44; p < 0.001), and cough (aOR = 1.98; 95% CI, 1.04–3.78; p = 0.039). Using the eight-item PST, having OD was a significant predictor of SARS-CoV-2 test positivity (aOR = 1.89; 95% CI, 1.04–3.46; p = 0.038). Additionally, a combination of OD and GD as detected by objective testing was a strong predictor of SARS-CoV-2 test positivity (aOR = 4.29; 95% CI, 1.47–12.52; p = 0.008). A combination of cough, fever, and an objective alteration in chemosensory function (as assessed by the PST and GDT) was the strongest independent predictor of SARS-CoV-2 test positivity (aOR = 7.33; 95% CI, 1.17–45.84; p = 0.033, Table 5).

Table 3. Self-reported symptoms and objective assessment results of the PST and GDT in the study participants.

| Parameter               | Category                     | All participants (N = 250) | SARS-CoV-2-positive (N = 74) | SARS-CoV-2-negative (N = 176) | p^a      | κ (SE)   | p^b      |
|-------------------------|------------------------------|----------------------------|----------------------------|----------------------------|----------|---------|----------|
| Olfactory dysfunction   | Self-reported hyposmia/anosmia | Yes                        | 16 (6.4)                   | 7 (9.5)                     | 9 (5.1)   | 0.200   | 0.13 (0.05) | 0.026    |
|                         | No                           | 234 (93.6)                 | 67 (90.5)                  | 167 (94.9)                 |          |         |          |
|                         | PST-based hyposmia/anosmia   | Yes                        | 113 (45.2)                 | 45 (60.8)                  | 68 (38.6) |         |          |
|                         | No                           | 137 (54.8)                 | 29 (39.2)                  | 108 (61.4)                 |          |         |          |
| Taste dysfunction       | Self-reported hypogeusia/ageusia | Yes                       | 10 (4.0)                   | 7 (9.5)                     | 3 (1.7)   | 0.004   | 0.10 (0.13) | 0.351    |
|                         | No                           | 240 (96.0)                 | 67 (90.5)                  | 137 (98.3)                 |          |         |          |
|                         | GDT-based hypogeusia/ageusia  | Yes                        | 27 (10.8)                  | 12 (16.2)                  | 15 (8.5)  |          |          |
|                         | No                           | 223 (89.2)                 | 62 (83.8)                  | 161 (91.5)                 |          |         |          |

^p value estimated using Pearson’s chi-square test; p value estimated using Cohen’s kappa (κ).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SE, standard error; PST, pocket smell test; GDT, gustatory dysfunction test.

Table 4. Diagnostic accuracy of the pocket smell test and the gustatory dysfunction test for detecting patients with severe acute respiratory syndrome coronavirus 2 infection.

| Parameter          | Value (95% CI) | p value^a | Value (95% CI) | p value^a |
|--------------------|----------------|-----------|----------------|-----------|
| Pocket smell test  |                |           | Gustatory dysfunction test |           |
| Sensitivity, %     | 60.81 (48.77–71.96) | 0.001     | 16.22 (8.67–26.61) | 0.074     |
| Specificity, %     | 61.36 (53.74–68.59) |           | 91.48 (86.33–95.15) |           |
| PPV, %             | 39.82 (33.76–46.21) |           | 44.44 (28.25–61.91) |           |
| NPV, %             | 78.83 (73.26–83.51) |           | 72.2 (69.94–74.35) |           |
| LR+                | 1.57 (1.21–2.04) |           | 1.9 (0.94–3.87) |           |
| LR−                | 0.64 (0.47–0.87) |           | 0.92 (0.82–1.02) |           |
| Accuracy           | 61.2 (54.86–67.28) |           | 69.2 (63.07–74.86) |           |
| AUC                | 0.611 (0.534–0.688) |           | 0.538 (0.458–0.619) |           |

^aThe p value was estimated using Pearson’s chi-square test.

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; AUC, area under the receiver operating characteristic curve.
Discussion

OD and GD have recently been raised as primary concerns in patients with suspected COVID-19 in multiple countries, and these disorders are prevalent in patients subsequently diagnosed with COVID-19. Recently, the American Academy of Otolaryngology-Head and Neck Surgery and the British Association of Otorhinolaryngology proposed that OD and GD could be used as potential screening tools for possible SARS-CoV-2 infection. However, the diagnostic potential of chemosensory dysfunction in screening methods at patients’ presentation has not been thoroughly investigated. In this study, OD and GD were prevalent in 45.2% and 10.8% of the patients presenting with respiratory symptoms, respectively, as shown by reliable objective tests. These tests could not be regarded as sensitive methods of screening for COVID-19. However, olfactory alterations were independently associated with SARS-CoV-2 positivity, particularly in the presence of concomitant fever, cough, and objectively measured GD.

To the best of our knowledge, this is the first study to assess the performance of objective chemosensory alterations in COVID-19 among the Saudi population. OD was detected by objective testing in 60.8% of patients who were subsequently diagnosed with COVID-19 (sensitivity), whereas the PST successfully detected 61.4% of SARS-CoV-2-negative patients (specificity). Romero-Gameros et al. found that a three-odor-based PST had a lower sensitivity (19.4%) and a higher specificity (95.5%) for COVID-19 than those in our study. Moreover, in our study, the PST and GDT had positive predictive values of 39.8% and 44.4%, respectively. This finding indicated that less than half of the patients with objective chemosensory dysfunction would have been diagnosed with COVID-19. However, the positive predictive value results might have been affected by the prevalence of COVID-19, potentially explaining variable diagnostic outcomes in other studies with a different prevalence of COVID-19. Based on these observations, the PST and GDT cannot

Table 5. Multivariable logistic regression analysis of predictors of severe acute respiratory syndrome coronavirus 2 positivity among the study participants (N = 250).

| Variable                        | aOR*  | 95% CI     | p     |
|---------------------------------|-------|------------|-------|
| Symptoms                        |       |            |       |
| Cough                           | 1.98  | 1.04–3.78  | **0.039** |
| Fever                           | 4.91  | 2.55–9.44  | **<0.001** |
| Self-reported GD                | 5.62  | 1.18–26.71 | **0.030** |
| Altered chemosensory function   |       |            |       |
| OOD                             | 1.89  | 1.04–3.46  | **0.038** |
| OGD                             | 2.41  | 0.98–5.92  | 0.055 |
| OOD + OGD                       | 4.29  | 1.47–12.52 | **0.008** |
| Combinations                    |       |            |       |
| OOD + fever                     | 3.02  | 1.53–5.94  | **0.001** |
| OOD + cough                     | 2.16  | 1.15–4.04  | **0.016** |
| OOD + cough + fever             | 2.79  | 1.33–5.87  | **0.007** |
| OOD + OGD + cough + fever       | 7.33  | 1.17–45.84 | **0.033** |

*The analysis was adjusted for the demographic variables of age, sex, nationality, and employment status.

aOR, adjusted odds ratio; CI, confidence interval; GD, gustatory dysfunction; OOD, objective olfactory dysfunction (assessed by the pocket smell test); OGD, objective gustatory dysfunction (assessed by the gustatory dysfunction test).
be used as screening tests for COVID-19, and they cannot be used alone in a single diagnostic instrument.

Nevertheless, in our study, patients presenting with dysosmia (as measured by the PST) and dysgeusia (as measured by the GDT) along with other respiratory symptoms were more likely to be diagnosed with COVID-19. In our analysis, although the PST-confirmed OD was a significant predictor of COVID-19 in the multiple regression analysis (aOR = 1.89), the independent association with COVID-19 was stronger with the addition of objective dysgeusia, cough, and fever (aOR = 7.33). Romero-Gameros et al.\textsuperscript{16} reported an OR of 8.25 for the combination of dysosmia as measured by PST, cough, and asthenia. In addition to the relevance of these findings for the development of future diagnostic scales for early detection of COVID-19, these outcomes might help raise the suspicion of COVID-19 in a subset of patients presenting with combined OD and GD, and respiratory symptoms. These patients might consequently require isolation, extensive monitoring, and comprehensive care until confirmation of SARS-CoV-2 by real-time RT-PCR.

This study showed incompatible outcomes between the objective and subjective methods of chemosensory assessment according to the results of the systematic difference in the proportion of SARS-CoV-2-positive patients (McNemar’s test) and the levels of agreement (κ analysis). These findings suggested that there was minimal or no agreement between the self-reported outcomes and those revealed by the objective tests. In brief, subjective methods are based on self-reported measures obtained through questionnaires or personal interviews with patients.\textsuperscript{14,33} Although subjective methods are easy and safe methods of measurement, they are prone to recall bias. Moreover, these methods inherently encompass a high degree of variability owing to the lack of standardized questions. OD and/or GD reported in subjective tests may be under or overestimated.\textsuperscript{34} In a recent meta-analysis of 28 studies (19,175 patients), qualitative subjective methods indicated a pooled OD prevalence of 44.6%.\textsuperscript{34} However, the prevalence of OD according to objective tests from six studies (571 patients with COVID-19) was 76.7%.\textsuperscript{35} Objective measurements entail quantifying human responses to physical stimuli using psychophysical techniques.\textsuperscript{36} Moreover, they are usually performed under standardized methodological approaches in a controlled environment, which reduces response and measurement bias. However, objective tests require face-to-face interviews,\textsuperscript{35} and they should be carried out by well-trained examiners with extreme caution to ensure safety during an ongoing pandemic. In our study, there was a poor agreement regarding chemosensory impairment between self-reporting and objective testing (κ = 0.13 and 0.10 for the PST and GDT, respectively). Similarly, Romero-Gameros et al.\textsuperscript{16} showed a κ value of 0.40 between the dysosmia self-perception questionnaire and PST results. This poor correlation might be attributable to variability in self-reported olfactory perceptions due to mood changes and the motivation and motives of patients.\textsuperscript{16}

Collectively, subjective and objective methods of smell and taste function may show significant differences in their performance in COVID-19 studies because of the detected prevalence of chemosensory disorders, applied methodological approach, and diagnostic potential of these tests for COVID-19. Accordingly, subjective assessment should be used with caution, while objective PST results can be considered reliable predictors of COVID-19 infection, especially when combined with other symptoms, such as fever and cough.
Importantly, the reliability of the outcomes in the current study is supported by several strengths of the methodological approach. First, the data were prospectively collected, and the analysis was adjusted for potential confounders that may affect causal associations between the smell test and SARS-CoV-2 test positivity. Second, the PST and GDT were carried out under strict measures of infection control, including a negative-pressure room environment, contactless data collection operations, and the use of specific, non-transmissible equipment. Third, the investigators were blinded to the correct results of smell strips and flavors to ensure unbiased ascertainment of outcomes, and they were unaware of the final real-time RT-PCR results for SARS-CoV-2. Finally, we used validated tests for the assessment of smell and taste function, which might be useful in future predictive models for COVID-19.

Limitations
This study has some limitations. The assessment of smell function might have been affected by inherent limitations of the PST, including the inability to quantify the threshold or discrimination of scents (rather than their identification) and the inability to confirm the existence of slight alterations in smell function owing to the small number of available scents compared with the full PST version (with 40 scents). The relatively small sample size might have contributed to the lack of distinct independent associations, particularly between objective GD and SARS-CoV-2 test positivity. The use of real-time RT-PCR as the gold standard test (based on nasopharyngeal swabs) might also be questionable because this test has a suboptimal sensitivity for SARS-CoV-2 detection (60%). However, this test is the best available gold standard test.

Conclusion
Under strict infection control measures, we used validated tests for the assessment of smell and taste function as potential screening tools for COVID-19 inpatients who presented with respiratory symptoms. This study shows slight agreement between the objective test results and the self-reported complaints of OD and GD. On the basis of the diagnostic accuracy indices, the PST and GDT cannot be exclusively used as a single screening instrument for the detection of COVID-19, although dysosmia detected by the PST is independently associated with this disease. However, patients with abnormal smell and taste, as measured by objective testing, combined with the symptoms of cough and fever, should be regarded as having a high probability of a COVID-19 diagnosis. Accordingly, such a symptomatic paradigm may further allow decision-makers to optimize test resource allocation in the clinical setting while ensuring patients’ and clinicians’ safety. Future studies based on larger sample sizes might confirm the reported results and assist in the development of robust diagnostic scales comprising a combination of objective chemosensory evaluation and respiratory symptomatology.

Author contributions
OK, AAA, and KS conceived the study and designed the trial. All authors supervised the conduct of the trial and data collection, undertook recruitment of participating centers and patients, and managed the data, including quality control. AAA chaired the data oversight committee. M Aljahany drafted the manuscript. All authors contributed substantially to revision of the manuscript. OK takes overall responsibility for the manuscript.

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The authors declare that there is no conflict of interest.
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References
1. Sun P, Qie S, Liu Z, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis. J Med Virol 2020; 92: 612–617.
2. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020; 34: 101623.
3. World Health Organization. Coronavirus disease (COVID-19) pandemic, https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (2021, accessed 25 March 2021).
4. Centers for Disease Control and Prevention. Symptoms of COVID-19, https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html (2021, accessed 25 March 2021).
5. Salepci E, Turk B, Ozcan SN, et al. Symptomatology of COVID-19 from the otorhinolaryngology perspective: A survey of 223 SARS-CoV-2 RNA-positive patients. Eur Arch Otorhinolaryngol 2021; 278: 525–535.
6. Sakalli E, Temirbekov D, Bayri E, et al. Ear nose throat-related symptoms with a focus on loss of smell and/or taste in COVID-19 patients. Am J Otolaryngol 2020; 41: 102622.
7. La Torre G, Massetti AP, Antonelli G, et al. Anosmia and ageusia as predictive signs of COVID-19 in healthcare workers in Italy: A prospective case-control study. J Clin Med 2020; 9: 2870.
8. Hummel T, Whitcroft KL, Andrews P, et al. Position paper on olfactory dysfunction. Rhinology 2016; 56: 1–30.
9. Van Riel D, Verdhij R and Kuiken T. The olfactory nerve: A shortcut for influenza and other viral diseases into the central nervous system. J Pathol 2015; 235: 277–287.
10. Lv H, Zhang W, Zhu Z, et al. Prevalence and recovery time of olfactory and gustatory dysfunction in hospitalized patients with COVID–19 in Wuhan, China. Int J Infect Dis 2020; 100: 507–512.
11. Bayomy HE, Malak SA, Alshbiny MT, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients in the Kingdom of Saudi Arabia. Medical Science 2020; 24: 4566–4575.
12. Zeng M, Wang DY, Mullol J, et al. Chemosensory dysfunction in patients with covid-19: What do we learn from the global outbreak? Curr Allergy Asthma Rep 2021; 21: 6.
13. Hopkins C, Surda P and Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. Rhinology 2020; 58: 295–298.
14. Lee Y, Min P, Lee S, et al. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020; 35: e174.
15. Gonçalves LF, Gonzáles AI, Paiva KM, et al. Smell and taste alterations in COVID-19 patients: A systematic review. Rev Assoc Med Bras 2020; 66: 1602–1608.
16. Romero-Gameros CA, Waizel-Haiat S, Mendoza-Zubieta V, et al. Evaluation of predictive value of olfactory dysfunction, as a screening tool for COVID-19. Laryngoscope Investig Otolaryngol 2020; 5: 983–991.
17. Saudi Center for Disease Prevention and Control. Coronavirus Disease COVID-19 Guidelines, V 2.0: Public Health Authority, Ministry of Health, https://covid19.cdc.gov.sa/professionals-health-workers/covid-19-coronavirus-disease-guidelines-en/ (2020, accessed 15 March 2021).
18. Al-Ani RM and Acharya D. Prevalence of Anosmia and Ageusia in Patients with COVID-19 at a Primary Health Center, Doha, Qatar. Indian J Otolaryngol Head Neck Surg 2020; 72: 306–309.
19. Doty RL, Shaman P and Dann M. Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiol Behav* 1984; 32: 489–502.

20. Hoffman HJ, Rawal S, Li CM, et al. New chemosensory component in the US National Health and Nutrition Examination Survey (NHANES): First-year results for measured olfactory dysfunction. *Rev Endocr Metab Disord* 2016; 17: 221–240.

21. Massarelli O, Vaira LA, Biglio A, et al. Sensory recovery of myomucosal flap oral cavity reconstructions. *Head Neck* 2018; 40: 467–474.

22. Loewen IJ, Boliek CA, Harris J, et al. Oral sensation and function: A comparison of patients with innervated radial forearm free flap reconstruction to healthy matched controls. *Head Neck* 2010; 32: 85–95.

23. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. *Head Neck* 2020; 42: 1252–1258.

24. Murphy C, Schubert CR, Cruickshanks KJ, et al. Prevalence of olfactory impairment in older adults. *JAMA* 2002; 288: 2307–2312.

25. Schubert CR, Cruickshanks KJ, Fischer ME, et al. Olfactory impairment in an adult population: The Beaver Dam Offspring Study. *Chem Senses* 2012; 37: 325–334.

26. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.

27. Watson PF and Petrie A. Method agreement analysis: A review of correct methodology. *Theriogenology* 2010; 73: 1167–1179.

28. McHugh ML. Interrater reliability: The kappa statistic. *Biochem Med* 2012; 22: 276–282.

29. Bagheri SHR, Asghari AM, Farhadi M, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak. *Med J Islam Repub Iran* 2020; 34: 62.

30. ENT UK. Loss of sense of smell as marker of COVID-19 infection, https://www.entuk.org/sites/default/files/files/Loss%20of%20sense%20of%20smell%20as%20marker%20of%20COVID.pdf (2020, accessed 25 April 2021).

31. American Academy of Otolaryngology-Head and Neck Surgery. AAO-HNS: Anosmia, hyposmia, and dysgeusia symptoms, https://www.entnet.org/content/aaohns-anosmia-hyposmia-and-dysgeusia-symptoms-coronavirus-disease. (2020, accessed 25 April 2021).

32. Kelly H, Bull A, Russo P, et al. Estimating sensitivity and specificity from positive predictive value, negative predictive value and prevalence: Application to surveillance systems for hospital-acquired infections. *J Hosp Infect* 2008; 69: 164–168.

33. Roland LT, Gurrola JG, Loftus PA, et al. Smell and taste symptom-based predictive model for COVID-19 diagnosis. *Int Forum Allergy Rhinol* 2020; 10: 832–838.

34. Mullol J, Allobid I, Marino-Sánchez F, et al. The loss of smell and taste in the COVID-19 outbreak: a tale of many countries. *Curr Allergy Asthma Rep* 2020; 20: 1–5.

35. Hannum ME, Ramirez VA, Lipson SJ, et al. Objective sensory testing methods reveal a higher prevalence of olfactory loss in COVID-19–positive patients compared to subjective methods: A systematic review and meta-analysis. *Chem Senses* 2020; 45: 865–874.

36. Wrobel BB and Leopold DA. Clinical assessment of patients with smell and taste disorders. *Otolaryngol Clin North Am* 2004; 37: 1127–1142.

37. Day SJ and Altman DG. Statistics notes: Blinding in clinical trials and other studies. *BMJ* 2000; 321: 504.

38. Joseph T, Auger SD, Peress L, et al. Screening performance of abbreviated versions of the UPSIT smell test. *J Neurol* 2019; 266: 1897–1906.

39. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; 323: 1843–1844.