

## Olfactory and gustatory dysfunction, evaluation and the impact on quality of life among COVID-19 patients: a multi-centre study

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**Background:** Olfactory and gustatory dysfunctions are frequently reported symptoms among COVID-19 patients. However, several reports suggested that there might be significant variation in the prevalence and clinical picture of chemosensory dysfunction in COVID-19 patients among different population.

**Objective:** To study the prevalence of chemosensory dysfunction, recovery time and its impact on quality of life (QoL) among COVID-19 patients in Saudi population.

**Methods:** This multi-centre observational study was conducted at three COVID-19 centres in Saudi Arabia. Epidemiological and clinical data were extracted at baseline and within the 2-month post-infection. Olfactory and gustatory dysfunctions were assessed via valid taste and smell questionnaire, electronically collected via online survey. Short version of questionnaire of Olfactory disorders-negative statements (sQOD-NS) was used to assess the impact on QoL.

**Result:** Total 1734 patients [926 males and 808 females, the mean age of patients was  $37.7 \pm 11.6$  years] with laboratory confirmed COVID-19 were recruited for this study. Chemosensory dysfunction was reported in 56.5% cases. olfactory and gustatory dysfunctions were significantly high in females (66.2%) and age group younger than or equal to 40 years (62.2%). Among patients with olfactory dysfunction and gustatory dysfunction, recovery rate was 757 (77.2%) and 702 (71.6%). Furthermore, the recovery time was within 8 days of onset of symptoms in 53.6% and 61.3% of olfactory dysfunction and gustatory dysfunction cases, respectively. Overall mean QoL score indicated Olfactory and gustatory dysfunction has significant impact on QoL [11.3 ± 6.2 (*P* value < 0.001)]. female as compared to males (12.8 ± 7). Females had significant impact on QoL (11.4 ± 6.6) as compared to males [12.8 ± 7 (*P* value < 0.001)].

**Conclusion:** Chemosensory dysfunction among Saudi population was comparable to the European data and significantly higher than Asian supporting the fact that these symptoms vary as per ethnicity. Olfactory and gustatory dysfunction significantly impaired QoL and could present as an early symptom of COVID-19. Recovery rate of these symptoms can serve as a good prognostic data for patient's counselling. Further long-term follow-up studies would lead to better understanding of prognosis and clinical outcomes.

Keywords: chemosensory, coronavirus, COVID-19, gustatory, olfactory dysfunction

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

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### Introduction

COVID-19, caused by SARS-CoV-2 originated in Wuhan Hubei Province of China in December 2019 and was later on declared as pandemic by the WHO in March  $2020^{[1,2]}$ .

Olfactory and gustatory dysfunctions (OGD) have been considered as the frequent key symptoms in COVID-19 patients with mild to moderate infection<sup>[3-6]</sup>. However, they were not considered as the symptoms for identifying SARS-CoV-2 infection or for prioritizing testing by the Centers for Disease Control and Prevention (CDC) or the WHO till August 2020<sup>[7]</sup>. A meta-analysis carried out by Chi et al.[8], showed that nearly half of COVID-19 patients suffer from olfactory and gustatory dysfunction and these were found to be the initial clinical manifestations in 15% of those patients. Various systemic reviews and meta-analyses have compiled the findings related to association of chemosensory dysfunction and diagnosis of COVID-19 with geographical variations<sup>[9,10]</sup>. In China, during the initial few months of the COVID-19 outbreak, Mao et al.[11] reported that smell and taste dysfunctions were noted only in 5.1-5.6% patients. During the same time, it was found that 33.9% of patients in Italy, which was the epicentre of COVID-19 in Europe<sup>[12]</sup>, exhibited at least one of these symptoms. This finding

was supported from further studies in Europe, which showed that 75-80% of COVID-19 patients experienced chemosensory dysfunction<sup>[13,14]</sup>. The USA reported a similar prevalence of taste and smell disorders in COVID-19 patients<sup>[15,16]</sup>. Noticeably, similar to data from China, Japan, Korea and India also reported low incidences of smell and taste<sup>[37-39]</sup>. In order to ascertain these differences, Song et al.<sup>[17]</sup> conducted a telephonic follow-up for re-checking the medical records at a hospital in China and these re-efforts also recorded very less events of smell and taste dysfunction (11.4 and 20.6%, respectively) in COVID-19 patients in China. All these reports suggest that there might be a significant variation in the prevalence and clinical picture of chemosensory dysfunction in COVID-19 patients among different population. A meta-analysis including 104 studies reported that chemosensory dysfunction is 3-6 times higher among Caucasians compared to East Asians<sup>[18]</sup>. In this meta-analysis, Bartheld and colleagues found that both dysfunctions reciprocally associated with old age, male sex and disease severity. Different explanations for variation in prevalence have been proposed by many authors including ethnicity, viral mutations and diversity of angiotensin-converting enzyme 2 expression levels (which is the receptor for SARS-CoV-2) between Asian and European populations<sup>[3,5,19]</sup>.

Moreover ,olfactory dysfunction is known to cause impairment in quality of life and risk the patients to depression<sup>[20,21]</sup>. COVID-19 infection found to be associated with depression and anxiety, these symptoms were significantly higher in patients presenting with loss of smell and taste<sup>[22]</sup>. The majority of patients showed early recovery from chemosensory dysfunction, however significant number might suffer from long-term impairment, given the fact of high infection rate worldwide<sup>[4,6,23]</sup>. The wide geographic variation of chemosensory dysfunction needs further evaluation. Our study aimed to estimate the prevalence, severity of chemosensory dysfunction among COVID-19 patients, recovery time and the impact on quality of life among COVID-19 patient in the Saudi population.

#### Materials and methods

This study was conducted recruiting 1740 SARS-CoV-2 positive patients between October and December 2020 at three COVID-19 centres in different regions of Saudi Arabia including; King Fahd Hospital of the University, ALKhobar, Qatif Central Hospital, AlQatif, and Ohud Hospital, AlMadinah Al Munawarah, Saudi Arabia. Inclusion criteria for the patients in the study included adult over 18 years of age, Real-time reverse transcriptase polymerase chain reaction confirmed SARS-CoV-2 infection within the period of less than 2 months and patients were required to be clinically available for completing the study. The study exclusion criteria were critically ill patients who were unable to fill the survey, patients younger than 18 years of age, patients diagnosed with SARS-CoV-2 within period more than 2 months, patients with previous history of smell and taste alternation, sinonasal disease, head trauma, psychological or neurological disorders.

The study protocol was approved by the Institutional Review Board of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. The patients who met the inclusion criteria were asked to give written informed consent for the study. The work has been reported in line with the STROCSS criteria<sup>[36]</sup>.

The clinical data were collected through medical records and electronically via an online survey. Patients received phone call

## HIGHLIGHTS

- Olfactory and Gustatory dysfunction is a frequent and highly reliable symptom of COVID-19.
- The occurrence of these chemosensory dysfunction symptoms in Saudi population was comparable to the European data and significantly higher than Asian supporting the fact that these symptoms vary as per ethnicity.
- Olfactory dysfunction was associated with impaired quality of life.

preceding the survey distribution. Demographic data and clinical data were collected including medical record number, age, sex, ethnicity, time of symptoms appearance, time of laboratory diagnosis, comorbidities, smoking history, and medication history. We also ask the patients if they have any pervious history of smell and taste alternation, sinonasal disease, head trauma, psychological or neurological disorders.

We classified the severity of the disease according to Saudi Ministry of Health (MOH) protocol for patients Suspected of/ confirmed with COVID-19. Mild cases were the one who were symptom free or had mild symptoms that did not necessitate hospital admission with common symptoms and signs (fever, sore throat, headache, loss of taste and/or smell, cough, nausea and vomiting) without shortness of breath or evidence of pneumonia. Moderate were the ones admitted to the medical wards with shortness of breath, and constitutional symptoms, but no oxygen requirements and no evidence of pneumonia, while the severe ones were the ones who needed intensive care unit admission with one or more of following findings: Respiratory rate greater than or equal to 30/min, blood oxygen saturation less than or equal to 93%, PaO2/FiO2 ratio less than 300, or lung infiltrates greater than 50% of the lung fields within 24–48 h.

General and otorhinolaryngological symptoms were collected and ranged in scale from (0-4), (0 = no symptoms 1 = almostnever 2 = sometimes 3 = almost always 4 = always).

The olfactory and gustatory symptoms were assessed using the taste and smell questionnaire<sup>[24]</sup>. The taste and smell questionnaire included 9 questions which addressed the changes of taste and five questions addressing the changes of smell. Patients were asked to categorize their taste and smell dysfunction as follows: insignificant, mild, moderate, severe, or incapacitating. Total score of taste was calculated by adding one point for each complaint and two points for rating severe or incapacitating for the taste abnormality question, total score ranging from 0 (no complaints) to 10 (many complaints). Similarly, total score of smell abnormality ranged from (0-6) calculated by one point for each complaint, two points for rating of severe or incapacitating for the smell overall abnormality question. Higher average score meant higher smell and taste abnormality. The impact of olfactory disorder (OD) on quality of life was evaluated using short version of the Questionnaire of Olfactory disorders-negative statements (sQOD-NS)<sup>[25]</sup>. sQOD-NS is a seven-item patientreported outcome questionnaire. Item proposition from 0 (agree) to 3 (disagree) were rated by the patients with total score ranging from 0 (significant impact of OD on QoL) to 21 (no impact on QoL). SPSS version 22, 0 was used to perform the statistical analyses. P less than 0.05 was considered as statistically significant.

#### Results

#### COVID-19 subjects and disease status

We recruited a total of 1734 COVID-19 positive patients for this multi-centre study. All patients were non vaccinated. Of the total of recruited patients 926 (53.4%) were males and 808 (46.6%) females. The mean age of patients was  $37.7 \pm 11.6$  years. Regarding the nationality, 1564 (90.2%) were Saudis, and 170 (9.8%) were non-Saudis. On assessing the disease status in these recruited patients, it was found that 898 (51.8%) were mild, 791 (45.6%) were moderate and 45 (2.6%) were severe cases.

# OGD in COVID-19 patients and association with sex, age, and ethnicity

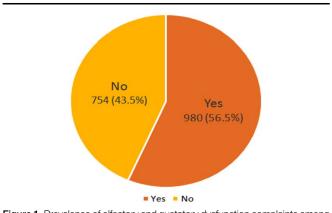
OGD was reported in 980 (56.5%) of the cases. (Fig. 1). Percentage of OGD was significantly higher in females compared to males (66.2%: 48.06%, respectively) and in Saudi compared to non-Saudi [(58.18%: 41.18%) P < 0.001]. In respect to age, OGD were significantly higher in cases with age younger than or equal to 40 years [(62.2%) P < 0.001] (Table 1). Sore throat, nasal congestion, postnasal drip and rhinorrhea were significantly associated with OGD.

#### Stratification by loss of smell and taste severity

Out of the total, complete sense of smell was lost in 30.3% cases and partial sense of smell was lost in 53.4% cases. While complete sense of taste was lost in 19.4% and partial sense of taste was lost in 59.7% cases. (Table 2). Almost 245 (14.1%) cases experienced bitter taste, while 52 (5.3%) experienced sweet, 50 (5.1%) salty and 37 (3.8%) cases experienced sour taste. According to severity of bad taste, 297 (30.3%) had moderate bad taste, 223 (22.8%) had severe and 142 (14.5%) incapacitating bad taste.

## OGD severity association with sex ,age and geography

According to smell and taste score, females had significantly higher number of complaints in both smell and taste (P values <0.0001 and 0.016, respectively). Saudi nationals also reported a significantly higher number of smell and taste complaints as compared to the non-Saudis (P values = 0.008 and 0.041, respectively). Cases with age younger than or equal to 40 years



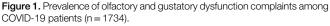


Table 1	
Demographic characteristic of COVID-19 patients with OG	D.

	Demographics	0GD, <i>n</i> (%)	Р
Sex	Male	445 (48.06)	< 0.001
	Female	535 (66.21)	
Nationality	Saudi	910 (58.18)	< 0.001
	Non-Saudi	70 (41.18)	
Age (Y)	≤40	708 (62.2)	< 0.001
	>40	272 (45.6)	
Severity	Mild	490 (54.6)	0.089
	Moderate-severe	490 (58.6)	
Smoking	Yes	171 (58.2)	0.4
	No	809 (56.1)	
Chronic disease	Yes	371 (56)	0.75
	No	609 (56.8)	

(n = 980 out of total n = 1734).

OGD, olfactory and gustatory dysfunction.

had significantly higher number of smell complaints (P value = 0.03), while abnormal taste dysfunction score was statistically similar in both age groups (P value = 0.3) (Table 3).

#### Recovery of olfactory and gustatory dysfunction

Among patients with olfactory dysfunction and gustatory dysfunction, total recovery rate for OD and GD were 757(77.2%) and& 702 (71.6%), respectively. Total of 625 patients (63.8%) reported recovery from both OGD, whereas 132 patients (13.4%) reported recovery from OD but not GD and 77 patients (7.8%) reported recovery from GD but not OD (Table 4).

Recovery from both loss of smell and taste was statistically equally distributed between both sexes and age groups (*P* values > 0.05). Regarding OD, the number of cases recovered was significantly higher in those who had anosmia compared to the ones who had hyposmia [(80.4%: 73.8%) *P* value = 0.03] (Table 2). According to mean taste and smell scores, recovered cases had significantly higher number of complaints (both smell and taste) (*P* values = 0.02 and < 0.0001, respectively) (Table 5).

Significant number of cases 525 (53.6%) and 601 (61.3%) reported complete recovery of OD and GD within 8 days of onset of the symptoms respectively (*P* value < 0.05), (Fig. 2). Furthermore, out of 980 cases, 213 (21.7%) received supportive treatments for loss of smell and only 2.2% cases received treatment for loss of taste.

## Effect of OGD on Quality of Life

Assessment of the overall mean of QoL score revealed that OGD disorders had significant impact on QoL  $[11.3\pm6.2 (P \text{ value} <$ 

Table 2Severity rate and recovery of OGD ( $n = 980$ ).				
	Sense of smell, <i>n</i> (%)	Sense of taste, <i>n</i> (%)	Olfactory dysfunction recovery, <i>n</i> (%)	Gustatory dysfunction recovery, <i>n</i> (%)
Complete loss Partial loss P values	297 (30.3) 523 (53.4)	190 (19.4) 585 (59.7)	239 (80.4) <sup>a</sup> 386 (73.8) 0.03	151 (79.5) 448 (76.6) 0.4

OGD, olfactory and gustatory dysfunction. <sup>a</sup>Significantly high.

Table 3Variations of mean taste and smell abnormality (n = 980).

	Smell score <sup>a</sup>		Taste score <sup>b</sup>	
	$Mean \pm SD$	Р	$\text{Mean} \pm \text{SD}$	Р
Male	2.7 ± 1.6	< 0.0001	$3.1 \pm 2.5$	0.016
Female	3.3 ± 1.5		$3.5 \pm 2.5$	
Saudi	$3.1 \pm 1.6$	0.008	$3.3 \pm 2.6$	0.041
Non-Saudi	$2.5 \pm 1.5$		$2.9 \pm 1.6$	
≤40	3.1 ± 1.5	0.03	3.4 ± 2.5	0.3
> 40	2.8 <u>+</u> 1.7		3.2 ± 2.4	

Higher average score means higher smell and taste abnormality.

<sup>a</sup>Total score of smell abnormality ranging from 0 (no complaint) to 6 (many complaints)

<sup>b</sup>Taste abnormality total score ranging from 0 (no complaints) to 10 (many complaints). \*refers to significant *P* value less than 0.05.

0.001)]. In respect to sex OGD among females had significant impact on QoL ( $11.4\pm6.6$ ) as compared to males [ $12.8\pm7$  (*P* value < 0.001)]. According to nationality, OGD had a significant impact on QoL ( $11.8\pm6.9$ ) of Saudi in comparison to non-Saudi cases [ $13.3\pm6.8$  (*P* value = 0.01)]. (Table 6).

## Discussion

Olfactory and gustatory dysfunctions are frequently reported symptoms among patients with COVID-19 based on various studies<sup>[4,5,7,10]</sup>. Therefore they were included in the list of key clinical symptoms for defining COVID-19 infection by the European Centre for Disease Prevention and Control as well as other organizations like CDC, WHO<sup>[7]</sup>. In the present study, these symptoms were present in 56.5% of the recruited population. Compared to the regional prevalence, Alfallaj and colleagues reported a prevalence of 68% of COVID-19 patients experiencing olfactory dysfunction. Additionally, they found the incidence of taste dysfunction to be 57%<sup>[40]</sup>. Similarly, Alrouqi et al.<sup>[50]</sup> reported a prevalence of 72% for olfactory dysfunction. The rate of chemosensory dysfunction found in our study was higher than that reported in other Asian studies  $(5-32\%)^{[11,19]}$ <sup>37–39]</sup>. This rate was more consistent with the results from Middle East . Europe and North America<sup>[3,4,6,40,41]</sup>. According to a study</sup> conducted in united Arabs Emirates ,Olfactory dysfunction and Gustatory dysfunction were present in (44%, 43%) respectively, they also found that Arab-Asians, Arabs and non-Arab Africans experienced a significantly greater decrease in their sense of smell and taste, whereas non-Arab Asians demonstrated the lowest average reduction in these sensations<sup>[41]</sup>. On the contrary, A study conducted in Qatar revealed a chemosensory dysfunction prevalence of  $\sim 24\%$ , which is lower than the reported prevalence in the region<sup>[51]</sup>. However, it is noteworthy that the study did not

Table 4   Total recovery rate among OGD cases (n = 980).				
	Recovered from lo	ss of taste, <i>n</i> (%)	Total, <i>n</i> (%)	
		Yes	No	<b>P</b> *
Recovere	d from loss of smell			
Yes	625 (63.8)	132 (13.4)	757 (77.2)	< 0.0001
No	77 (7.8)	146 (15)	223 (22.8)	
Total	702 (71.6)	278 (28.4)	980	

\* Significant P value less than 0.05.

Table 5
Comparison of mean taste and smell abnormality scores between
recovery ( <i>n</i> = 980).

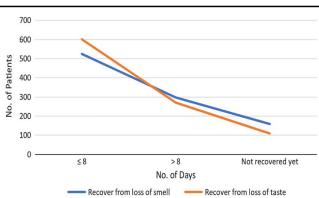
Recovery	Smell scores mean ( $\pm$ SD)	Taste scores mean ( $\pm$ SD)
Recovered	3.1 (±1.5)	3.8 (±2.4)
Not recovered P values	2.7 (±1.7) 0.02	2.1 (±2.4) < 0.0001

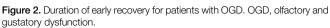
Higher average score means higher smell and taste abnormality.

<sup>a</sup>Total score of smell abnormality ranging from 0 (no complaint) to 6 (many complaints) and.

<sup>b</sup>Taste abnormality total score ranging from 0 (no complaints) to 10 (many complaints).

specify the ethnicity of the patients. Considering the demographic composition of Qatar, where the majority of the population consists of migrants on short-term contracts from various Arab and global regions, this ethnic diversity should be taken into account when interpreting the study findings<sup>[52]</sup>, similarly to our result, high prevalence of olfactory dysfunction were also noted in Egypt and Iraq (78.4%, 89.23%), respectively<sup>[53,54]</sup>. Ethnicity might be a possible explanation for this, as proposed by a metaanalysis which showed that Caucasians had higher prevalence of olfactory and gustatory dysfunction (43.2%; 38.3%, respectively) compared to East Asian populations (15.1%; 6.4%, respectively)<sup>[18]</sup>. ACE2 is known to be the functional receptor for the COVID-19 virus, with the help of a priming protease TMPRSS2 to facilitate viral uptake. In respiratory epithelium, SUS and other supporting cells express a high level of ACE2 receptors. The COVID-19 virus infects supporting cells, which indirectly results in damage to olfactory sensory neurons<sup>[42]</sup>. One reason for difference in OGD with reference to geographical differences could be mutation in the virus causing difference in infectivity. A study found that when the same population was infected mostly with the G614 variant as opposed to the D614 virus, there was a higher incidence of impaired olfaction, indicating that the difference in loss of smell between Western and Asian countries was largely due to infection with different virus variants<sup>[43]</sup>. recent studies showed that omicron variant causes a lower prevalence of chemosensory dysfunction compared to the pervious variants; however, according to recent meta-analysis significant differences of chemosensory dysfunction between ethnicities were noted with estimate prevalence in European populations is 11.7%, while it is significantly lower in all other populations, ranging between 1.9 and 4.9%<sup>[44]</sup>. In Saudi Arabia





#### Table 6

Comparison of mean scores of short versions of questionnaire of olfactory disorders-negative statements of patient, Quality of Life-QoL between sex, Nationality and OGD (n = 980).

Overall QOL	Р
12.8 ± 7	< 0.001
$11.4 \pm 6.6$	
$11.8 \pm 6.9$	0.01
13.3 ± 6.8	
11.3 ± 6.2	< 0.001
$12.9 \pm 7.6$	
	$12.8 \pm 7$ $11.4 \pm 6.6$ $11.8 \pm 6.9$ $13.3 \pm 6.8$ $11.3 \pm 6.2$

Overall QoL rated 0-21, with higher scores reflecting better olfactory-specific QOL \* By using independent *t*-test.

OGD, olfactory and gustatory dysfunction; QOL, quality of life.

the D614G spike mutation-carrying SAR-CoV-2 virus was initially introduced in February 2020, but over time, between February and August of that year, there was an increase in the reported cases of patients infected with the wild-type virus<sup>[45]</sup>. In The present study, data were collected from October to December 2020, during which time there was a possibility of both viral mutations being present in the sample.

ACE2 has many genetic variants that might also be a another reason for the difference in prevalence of chemosensory dysfunction among different ethnicity as pointed out by Lechien *et al.*<sup>[3]</sup> as these variants found to differ in frequency between Asian and European population<sup>[27]</sup>. However, recent research indicates that differences in ACE2 expression levels among populations do not correspond with infection or chemosensory dysfunction and cannot account for the observed phenotypes<sup>[26,32,33,46]</sup>. Instead, a genome-wide association study carried out with a large sample size has identified the UGT2A1/A2 locus as the genetic locus related to the difference in anosmia prevalence among various populations<sup>[47]</sup>.

OGD was predominant in patients younger than forty (67.3%) and in females (66.2%) in this study. Similar finding was reported in other studies<sup>[3,5,14]</sup>. A possible explanation for higher incidence of OGD in females could be the differences in inflammatory response between males and females<sup>[3,5]</sup>.

Interestingly, our results showed no difference in prevalence of OGD between mild, moderate and severe COVID-19 cases. On the contrary, Panderno *et al.*<sup>[14]</sup> found that chemosensory dysfunction were higher in younger and mildly symptomatic patients under quarantine. Another study also showed that Olfactory dysfunction was a key symptom in mild to moderate COVID-19 infection<sup>[5]</sup>. Yan *et al.*<sup>[28]</sup> reported that COVID-19 patients with anosmia are ten times less likely to be hospitalized and anosmia may be a prognostic marker for mild COVID-19. However, chemosensory dysfunction has been underestimated in the case of severe disease as proposed by Varia *et al.*<sup>[4]</sup>, who found no correlation of these symptoms with severe disease. This finding was supported by other authors<sup>[19]</sup>.

Most of the patients recovered within 8 days of resolution of COVID-19 symptoms. No significant correlation was found between recovery rate, sex, and age. Recovery rate in complete loss was higher compared to the partial loss of olfactory dys-function (80.4%; 73.8). Other studies also suggested recovery within few weeks from onset<sup>[4,6,23]</sup>. Objective evaluation of

patients who reported complete recovery from chemosensory dysfunction showed mild to moderate hyposomnia in 69.9% and mild to moderate hypogeusia in 28.8%. Follow-up of these patients showed almost complete recovery from ageusia within 15 days with residual hyposmia even in third or fourth week<sup>[4]</sup>. According to a recent meta-analysis, most patients are expected to recover their olfactory and gustatory dysfunction within the first three months. However, ~5% of patients may not fully recover<sup>[56]</sup>. A study demonstrated that after two years since COVID-19, 29.8% of patients reported persistent olfactory dysfunction. Interestingly, among these individuals, only 2.9% exhibited abnormal results in identification psychophysical evaluations<sup>[57]</sup>.

Our result showed significant impairment of quality of life among patients with OTD (P value < 0.0001). Depression and anxiety observed in COVID-19 patients was strongly associated with loss of smell and taste<sup>[22]</sup>. Reports suggest that chronic hyposmia or anosmia associated with depression negatively impacted the quality of life<sup>[20,21]</sup>. Olfactory dysfunction could affect social life and eating behaviour as it leads to loss of pleasure in taste and decrease in food intake<sup>[20]</sup>. Moreover, it could be life threatening as it impairs detection of hazards like fire or smoke<sup>[20]</sup>, while Various therapies have been attempted to treat olfactory dysfunction post COVID-19, there is no validated medication available. Although some randomized control trials have demonstrated short-term benefits of using topical or oral corticosteroids, large-scale trials investigating their efficacy are yet to be conducted<sup>[48]</sup>. olfactory training have been shown to symptomatically improve olfactory dysfunction in both the acute and chronic phases<sup>[49]</sup>.

Patients with post COVID-19 olfactory dysfunction should receive counselling to improve their quality of life, nutrition, and safety by monitoring food expiration dates, ensuring proper functioning of detectors, and quitting smoking<sup>[48]</sup>.

Several mechanisms have been suggested for olfactory and gustatory dysfunction in COVID-19 infection. Anosmia have been reported to be associated with human coronavirus 229E which causes common cold and impairment of smell ability was correlated with nasal congestion<sup>[29]</sup>. Various other studies have on the contrary showed no correlation between olfactory dysfunction and nasal congestion in COVID-19 disease<sup>[3,4]</sup>. Moreover, endoscopic and radiological findings of olfactory clefts in anosmic COVID-19 patients were found to be clear, suggesting that the mechanism is not related primarily to olfactory cleft obstruction<sup>[30]</sup>. However, our data showed almost 44% of patients with OGD had nasal congestion and 36% had rhinorrhea which supported conductive mechanism of chemosensory dysfunction in COVID-19. Another potential mechanism as proposed earlier is virus invading the olfactory epithelium but not olfactory neurons themselves through ACE2 receptors<sup>[31]</sup>.

It remains unclear, if SARS-CoV-2 can cause olfactory dysfunction through invading the central nerves system (CNS). Han *et al.* demonstrated that some coronavirus strains have neuroinvasive and neurodegenerative potentials, and therefore, olfactory dysfunction with SARS-CoV-2 may indicate neuroinvasion<sup>[34]</sup>. Other studies suggested that olfactory dysfunction may not be related to CNS invasion, depending on the fact of early recovery of olfactory dysfunction gared to olfactory dysfunction<sup>[4]</sup>. Gustatory dysfunction might be secondary to olfactory dysfunction as smell is one

of the components of flavour sensation. However, Vaira *el al*.<sup>[4]</sup> reported isolated gustatory dysfunction in patients with normal sense of smell objectively. Noticeably, ACE2 receptors were found in oral cavity with higher percentage in tongue, which might explain the gustatory dysfunction among COVID-19 patients<sup>[35]</sup>. Furthermore, the fact that some of our patients recovered from olfactory dysfunction and not the gustatory dysfunction supported the effect of ACE2 receptors in the tongue.

Our study had some limitations. Our data were collected during the first wave of the pandemic in SA, we were unable to perform comprehensive clinical evaluations or objective tests for smell and taste dysfunction on COVID-19 patients due to patient consultation restrictions in medical centres of our country. We used subjective evaluation method for smell and taste dysfunction, thus the prevalence might be underestimated especially in cases with moderate to severe COVID-19 disease in which these symptoms might have been ignored. Additionally, flavour perception is influenced by retronasal olfaction, some patients might describe the change in the flavour as loss of taste, As a result, the prevalence of objectively assessed gustatory deficits may be lower compared to self-reported cases, as self-reporting may encompass a broader range of subjective flavour-related experiences<sup>[55]</sup>. Furthermore, our study was for shorter time duration with lack of prolonged follow-up, therefore the percentage of recovery might be underestimated.

#### Conclusion

The occurrence of chemosensory dysfunction symptoms in Saudi population was comparable to the European data and significantly higher than Asian supporting the fact that these symptoms vary as per ethnicity. Recovery rate for these symptoms was found to be good and spontaneous within a short period of time. The effect of these symptoms was found to be considerable on quality of life. However, for more conclusive data long-term follow studies are needed.

## **Ethical approval**

The study protocol was approved by the Institutional Review Board of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.

## Consent

All participants were asked to give written informed consent for the study.

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No financial disclosure concerning the article.

## **Author contribution**

A.S.A., M.A.A., D.H.A., M.M.S.A., R.T.H., T.L.M.: study design, data collection, data analysis, and writing the paper. M.J. A., L.A.B.: study design, data collection, and writing the paper.

#### **Conflicts of interest disclosure**

The authors declare no conflict of interest. This manuscript was not presented at any meeting.

# Research registration unique identifying number (UIN)

- 1. 1. Registry used: Chinese Clinical Trial Registry chictr.org.cn.
- 2. registration ID: ChiCTR2300073999.
- Link: https://www.chictr.org.cn/showprojEN.html?proj= 202741

#### Guarantor

Abdulaziz Saud AlEnazi and Maha Abdullah Alharbi.

#### **Data availability statement**

Data are available upon reasonable request.

#### Provenance and peer review

Not commissioned, externally peer-reviewed.

### References

- Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506; Published online.
- [2] World Health Organization. WHO COVID-19 global table data December 1st 2020 at 11. WHO Coronavirus Dis.: 2020. https://covid19. who.int/
- [3] Lechien JR, Chiesa-Estomba CM, De Siati DR, *et al.* Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Oto-Rhino-Laryngology 2020;277:2251–61.
- [4] Vaira LA, Hopkins C, Salzano G, et al. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. Head Neck 2020;42:1560–9.
- [5] Lechien JR, Chiesa-Estomba CM, Place S, et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med 2020;288:335–44.
- [6] Yan CH, Faraji F, Prajapati DP, et al. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020;10:806–13; Published online.
- [7] Cirillo N. Taste alteration in COVID-19: a rapid review with data synthesis reveals significant geographical differences exist in the prevalence of the symptom. J Infect Public Health 2021;14:1099–105.
- [8] Chi H, Chiu NC, Peng CC, et al. One-seventh of patients with covid-19 had olfactory and gustatory abnormalities as their initial symptoms: a systematic review and meta-analysis. Life 2020;10:158; Published online.
- [9] Rocke J, Hopkins C, Philpott C, *et al.* Is loss of sense of smell a diagnostic marker in COVID-19: a systematic review and meta-analysis. Clin Otolaryngol 2020;45:914–22; Published online.
- [10] Tong JY, Wong A, Zhu D, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and metaanalysis. Otolaryngol Head Neck Surg (United States) 2020;163:3–11; Published online.
- [11] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683–90.
- [12] Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory Coronavirus 2 infection: a cross-sectional study. Clin Infect Dis 2020;71:889–90.
- [13] Patel A, Charani E, Ariyanayagam D, et al. New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection. Clin Microbiol Infect 2020;26:1236–41.

- [14] Paderno A, Schreiber A, Grammatica A, et al. Smell and taste alterations in COVID-19: a cross-sectional analysis of different cohorts. Int Forum Allergy Rhinol 2020;10:955–62.
- [15] Kempker RR, Kempker JA, Peters M, et al. Loss of smell and taste among healthcare personnel screened for Coronavirus 2019. Clin Infect Dis 2020;72:1244–6; Published online.
- [16] Chiesa-Estomba CM, Lechien JR, Portillo-Mazal P, et al. Olfactory and gustatory dysfunctions in COVID-19. First reports of Latin-American ethnic patients. Am J Otolaryngol 2020;41:102605.
- [17] Mutiawati E, Fahriani M, Mamada SS, et al. Anosmia and dysgeusia in SARS-CoV-2 infection: incidence and effects on COVID-19 severity and mortality, and the possible pathobiology mechanisms - a systematic review and meta-analysis. F1000Res. 2021;10:40.
- [18] Von Bartheld CS, Butowt R, Hagen MM. Prevalence of chemosensory dysfunction in COVID-19 patients: a systematic review and metaanalysis reveals significant ethnic differences. ACS Chem Neurosci 2020; 11:2944–61; Published online.
- [19] Qiu C, Cui C, Hautefort C, et al. Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: an international multicenter study. Otolaryngol Head Neck Surg (United States) 2020;163:714–21.
- [20] Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life-an updated review. Chem Senses 2014;39:185–94.
- [21] Neuland C, Bitter T, Marschner H, et al. Health-related and specific olfaction-related quality of life in patients with chronic functional anosmia or severe hyposmia. Laryngoscope 2011;121:867–72; Published online.
- [22] Speth MM, Singer-Cornelius T, Oberle M, et al. Mood, anxiety and olfactory dysfunction in COVID-19: evidence of central nervous system involvement? Laryngoscope 2020;130:2520–5.
- [23] Hopkins C, Surda P, Whitehead E, et al. Early recovery following new onset anosmia during the COVID-19 pandemic—An observational cohort study. J Otolaryngol Head Neck Surg 2020;49:26; Published online.
- [24] Heald AE, Pieper CF, Schiffman SS. Taste and smell complaints in HIVinfected patients. Aids 1998;12:1667–74.
- [25] Mattos JL, Edwards C, Schlosser RJ, et al. A brief version of the questionnaire of olfactory disorders in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 2019;9:1144–50; Published online.
- [26] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–280.e8.
- [27] Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 2020;6:11; Published online.
- [28] Yan CH, Faraji F, Prajapati DP, *et al.* Self-reported olfactory loss associates with outpatient clinical course in COVID-19. Int Forum Allergy Rhinol 2020;10:821–31.
- [29] Åkerlund A, Bende M, Murphy C. Olfactory threshold and nasal mucosal changes in experimentally induced common cold. Acta Otolaryngol 1995;115:88–92.
- [30] Lechien JR, Michel J, Radulesco T, et al. Clinical and radiological evaluations of COVID-19 patients with anosmia: preliminary report. Laryngoscope 2020;130:2526–31.
- [31] Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020;6:eabc5801.
- [32] Forster P, Forster L, Renfrew C, et al. Phylogenetic network analysis of SARS-CoV-2 genomes. Proc Natl Acad Sci 2020;117:9241–3.
- [33] Benetti E, Tita R, Spiga O, et al. ACE2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population. Eur J Hum Genet 2020;28:1602–14; Published online.
- [34] Han AY, Mukdad L, Long JL, et al. Anosmia in COVID-19: mechanisms and significance. Chem Senses 2020;45:423–8.
- [35] Xu H, L Z, J D, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 2020;12:8; Published online.
- [36] Mathew G, Agha R. for the STROCSS Group. STROCSS 2021: Strengthening the Reporting of cohort, cross-sectional and case-control studies in Surgery. Int J Surg 2021;96:106165.

- [37] Komagamine Junpei, Yabuki Taku. Initial symptoms of patients with coronavirus disease 2019 in Japan: a descriptive study. J Gen Fam Med 2021;22:61–4.
- [38] Kang JW, Lee YC, Han K, *et al*. Epidemiology of anosmia in South Korea: a nationwide population-based study. Sci Rep 2020;10:1–8.
- [39] Sahoo PR, Sahu M, Surapaneni PS, et al. Evolution of olfactory and gustatory dysfunctions in COVID-19 patients in India. Eur Arch Otorhinolaryngol 2021;278:2875–81.
- [40] Alfallaj R, AlSkait G, Alamari N, et al. Incidence of olfactory dysfunction in patients with COVID-19 in a tertiary hospital in Saudi Arabia. Allergy Rhinol (Providence) 2022;13:21526575221140809.
- [41] Al-Rawi NH, Sammouda AR, AlRahin EA, et al. Prevalence of anosmia or ageusia in patients with COVID-19 among United Arab Emirates population. Int Dent J 2022;72:249–56.
- [42] Butowt R, Bilinska K, von Bartheld CS. Olfactory dysfunction in COVID-19: new insights into the underlying mechanisms. Trends Neurosci 2023; 46:75–90.
- [43] von Bartheld CS, Hagen MM, Butowt R. The D614G virus mutation enhances anosmia in COVID-19 patients: evidence from a systematic review and meta-analysis of studies from South Asia. ACS Chem Neurosci 2021;12:3535–49.
- [44] von Bartheld CS, Wang L. Prevalence of olfactory dysfunction with the Omicron variant of SARS-CoV-2: a systematic review and meta-analysis. Cells 2023;12:430.
- [45] Obeid DA, Alsanea MS, Alnemari RT, et al. SARS-CoV-2 genetic diversity and variants of concern in Saudi Arabia. J Infect Dev Ctries 2021;15:1782–91.
- [46] Braga-Paz I, Ferreira de Araújo JL, Alves HJ, et al. Negative correlation between ACE2 gene expression levels and loss of taste in a cohort of COVID-19 hospitalized patients: new clues to long-term cognitive disorders. Front Cell Infect Microbiol 2022;12:905757.
- [47] Shelton JF, Shastri AJ, Fletez-Brant K. 23andMe COVID-19 Team, et al. The UGT2A1/UGT2A2 locus is associated with COVID-19-related loss of smell or taste. Nat Genet 2022;54:121–4.
- [48] Wu TJ, Yu AC, Lee JT. Management of post-COVID-19 olfactory dysfunction. Curr Treat Options Allergy 2022;9:1–18.
- [49] Hwang SH, Kim SW, Basurrah MA, et al. The efficacy of olfactory training as a treatment for olfactory disorders caused by Coronavirus Disease-2019: a systematic review and meta-analysis. Am J Rhinol Allergy 2023;37:495–501.
- [50] Alroqi A, Alothaim L, Albugami S, et al. Smell disturbance among Saudi COVID-19 patients. J Nat Sci Med 2021;4:348–51.
- [51] Al-Ani RM, 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 2022;74(suppl 2):2703–9.
- [52] De Bel-Air F. Demography, migration, and labour market in Qatar, Migration Policy Centre, GLMM, Explanatory note, 8/2014, - https:// hdl.handle.net/1814/324315
- [53] Abdelmaksoud AA, Ghweil AA, Hassan MH, et al. Olfactory disturbances as presenting manifestation among Egyptian patients with COVID-19: possible role of zinc. Biol Trace Elem Res 2021;199:4101–8.
- [54] Al-Zaidi HMH, Badr HM. Incidence and recovery of smell and taste dysfunction in COVID-19 positive patients. Egypt J Otolaryngol 2020; 36:47.
- [55] Hintschich CA, Masha YN, Hummel T. The taste of the pandemic contemporary review on the current state of research on gustation in coronavirus disease 2019 (COVID-19). Int Forum Allergy Rhinol 2022; 12:210–6.
- [56] Tan BKJ, Han R, Zhao JJ, et al. Prognosis and persistence of smell and taste dysfunction in patients with covid-19: meta-analysis with parametric cure modelling of recovery curves. BMJ (Clinical research ed) 2022;378:e069503.
- [57] Lechien JR, Luigi AV, Saussez S. Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: a multicentre prospective study. J Intern Med 2023;293:82–90.