The Journal of Laryngology & Otology

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Olfactory dysfunction and coronavirus disease 2019 severity: a prospective cohort study

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Abstract

Objective. The primary goal of this study was to evaluate the association between olfactory dysfunction or taste impairment and disease severity and radiological findings in coronavirus disease-2019. The secondary goal was to assess the prevalence, severity and course of olfactory dysfunction or taste impairment in patients with coronavirus disease 2019.

Method. This prospective observational cohort study evaluated patients hospitalised with coronavirus disease 2019 between April 1 and 1 May 2020. Olfactory dysfunction and taste impairment were evaluated by two questionnaires. Chest computed tomography findings and coronavirus disease-2019 severity were assessed.

Results. Among 133 patients, 23.3 per cent and 30.8 per cent experienced olfactory dysfunction and taste impairment, respectively, and 17.2 per cent experienced both. The mean age was 56.03 years, and 64.7 per cent were male and 35.3 per cent were female. No statistically significant association was found between olfactory dysfunction ($p = 0.706$) and taste impairment ($p = 0.35$) with either disease severity or chest computed tomography grading.

Conclusion. Olfactory dysfunction or taste impairment does not have prognostic importance in patients with coronavirus disease 2019.

Introduction

Different levels of olfactory and gustatory dysfunction in patients with coronavirus disease-2019 (COVID-19) have been reported since the beginning of the pandemic. In order to prevent further spread of COVID-19, early identification and isolation are of great importance. ENT-UK advised people experiencing new onset of anosmia even without any other symptom to isolate themselves.[1] The American Academy of Otolaryngology-Head and Neck Surgery proposed the use of these symptoms as a screening tool.[2] Additionally, some authors believe that guidelines should include testing of patients with olfactory or gustatory dysfunctions for COVID-19.[3] Olfactory and gustatory dysfunction are now accepted as manifestations of this novel disease,[4] although a thorough explanation of the relationship requires more work.

This study aimed to assess the prevalence, onset, course and severity of olfactory dysfunction and taste impairment among patients in our hospital's COVID-19 in-patient clinic. We also planned to scrutinise their accompanying nasal symptoms, possible correlation with laboratory results, pulmonary status determined by imaging and COVID-19 severity.

This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[5]

Materials and methods

We designed a prospective observational cohort study of patients with confirmed COVID-19 who were admitted to our hospital's COVID-19 isolation units between 1 April and 1 May. This study was approved by the Turkish Ministry of Health and the local ethics committee (reference number: 2020/521). Verbal informed consent was obtained from all participants by telephone interview.

Patients who were available to be contacted by telephone within their first three days of hospital admission were included in the study. Exclusion criteria were patients who (1) had a history of permanent smell or taste loss, (2) had a history of rhinological disease or surgery, (3) had diseases causing cognitive problems, and (4) were misdiagnosed with COVID-19.

All eligible patients were reached by telephone to minimise the risk of transmission to healthcare workers and cross infection. Patients were asked to participate in an 11-item questionnaire survey. They were also informed that they would be contacted by phone two weeks after completion of their treatments for another eight-item questionnaire

Main Article

Dr C Sen takes responsibility for the integrity of the content of the paper

Cite this article: Aydemir L *et al*. Olfactory dysfunction and coronavirus disease 2019 severity: a prospective cohort study. *J Laryngol Otol* 2021;**135**:1010–1018. https://doi.org/10.1017/S0022215121002425

Accepted: 23 July 2021
First published online: 9 September 2021

Key words:
COVID-19; Smell; Anosmia; Ageusia; Dysgeusia

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interview if they reported olfactory dysfunction or taste impairment in the first survey. Patients who agreed to join the study and gave consent by telephone were enrolled in the study.

Additionally, data about patient characteristics and comorbidities were reviewed from electronic medical records. Clinical features, baseline levels of serum biochemical parameters (neutrophil-to-lymphocyte ratio, C-reactive protein (CRP), ferritin, d-dimer and fibrinogen) possibly related to prognosis,[6–8] oxygen saturation, duration of hospitalisation, need for mechanical ventilation and admission to the intensive care unit were also noted. A thoracic radiologist examined chest computed tomography (CT) findings of all patients. Chest CT scores were assessed, and pulmonary findings were classified as: 1, mild; 2, moderate and 3, severe.[9,10] The patients were categorised into three groups (1, mild/moderate group; 2, severe group; and 3, critical group) according to the disease severity classification recommended by the World Health Organization (WHO).[11]

Given the cross-sectional observational nature of the study, sampling bias and recall bias could occur. We followed the patients' clinic status and excluded misdiagnosed cases to overcome sampling bias. However, we did not use any randomisation method for participant selection, which may cause sampling bias. We preferred to include all eligible patients who were treated within a pre-determined time frame. By contacting the patients within the early period of their hospital stay and shortly after they were healed, we believe we decreased the risk of reporting errors to a low level.

Results

Statistical analysis

Power analysis for a bivariate correlation was performed in G*Power (Heinrich Heine University Düsseldorf, Germany) statistical power calculator to determine an adequate sample size with an alpha of 0.05, a power of 0.95 and a medium effect size ($\rho = 0.3$) in a two-tailed analysis.[12] Based on the above assumptions, the required sample size was calculated as 134.

Descriptive statistics were used to define categorical variables. Associations between categorical variables were evaluated by chi-square or Fisher's exact test. Normality assumption was not satisfied by the continuous variables of the study. Therefore, non-parametric tests were used for further analysis. Spearman's rho was performed to assess the correlation between two continuous variables. Group comparisons were performed with the Mann–Whitney U test for two independent groups, with the Wilcoxon signed-rank test for more than two independent groups and Friedman's test for more than two dependent groups. Pairwise comparisons with Bonferroni correction after omnibus tests were performed. The analyses were conducted using MedCalc statistical software (version 12.7.7; Ostend, Belgium).

A total of 172 patients with COVID-19 were eligible during the study period. Among these patients, 145 responded to the first questionnaire. Five patients declared history of olfactory dysfunction. Seven patients were eventually diagnosed with other diseases mimicking COVID-19 symptoms. Finally, 133 patients were included in the study. Moreover, 46 of 49 patients who had olfactory dysfunction, taste impairment or both were able to fill out the second questionnaire (second interview could not be set with 3 patients because of intensive care unit admission).

Table 1. Descriptive and clinical data

Parameter	Value
Gender (male:female; *n*)	86:47
Age (mean (standard deviation); years)	56.03 (14.05)
Olfactory dysfunction (*n* (%))	31 (23.3)
– Anosmia (*n*)	6
– Hyposmia (*n*)	25
Onset of olfactory dysfunction (*n*)	
– Prior to other symptoms	3
– Concomitant with other symptoms	12
– After other symptoms	15
Taste impairment (*n* (%))	41 (30.8)
Onset of taste impairment (*n*)	
– Prior to other symptoms	3
– Concomitant with other symptoms	18
– After other symptoms	20
Nasal obstruction (*n* (%))	18 (13.5)
Nasal discharge (*n* (%))	13 (9.8)
Itchy nose (*n* (%))	2 (1.5)
Disease severity (*n* (%))	
– Mild/moderate	88 (66.2)
– Severe	36 (27.1)
– Critical	9 (6.8)
Chest computed tomography grading (*n* (%))	
– Mild	32 (24.8)
– Moderate	70 (54.3)
– Severe	27 (20.9)

The mean (± standard deviation (SD)) patient age was 56.03 ± 14.05 years (range, 27–93 years), and 56 patients (64.7 per cent) were male and 47 patients (35.3 per cent) were female. Demographic data, ratios of the patients who had olfactory dysfunction or taste impairment, chest CT scores and grading, and disease severity classification of the patients are presented in Table 1.

A total of 49 patients (36.8 per cent) reported having olfactory dysfunction, taste impairment or both. Moreover, 31 (23.3 per cent) and 41 (30.8 per cent) patients experienced olfactory dysfunction and taste impairment, respectively, and 23 (17.2 per cent) patients had both. Among these patients, six reported anosmia and ageusia, seven reported ageusia without any olfactory problem, and one reported ageusia with hyposmia. Olfaction and taste recovered totally in almost all patients. Only two of the patients reported partial recovery. No patient reported a permanent loss without any degree of recovery.

The average recovery (mean ± SD) time for olfactory dysfunction and taste impairment was 6.4 ± 2.12 and 6.18 ± 1.75 days, respectively. Remarkable differences were noted in the median verbal rating scale scores for olfactory function during the active phase of the disease (median, 3; range, 0–6) compared with the time prior to the disease (median, 10; range, 7–10) and 2 weeks after healing (median, 10; range, 5–10; $p < 0.001$). In addition, the verbal rating scale scores were significantly lower for taste sensation during the course of the disease (median, 3; range, 0–8) compared with that prior to

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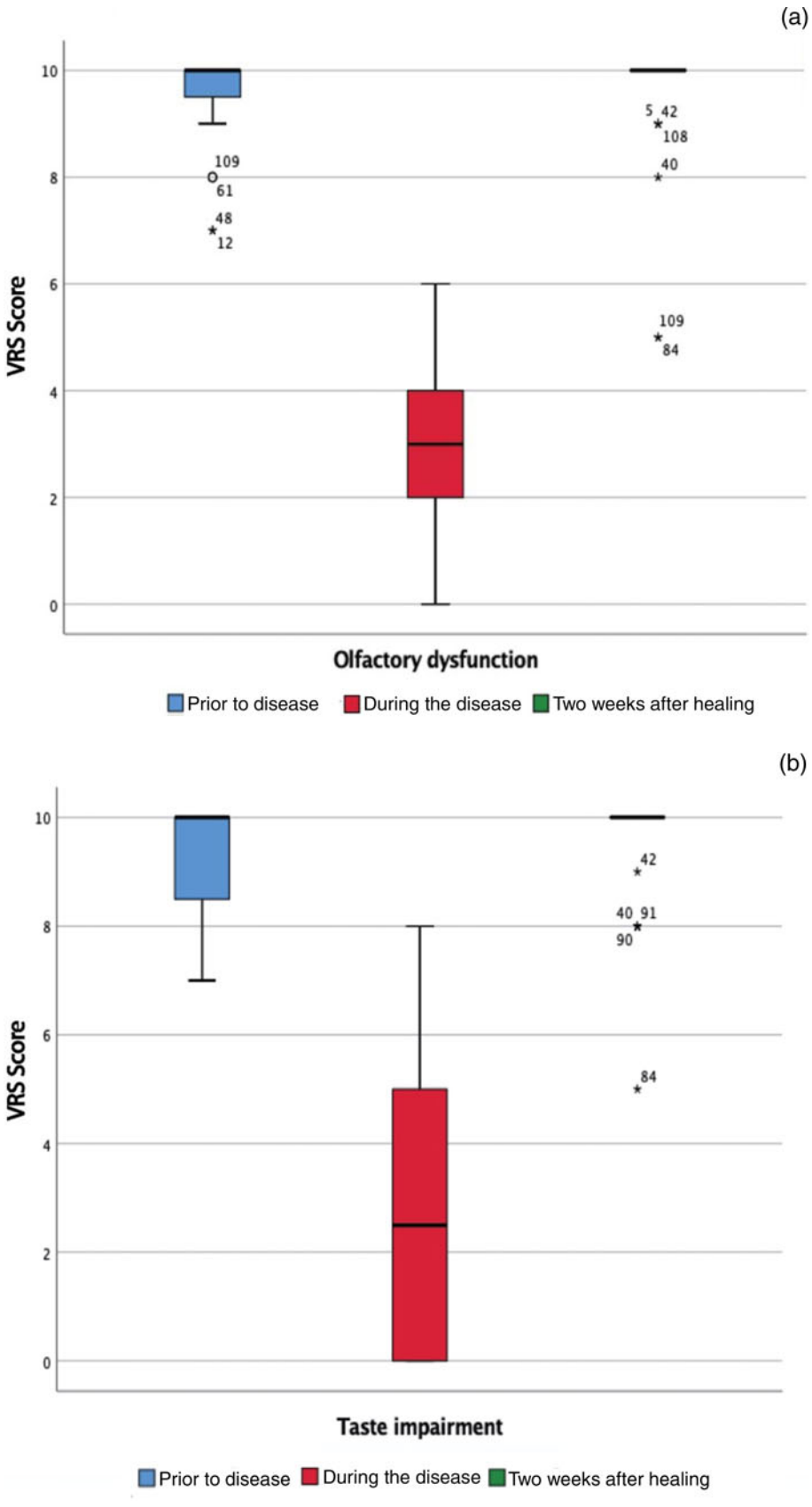

Fig. 1. Verbal rating scale score for olfactory dysfunction and taste impairment prior to disease, during the disease and two weeks after healing. (a) Verbal rating scale score for olfactory dysfunction and (b) verbal rating scale score for taste impairment. VRS = verbal rating scale

disease (median, 10; range, 7–10) and 2 weeks after healing (median, 10; range, 5–10; $p < 0.001$) (Figure 1).

No significant differences in the distributions of sex, age and comorbidities were observed between the patients who suffered from olfactory dysfunction or taste impairment (Table 2). However, the median recovery time from hyposmia was 1.5 days longer in female patients (median, 7; range, 5–10) than in male patients (median, 5.5; range, 2–10; $p = 0.047$). Additionally, patients with hypertension reported longer recovery time from both hyposmia and dysgeusia than patients without hypertension ($p = 0.033$ and $p = 0.032$, respectively).

A significant association was found between olfactory dysfunction or taste impairment and nasal obstruction ($p = 0.001$). Although 10 (32.3 per cent) of 31 patients with olfactory

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Table 2. Relationship between descriptive data and olfactory dysfunction or taste impairment

	Olfactory dysfunction			Taste impairment		
Parameter	Yes*	No†	*P*-value	Yes‡	No**	*P*-value
Age (mean (standard deviation); years)	52.69 (13.61)	57.03 (14.09)	0.132	52.29 (11.80)	57.68 (17.71)	0.056
Gender (*n*)						
– Male	18	68	0.398	27	59	1
– Female	13	34		14	33	
Comorbidities (*n*)						
– Hypertension	14	37	0.404	17	34	0.7
– Diabetes mellitus	7	22	1	10	19	0.65
– Chronic obstructive pulmonary disease	1	3	1	0	4	0.311
– Malignancy	1	6	1	1	6	0.436
– Asthma	1	2	0.552	1	2	1
Other nasal symptoms (*n*)						
– Nasal obstruction	10	8	**0.001**	12	6	**0.001**
– Nasal discharge	3	10	1	3	10	0.754
– Itchy nose	0	2	1	1	1	0.523

*$n = 31$; †$n = 102$; ‡$n = 41$; **$n = 92$

dysfunction had a new-onset nasal obstruction, 12 (29.3 per cent) of 41 patients with dysgeusia reported a new-onset nasal obstruction. However, no association with other nasal symptoms was observed (Table 2).

No statistically significant association was found between olfactory dysfunction ($p = 0.706$) and taste impairment ($p = 0.35$) with either disease severity or CT grading. However, the onset of olfactory dysfunction compared with other classical symptoms of COVID-19 was the latest to occur in patients with critical disease ($p = 0.04$).

No statistically significant association was observed between any parameters related to olfactory dysfunction or taste impairment and duration of hospitalisation ($p > 0.05$). Furthermore, no correlation was noted between olfactory dysfunction or taste impairment verbal rating scale scores and laboratory parameters and CT scores ($p > 0.05$).

Statistically significant differences were observed in the distributions of the neutrophil count, neutrophil-to-lymphocytes ratio, CRP and fibrinogen between the patient groups when categorised based on their disease severity and CT grading. The median and *p*-values of the parameters are given in Tables 3 and 4. Additionally, a moderate correlation was noted between CT scores and CRP ($r_s = 0.396$; $p < 0.001$) and fibrinogen levels ($r_s = 0.33$; $p < 0.001$). Moreover, a weak correlation was found between CT scores and ferritin levels ($r_s = 0.207$; $p = 0.018$) and peripheral capillary oxygen saturation (SpO2) ($r_s = -0.228$; $p = 0.009$). However, no significant difference was observed in the initial laboratory parameters between patients who showed a CT scoring progression and the ones who did not ($p > 0.05$).

Nine (6.7 per cent) patients needed treatment in the intensive care unit after hospital admission. Of them, two patients had only hyposmia, while one had both hyposmia and dysgeusia. Four patients died among the patients transferred to the intensive care unit, and two of them reported hyposmia.

Discussion

A wide range of clinical presentations have been reported in COVID-19.[8,13] While the spread of this disease has expanded, physicians began to encounter more patients complaining of olfactory dysfunction and taste impairment.[14–18] Personal observations and studies from several countries have been shared rapidly to call attention to the association between COVID-19 and olfactory dysfunction.[14,18–20] In this study, we evaluated olfactory dysfunction and taste impairment in patients hospitalised for COVID-19 and their relation with COVID-19 pneumonia and disease severity. Olfactory dysfunction and taste impairment were assessed by questionnaire survey conducted over the telephone, including a verbal rating scale. A subjective method was preferred as similar to other studies in the literature.[19,21–29]

We found that the presence of olfactory dysfunction or taste impairment did not correlate with disease severity in patients hospitalised for COVID-19. Although two studies[21,30] have suggested that olfactory dysfunction or taste impairment is a prognostic factor for the milder form of COVID-19, both studies were conducted in out-patients. Therefore, the possibility of the difference in reporting olfactory dysfunction or taste impairment between hospitalised patients and those not hospitalised should be kept in mind when interpreting these data. In this study, we assessed a certain cohort of patients (only hospitalised) to reduce this bias. Similar to our findings, studies using objective olfactory measurement methods from Italy and Iran have reported no association between chemosensory dysfunction and disease severity.[31–33] We defined disease severity according to the classification proposed by the WHO,[11] which is based on reports from China,[34] while in the study by Moein *et al.*,[31] the criteria of the Massachusetts General Hospital COVID-19 treatment guidance were used. The presence of pneumonia and the criteria proposed by Tian *et al.*[35] was used to determine disease severity in studies conducted by Vaira *et al.*[32,33] With regard to the distribution of disease severity, our cross-sectional cohort is consistent with other large cohort studies and data stated by the WHO.[11,34]

Another key finding was that no statistically significant association was found between olfactory dysfunction or taste impairment and chest CT grading. Early personal observations

https://doi.org/10.1017/S0022215121002425 Published online by Cambridge University Press

https://doi.org/10.1017/S0022215121002425 Published online by Cambridge University Press

Table 3. Association of disease severity with clinical findings

	Disease severity				*P*-value for pairwise comparison[§]		
Parameter	Mild/moderate[†]	Severe[‡]	Critical**	*P*-value	M-S	M-C	S-C
Olfactory dysfunction (*n*)	20	8	3	0.706			
Onset of olfactory dysfunction (*n*)							
– Prior to other symptoms	3	0	0	0.04*			
– Concomitant with other symptoms	6	6	0				
– After other symptoms	11	1	3				
– Taste impairment	30	10	1	0.35			
Onset of taste impairment (*n*)							
– Prior to other symptoms	3	0	0	0.575			
– Concomitant with other symptoms	12	6	0				
– After other symptoms	15	4	1				
Laboratory parameter (median (minimum–maximum))							
– C-reactive protein (mg/l)	27.97 (4.12–273.13)	79.05 (13.01–283.13)	56.38 (15.17–254.52)	0.001*	<0.001	0.029	0.625
– Neutrophil count (10^3/mcl)	3.38 (0.62–12.07)	4.81 (2.21–22.67)	4.96 (2.17–15.87)	0.001*	0.001	0.035	0.813
– Lymphocyte count (10^3/mcl)	1.29 (0.17–2.56)	1.04 (0.22–3.6)	0.96 (0.42–1.38)	0.077			
– Neutrophil to lymphocyte ratio	2.62 (0.86–48.59)	4.72 (0.73–25.47)	4.06 (2.28–37.79)	<0.001*	0.001	0.014	0.645
– Fibrinogen (mg/dl)	518.5 (146–901)	614.5 (365–816)	489 (305–674)	0.006*	0.002	0.645	0.081
– Ferritin (ng/ml)	296.3 (25.73–5450)	419.45 (57–2256)	743.8 (153.4–3125)	0.09			
– D-dimer (ng/ml)	590 (240–15950)	685 (290–12940)	870 (260–2860)	0.068			

Statistical significance was observed. [†]*n* = 88; [‡]*n* = 36; ***n* = 9; [§]Bonferroni correction was applied. M = mild/moderate; S = severe; C = critical

Table 4. Association of chest CT grading with clinical findings

Parameter	Chest CT grading			*P*-value	*P*-value for pairwise comparison†		
	Mild	Moderate	Severe		Mild to moderate	Mild to severe	Moderate to severe
Olfactory dysfunction (*n*)	4	20	6	0.213			
Onset of olfactory dysfunction (*n*)							
– Prior to other symptoms	1	2	0	0.25			
– Concomitant with other symptoms	1	6	4				
– After other symptoms	2	12	1				
– Taste impairment	7	25	8	0.361			
Onset of taste impairment (*n*)							
– Prior to other symptoms	1	2	0	0.952			
– Concomitant with other symptoms	3	10	4				
– After other symptoms	3	13	4				
Laboratory parameters (median (minimum–maximum))							
– C-reactive protein (mg/l)	24.8 (4.12–273.13)	40.65 (4.67–283.13)	77.52 (16.35–200.62)	<0.001*	0.055	<0.001	0.001
– Neutrophil count (10^3/mcl)	3.71 (0.83–22.67)	3.33 (0.62–15.87)	4.86 (2.21–16.6)	0.01*	0.314	0.069	0.002
– Lymphocyte count (10^3/mcl)	1.19 (0.24–2.1)	1.31 (0.17–3.2)	1 (0.22–3.6)	0.155			
– Neutrophil to lymphocyte ratio	3.51 (1.3–31.29)	2.57 (0.86–48.59)	4.68 (0.73–18.91)	<0.001*	0.061	0.124	0.001
– Fibrinogen (mg/dl)	496 (146–812)	532 (300–901)	628.5 (365–768)	0.002*	0.107	0.001	0.005
– Ferritin (ng/ml)	260 (27.4–5450)	313.8 (25.73–2797)	475.7 (57–3125)	0.0157			
– D-dimer (ng/ml)	610 (260–3520)	615 (240–15950)	690 (350–12940)	0.204			

*Statistical significance was observed; †Bonferroni correction was applied. CT = computed tomography; M = mild/moderate; S = severe; C = critical; CRP = C-reactive protein

in our clinical practice led us to probe if there was less lung involvement in patients reporting chemosensory dysfunction. The results of the study do not support our initial hypothesis. To the best of our knowledge, this is the first study investigating the association between olfactory dysfunction or taste impairment and COVID-19 pneumonia in patients hospitalised for COVID-19.

The prevalence of olfactory dysfunction or taste impairment in patients with COVID-19 has ranged from 5 per cent up to 98 per cent in the literature.[13,31] Such a wide range may be explained with the heterogeneity of the study protocols.[36] Our results are consistent with those of other studies conducted with hospitalised patients.[19,37] On the contrary, some studies have reported lower or higher olfactory dysfunction or taste impairment.[24,27,29–33,38,39]

The study cohort had a male predominance, with a mean age of 56 years, reflecting the previously reported demographic and clinical characteristics of the disease.[8,40] The median recovery time from olfactory dysfunction was 1.5 days longer in female than in male patients. Although a study from Italy reports similar observations,[25] our data show similar mean recovery time and maximum range in both female and male patients, so these should be interpreted cautiously. An unexpected finding was that patients with hypertension reported longer recovery time from both hyposmia and dysgeusia than patients without hypertension. This may be associated with the altered expression of angiotensin-converting-enzyme-2 receptor on the mucosa of the oral cavity, epithelial cells of the tongue, olfactory sustentacular cells and olfactory stem cells, especially in patients taking angiotensin-converting-enzyme-inhibitor drugs.[41] Further studies are needed to clarify this issue.

Permanent anosmia did not occur in any of the patients. After two weeks, olfaction and taste recovered totally in almost all patients. Only two patients reported a partial recovery. Together with the average recovery time for olfactory dysfunction and taste impairment, these findings support published reports suggesting an early and high rate of recovery.[4,19,22,24,30,32,42] This finding distinguishes COVID-19 olfactory dysfunction from other post-viral olfactory dysfunctions, which mostly recover after longer than a year.[43] Vaira *et al.*[44] and Meini *et al.*[25] suggested that olfactory dysfunction in severe acute respiratory syndrome coronavirus-2 is not related to definitive damage from the virus to the neuronal cells, considering the high rate of rapid recovery. Eliezer *et al.*[14] reported normal magnetic resonance imaging findings of the olfactory bulb in COVID-19-related olfactory dysfunction and supported this hypothesis.

Although Speth *et al.*[26] showed no correlation between olfactory dysfunction and nasal obstruction and rhinorrhoea, our study showed a significant association between olfactory dysfunction or taste impairment and nasal obstruction symptoms ($p = 0.001$). New-onset nasal obstruction was found in 32.3 per cent and 9.3 per cent of patients with olfactory dysfunction and taste impairment, respectively. These rates are similar to those reported from three different continents.[21,22,45] In a prospective study, Lechien *et al.*[27] showed an even higher rate (48.7 per cent) of concomitant nasal obstruction. Hence, nasal obstruction was not present in all patients with olfactory dysfunction, and they suggested this finding as an indicator for 'neural' loss of smell. We think that the coexistence of nasal obstruction in COVID-19-related olfactory dysfunction (a statistically significant association in our study) supports a 'conductive' loss hypothesis. Moreover, in the light of previous reports,[14,25,44] we agree with the 'olfactory cleft syndrome with mucosal obstruction' hypothesis proposed by Gane *et al.*[15]

The present study contradicts most reports showing a relatively higher rate of chemosensory dysfunction as an initial presenting symptom,[4,19,22,46] while a few studies have reported similar findings.[21,24] We found no relation between the duration of hospitalisation and the presence of olfactory dysfunction or taste impairment. Since patients with more severe disease would have had a longer hospital admission, this finding can be considered an internal verification of the study because it corroborates the previous statement that olfactory dysfunction or taste impairment are not associated with disease severity.

In this study, no correlation was noted between olfactory dysfunction or taste impairment verbal rating scale scores and laboratory parameters ($p > 0.05$). These results were expected as olfactory dysfunction or taste impairment, as previously mentioned, were not associated with disease severity and COVID-19 pneumonia. Obtained data about laboratory parameters are consistent with the current literature.[6,8,34] We believe that all these data regarding laboratory parameters show that the study group represents a well-distributed cohort with possible but minimal sampling bias and a natural disease course.

Among the strengths of the present study are: (1) the prospective design of data collection, (2) follow-up data for olfactory dysfunction or taste impairment after the first questionnaire, (3) the first study to evaluate the association between olfactory dysfunction or taste impairment and chest CT grading, and (4) grading chest CT (by an experienced thoracic radiologist) and disease severity according to validated criteria.

The major limitations of this study are: (1) lack of data concerning the period after the first questionnaire interview for patients without olfactory dysfunction or taste impairment, (2) lack of objective olfactory assessment, (3) a relatively small study population, and (4) lack of patients who were not admitted to hospital. Future prospective, controlled studies with objective olfactory assessment tools are needed to establish the association between olfactory dysfunction or taste impairment and pulmonary involvement and disease severity in COVID-19.

- Different levels of olfactory and gustatory dysfunction in patients with coronavirus disease (COVID-19) have been reported
- Olfactory dysfunction or taste impairment do not have clinical repercussions on disease severity
- Olfactory dysfunction or taste impairment do not have clinical repercussions on chest computed tomography findings
- Nasal obstruction is observed frequently as an accompanying symptom of olfactory dysfunction or taste impairment compared with other nasal symptoms
- The onset of olfactory dysfunction compared with other classical symptoms of COVID-19 was found the latest in patients with critical disease

Conclusion

Patients with COVID-19 often report olfactory dysfunction or taste impairment. Nasal obstruction may be present as an accompanying symptom. Olfactory dysfunction or taste impairment do not have clinical repercussions on disease severity and chest CT findings.

Competing interests. None declared

https://doi.org/10.1017/S0022215121002425 Published online by Cambridge University Press

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