ORIGINAL ARTICLE

Smell and Taste Dysfunction in COVID-19 Is Associated With Younger Age in Ambulatory Settings: A Multicenter Cross-Sectional Study

Izquierdo-Domínguez A[1,2,3,*], Rojas-Lechuga MJ[4,5,6,*], Chiesa-Estomba C[7], Calvo-Henríquez C[8], Ninchritz-Becerra E[7], Soriano-Reixach M[7], Poletti-Serafini D[9], Maria Villarreal I[10], Maza-Solano JM[11], Moreno-Luna R[11], Villarroel PP[12], Mateos-Serrano B[13], Agudelo D[14], Valcarcel F[15], del Cuvillo A[16], Santamaría A[17], Mariño-Sánchez F[5,6,17], Aguilar J[18], Vergés P[19], Inciarte A[20], Soriano A[20], Mullol J[4,5,6,**], Alobid I[2,4,5,6,**]

[1]Department of Allergy, Consorci Sanitari de Terrassa, Barcelona, Spain
[2]Unidad Alergo Rino, Centro Médico Teknon, Barcelona, Spain
[3]Department of Allergy, Clínica Diagonal, Barcelona, Spain
[4]Rhinology Unit & Smell Clinic, Department of Otorhinolaryngology, Hospital Clinic Barcelona, Universitat de Barcelona, Barcelona, Spain
[5]Clinical and Experimental Respiratory Immunoallergy, IDIBAPS, Barcelona, Spain
[6]CIBER of Respiratory Diseases (CIBERES), Spain
[7]Department of Otorhinolaryngology, Donostia University Hospital, San Sebastian, Spain
[8]Department of Otorhinolaryngology, Hospital Complex of Santiago de Compostela, Santiago de Compostela, Spain
[9]Rhinology Section, Department of Otorhinolaryngology, Hospital General Universitario Gregorio Marañón and Hospital La Milagrosa, Spain
[10]Department of Otorhinolaryngology, Hospital Universitario de Fuenlabrada and Hospital La Milagrosa, Spain
[11]Rhinology and Skull Base Unit, Department of Otorhinolaryngology, University Hospital Virgen de la Macarena, Seville, Spain
[12]Department of Otorhinolaryngology, Hospital Universitario Virgen de las Nieves, Granada, Spain
[13]Department of Otolaryngology, Hospital Universitario La Paz, Spain
[14]Department of Otorhinolaryngology, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain
[15]Rhinology Section, Department of Otorhinolaryngology, Hospital Universitario de Cruces, Bilbao, Spain
[16]Rhinology and asthma Unit, UGC ORL Hospital de Jerez, Servicio Andaluz de Salud, Cadiz, Spain
[17]Department of Otorhinolaryngology, Hospital Ramón y Cajal, Madrid, Spain,
[18]Department of Otorhinolaryngology, Hospital Reina Sofía de Córdoba, Córdoba, Spain
[19]Department of Otorhinolaryngology, Hospital Vall d'Hebron, Barcelona, Spain
[20]Department of Infectious Diseases, Hospital Clínic Barcelona, Universitat de Barcelona, Barcelona, Spain
*These authors share first-author responsibilities.
**These authors equally contribute as senior and corresponding authors.

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Abstract

Background: Since the initial anecdotal reports of coronavirus disease 2019 (COVID-19) from China, a growing number of studies have reported on smell and/or taste dysfunction (STD).
Objective: The aim of our study was to investigate the frequency and severity of STD in COVID-19 patients and to evaluate the association with demographic characteristics, hospital admission, symptoms, comorbidities, and blood biomarkers.
Methods: We performed a multicenter cross-sectional study on patients who were positive for SARS-CoV-2 (n=846) and controls (n=143) from 15 Spanish hospitals. Data on STD were collected prospectively using an in-person survey. The severity of STD was categorized using a visual analog scale. We analyzed time to onset, recovery rate, time to recovery, hospital admission, pneumonia, comorbidities, smoking, and symptoms.
Results: STD was at least 2-fold more common in COVID-19–positive patients than in controls. COVID-19–positive hospitalized patients were older, with a lower frequency of STD, and recovered earlier than outpatients. Analysis stratified by severity of STD showed that more than half of COVID-19 patients presented severe loss of smell (53.7%) or taste (52.2%); both senses were impaired in >90%. In the multivariate analysis, older age (>60 years), being hospitalized, and increased C-reactive protein were associated with a better sense of smell and/or taste. COVID-19–positive patients reported improvement in smell (45.6%) and taste (46.1%) at the time of the survey; in 90.6% this was within 2 weeks of infection.
Conclusion: STD is a common symptom in COVID-19 and presents mainly in young and nonhospitalized patients. More studies are needed to evaluate follow-up of chemosensory impairment.

Key words: Loss of smell. Loss of taste. SARS-CoV-2. COVID-19. Hospital admission.

Resumen

Introducción: Desde los informes anecdóticos iniciales de China sobre la enfermedad por coronavirus 2019 (COVID-19), ha habido un número creciente de estudios que describen disfunción del olfato y/o del gusto (DOG).
Objetivo: El objetivo fue investigar la frecuencia y la gravedad de la DOG en pacientes con COVID-19 y evaluar su asociación con características demográficas, ingreso hospitalario, síntomas, comorbilidades y biomarcadores sanguíneos.
Métodos: Estudio transversal multicéntrico en pacientes con SARS-CoV-2 positivo (n=846) y controles (n=143) de 15 hospitales españoles. Los datos de DOG fueron recopilados de manera prospectiva con una encuesta realizada en persona. La gravedad de la DOG se clasificó por escala visual analógica. Se analizaron el tiempo de aparición de DOG, tasa de recuperación, tiempo de recuperación, ingreso hospitalario, diagnóstico de neumonía, comorbilidades, tabaquismo y síntomas.
Resultados: La DOG fue al menos 2 veces más común en pacientes COVID-19 en comparación con los controles. Los pacientes hospitalizados con COVID-19 eran mayores, presentaban una menor frecuencia de DOG y se recuperaron antes que los pacientes ambulatorios. El análisis estratificado por gravedad de la DOG mostró que más de la mitad de los sujetos con COVID-19 presentaron pérdida severa del olfato (53,7%) o del gusto (52,2%), en> 90% este deterioro fue de ambos sentidos. En el análisis multivariante, una edad mayor (>60 años), ser hospitalizado y un mayor nivel de proteína C reactiva fueron factores asociados con un mejor sentido del olfato y/o sabor. Los pacientes positivos para COVID-19 informaron una mejoría del olfato (45,6%) y del gusto (46,1%) en el momento de la encuesta, de ellos, un 90,6% en menos de dos semanas después de la infección.
Conclusión: DOG es un síntoma común en COVID-19, y principalmente presente en pacientes jóvenes y no hospitalizados. Se necesitan más estudios para evaluar el seguimiento de la discapacidad quimio-sensorial.

Palabras clave: Pérdida del olfato. Pérdida del gusto. SARS-CoV-2. COVID-19. Ingreso hospitalario.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 coronavirus infection [1] and may present as mild to severe acute respiratory syndrome (SARS) [2,3].

The most common symptoms are fever, fatigue, cough, dyspnea, and expectoration, with rhinorrhea and sore throat being less frequent [3]. Common laboratory findings include lymphocytopenia and increased values for C-reactive protein (CRP), lactate dehydrogenase, ferritin, D-dimer, and erythrocyte sedimentation rate [4]. Bilateral pneumonia is commonly observed on chest x-ray or computed tomography (CT) scans, and bilateral lung involvement and pneumonia are common [3,4]. Reverse polymerase chain reaction (RT-PCR) assay is currently considered the gold standard for diagnosis of SARS-CoV-2 infection. RT-PCR can be performed using both nasopharyngeal and oropharyngeal swabs [5,6].

Smell/flavor dysfunction in viral upper respiratory tract infections is common [7-9]. Our team demonstrated that the sense of smell is impaired in 2 out of 3 patients with common cold or postviral acute rhinosinusitis and that the degree of impairment correlates mainly with disease severity [8]. A follow-up of postviral smell loss revealed that over 80% of patients reported subjective recovery after 1 year [10]. The role of real taste dysfunction (not retronasal smell loss) is less clear in the common cold, although it has recently been reported to be associated with COVID-19 [11].

The exact pathophysiology of postviral olfactory dysfunction is not well understood. In COVID-19, angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS-CoV-2 [12]. As the respiratory epithelium is the primary site of SARS-CoV-2 and many other viruses, it is not surprising that COVID-19 affects the olfactory neuroepithelium [13,14]. The expression and distribution of ACE2 indicate that SARS-CoV-2 may cause neurologic manifestations through direct or indirect mechanisms [15].

Since the initial anecdotal reports from China [16], a growing number of studies have reported the frequency of smell and/or taste dysfunction (STD), which ranges widely from 5% to 88% in COVID-19 patients [17-19].

The aim of the present study was to investigate the frequency and severity of chemosensory dysfunction in COVID-19 patients and to evaluate the association between STD and its severity and demographic characteristics, hospital admission, symptoms, comorbidities, and blood biomarkers.

2. Materials and Methods

2.1. Ethical Issues

This observational study was approved by the Ethics Committee of Hospital Clinic Barcelona (HCB/2020/0402), Consorci Sanitari de Terrassa (02-20-188-023), and University Hospital Virgen Macarena (COD.PEIBA-0810-N-20). Local ethics committee approvals for other Spanish autonomous regions were also obtained. Verbal informed consent was obtained from all patients.

2.2. Study Design

A multicenter prospective cross-sectional study on SARS-CoV-2–positive patients and controls was performed from March 21 to April 18, 2020. Controls were defined as patients with common cold/flu-like symptoms and 2 consecutive negative COVID-19 RT-PCR test results. Participants were included from 15 Spanish University Hospitals grouped by autonomous community, as follows: Catalonia (Hospital Clínic Barcelona, Consorci Sanitari Terrassa, Hospital Sant Joan Despí Moisès Broggi, and Hospital Vall d'Hebron); Madrid (Hospital General Gregorio Marañón, Hospital Ramón y Cajal, Hospital La Paz, and

Hospital de Fuenlabrada); Andalusia (Hospital Virgen Macarena, Hospital Virgen de las Nieves, Hospital de Jerez, and Hospital Reina Sofía); Basque Country (Hospital Cruces, Hospital Donostia); and Galicia (Hospital Complex of Santiago de Compostela).

2.3. Study Population

Participants had to meet a series of inclusion criteria depending on the group. COVID-19 cases were patients of both sexes aged ≥18 years, with symptoms suggestive of the disease and a positive RT-PCR result. Controls were patients of both sexes aged ≥18 years with common cold/flu-like symptoms and 2 negative RT-PCR results for COVID-19. All participants were able to be interviewed and complete the questionnaire. The exclusion criteria for both groups were pregnancy, language barrier, psychiatric or neurocognitive impairment, quantitative or qualitative altered state of consciousness, and previous history of STD.

All testing was performed with the highest regard for patients' and examiners' safety using appropriate personal protective equipment.

2.3.1. Outcomes

2.3.1.1. Assessment of olfactory and gustatory function

A complete questionnaire exploring STD was created and administered in person to all patients with COVID-19 (hospitalized or outpatient) using appropriate personal protective equipment.

The questionnaire included 4 items: (*1*) a visual analog scale (VAS) to assess loss of smell (0-10 cm, with 0 indicating no smell loss and 10 maximum smell loss) focusing on smell and food/drink flavor; (*2*) a VAS to assess loss of taste with the same score range where, in order to avoid confusion between taste and smell/flavor, real taste perceptions (salty, sweet, bitter, and sour/acidic) were emphasized; (*3*) a question about onset of STD symptoms (days before or after the other COVID-19 symptoms); and (*4*) a question about recovering from STD (durations of STD symptoms in days). Patients were specifically asked about the timeline of onset and duration of the chemosensory symptoms and their eventual recovery from these symptoms. The VAS for sinonasal symptoms is currently being used in clinical practice and is based on the EPOS guidelines, with chronic rhinosinusitis classified as mild (VAS >0-3), moderate (VAS >3-7) and severe (VAS >7-10) disease [20]. Using this criterion, we stratified patients according to their VAS score as normosmic-mild (VAS 0-3), moderate (VAS 4-6), and severe olfactory loss (VAS 7-10) (see Supplementary Document).

Owing to limitations related to the severity of COVID-19, the state of emergency, and the physician and patient's safety, additional diagnostic methods such as nasal endoscopy, instrumental assessment of smell, and chemical gustometry were not performed. As for the risk-benefit balance, implementation of these methods was considered an unnecessary additional exposure of physicians to COVID-19 patients, as well as an unnecessary safety risk and annoyance for patients given their medical condition.

2.3.1.2. Demographics, symptoms, comorbidities, and blood biomarkers

Sex, age, symptom onset date, and clinical setting (outpatient, inpatient) were recorded.

COVID-19 patients were stratified according to whether they were hospitalized or not as an indicator of severity of systemic involvement or complication of pneumonia. Patients were asked about their symptoms (fever, rhinorrhea, sore throat, cough, and dyspnea), and blood biomarkers were analyzed, including CRP (mg/dL), ferritin (ng/dL), lymphocytes (109 cells/L), and D-dimer (ng/dL).

Medical records were also analyzed to obtain information on smoking habit, body mass index (BMI), and comorbidities (hypertension, diabetes mellitus, chronic kidney disease, cardiovascular diseases, neurological diseases, autoimmune diseases, respiratory diseases, immunosuppression, and cancer).

2.4. Statistical Analysis

In the descriptive analysis, age is expressed as mean (SD); the remaining continuous variables are expressed as median (IQR). Qualitative variables are expressed in absolute frequencies and percentages. The normality of the continuous variables was evaluated using the Shapiro-Wilk test with a significance level of P=.01.

The χ^2 test and Fisher exact test were used to compare categorical variables between COVID-19 patients and controls and hospitalized and nonhospitalized patients, and to assess the severity of loss of smell and taste. The *t* test or Mann-Whitney test was used to compare continuous quantitative variables. Quantitative continuous variables were compared using analysis of variance (ANOVA) and the Kruskal-Wallis test.

Logistic regression has been used to estimate the association (odds ratio) between STD in COVID-19–positive patients and independent variables. The models were built including several variables, as follows: (*1*) age, sex, and hospitalization; (*2*) pneumonia; (*3*) symptoms; (*4*) blood biomarkers; and (*5*) comorbidities. Statistical significance was set at P<.05. Data were analyzed using RStudio Team (2016). RStudio: Integrated Development for R (RStudio, Inc., http://www.rstudio.com/), version 1.1.453.

3. Results

3.1. COVID-19 Patients and Controls

A total of 846 COVID-19–positive patients (mean age, 56.8 [15.7] years, range 19-92, 47.3% female) and 143 COVID-19–negative patients (mean age, 53.5 [16.6] years, range 20-88 years, 49% female) completed the survey. Demographics and clinical characteristics are summarized in Table 1.

The frequency of loss of smell and taste was significantly higher in COVID-19–positive patients (53.7% and 52.2%, P<.001) than in the control group (30.1% and 31.5%) (Figure 1A). Simultaneous STD was more frequent in COVID-19–positive patients than in the control group (47.2% vs 21.7%, P<0.001). STD was at least 2-fold more common in

Table 1. Characteristics of COVID-19 Patients Compared With Controls

Characteristics	COVID-19– Positive (n=846)	COVID-19– Negative (n=143)	*P* value
Mean (SD) age, y	56.8 (15.7)	53.5 (16.6)	.028
Female, No. (%)	400 (47.3)	70 (49.0)	.780
(*a*) Loss of smell			
Frequency, No. (%)	454 (53.7)	43 (30.1)	<.001
Median (IQR) severity, VAS (0-10 cm)	8.0 (5.0)	7.0 (5.0)	.526
Mild (>0-3 cm), No. (%)	58 (12.8)	9 (20.9)	.316
Moderate (>3-7 cm), No. (%)	154 (33.9)	14 (32.6)	
Severe (>7-10 cm), No. (%)	242 (53.3)	20 (46.5)	
As first symptom, No. (%)	78 (18.5)	6 (26.1)	.425
Recovery, No. (%)	192 (45.6)	10 (58.8)	.189
Median (IQR) recovery time, d	7.0 (6.0)	6.0 (2.0)	.642
(*b*) Loss of taste			
Frequency, No. (%)	442 (52.2)	45 (31.5)	<.001
Median (IQR) severity, VAS (0-10 cm),	8.0 (5.0)	6.0 (5.0)	.005
Mild (0-3 cm), No. (%)	44 (9.95)	13 (28.9)	<.001
Moderate (>3-7 cm), No. (%)	164 (37.1)	17 (37.8)	
Severe (>7-10 cm), No. (%)	234 (52.9)	15 (33.3)	
As first symptom, No. (%)	78 (19.1)	6 (23.1)	.694
Recovery, No. (%)	189 (46.1)	13 (61.9)	.308
Median (IQR) recovery time, d	7.0 (5.0)	7.0 (2.0)	.712

Abbreviations: COVID-19, coronavirus disease 2019; VAS, visual analog scale.

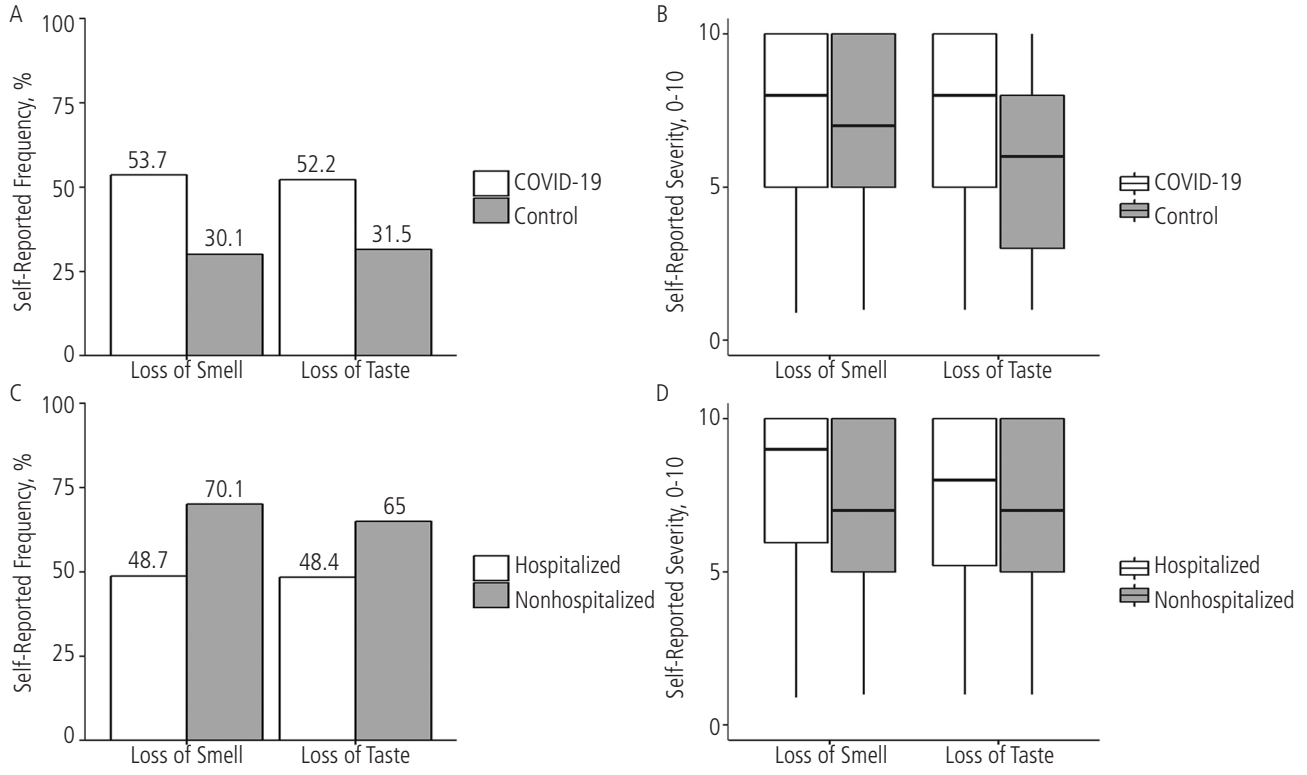

Figure 1. Frequency and severity of loss of smell or taste in COVID-19 patients. A, Self-reported frequency of loss of smell and taste in COVID-19 (+) vs controls. B, Self-reported severity by visual analog scale (VAS, 0-10 cm) of loss of smell and taste in COVID-19 (+) vs controls. C, Self-reported frequency of loss of smell and taste in hospitalized vs nonhospitalized COVID-19 patients. D, Self-reported severity by VAS of loss of smell and taste in hospitalized COVID-19 (+) patients vs nonhospitalized patients. COVID-19 indicates coronavirus disease 2019.

COVID-19–positive patients than in the control group for loss of smell (OR, 2.69; 95%CI, 1.84-3.97), loss of taste (OR, 2.38; 95%CI, 1.64-3.50), and both loss of smell and taste (OR, 3.16; 95%CI, 2.06-4.95). No differences were reported for recovery rate or recovery time. The severity of loss of smell by VAS (median, 8.0 vs 7.0) and loss of taste (median, 8.0 vs 6.0, *P*=.005) were scored higher by COVID-19–positive patients than controls, with the only significant difference being for the loss of taste (Figure 1B). No differences were recorded for the recovery rate or time for the loss of smell or taste.

In the COVID-19 group, 5.1% (n=43) reported exclusively loss of taste, 6.5% (n=55) exclusively loss of smell, and 47.2% (n=399) reported loss of both senses.

The recovery rate for STD in COVID-19–positive patients was 45.5% (n=170) at the time of the survey; recovery took <2 weeks in 90.6% (n=154) and >2 weeks in 9.4% (n=16). However, 54.5% of patients (n=204) did not recover: 38.5% (n=144) still had general or respiratory symptoms, and 16% (n=60) had only STD.

3.2. Severity of COVID-19 by Hospital Admission Status

Analysis of the COVID-19–positive group (n=846) according to disease severity by hospital admission status (Table 2) revealed that 649 patients were hospitalized (mean age, 60 [14.6] years, 42.4% female), while 197 were managed in an outpatient setting (mean age, 46.5 [14.5] years, 63.5% female). The incidence of pneumonia was higher in hospitalized than in nonhospitalized patients (97.5% vs 41.6%, *P*<.001). The frequency of loss of smell was significantly higher in nonhospitalized patients (70.1% vs 48.7%) (Figure 1C), as was severity (9.0 vs 7.0) (Figure 1D) (*P*<.005). The frequency of recovery of smell was lower among nonhospitalized patients (40.9% vs 47.6%, *P*<.005). Similar results were observed concerning the loss of taste and its recovery. Hospitalized patients had significantly more frequent cough, fever, and dyspnea (*P*<.01).

Table 2. Characteristics of Patients According to Severity by Hospital Admission (Hospitalized and Nonhospitalized) With Confirmed COVID-19

Characteristics	Hospitalized (n=649)	Nonhospitalized (n=197)	*P* value
Mean (SD) age, y	60.0 (14.6)	46.5 (14.5)	<.001
Female sex, No. (%)	275 (42.4)	125 (63.5)	<.001
Pneumonia, No. (%)	475 (97.5)	47 (41.6)	<.001
(*a*) Loss of smell			
Frequency, No. (%)	316 (48.7)	138 (70.1)	<.001
Median (IQR) severity, VAS (0-10 cm)	7.0 (5.0)	9.0 (3.0)	<.001
Mild (>0-3 cm), No. (%)	50 (15.8)	8 (5.80)	<.001
Moderate (>3-7 cm), No. (%)	122 (38.6)	32 (23.2)	
Severe (>7-10 cm), No. (%)	144 (45.6)	98 (71.0)	
As first symptom, No. (%)	57 (19.3)	21 (16.8)	.079
Median (IQR) no. of days prior to other symptoms	3.0 (2.0)	2.0 (3.5)	0.993
Recovery, No. (%)	140 (47.6)	52 (40.9)	<.001
Median (IQR) recovery time, d	7.0 (6.0)	7.0 (5.0)	.484
(*b*) Loss of taste			
Frequency, No. (%)	314 (48.4)	128 (65.0)	<.001
Median (IQR) severity, VAS (0-10 cm)	7.0 (5.0)	9.0 (3.6)	<.001
Mild (0-3 cm), No. (%)	36 (11.5)	8 (6.25)	.003
Moderate (>3-7 cm), No. (%)	128 (40.8)	36 (28.1)	
Severe (>7-10 cm), No. (%)	150 (47.8)	84 (65.6)	
As first symptom, No. (%)	58 (19.5)	20 (18.2)	.360
Median (IQR) no. of days prior to other symptoms	3.0 (2.0)	3.0 (3.5)	.978
Recovery, No. (%)	147 (49.3%)	42 (37.5%)	<.001
Median (IQR) recovery time, d	7.0 (5.0)	7.0 (6.0)	.162
(*c*) Symptoms, No. (%)			
Rhinorrhea	31 (9.28)	0 (0.00)	.058
Sore throat	19 (5.69)	3 (7.89)	.481
Cough	252 (75.4)	5 (13.2)	<.001
Dyspnea	64 (19.2)	0 (0.00)	.006
Fever	295 (88.3)	7 (18.4)	<.001

Abbreviations: COVID-19, coronavirus disease 2019; VAS, visual analog scale.

Table 3. Characteristics of COVID-19 Patients Stratified by Severity of Loss of Smell

Characteristics	No Loss of Smell (VAS 0 cm) (n=392)	Mild (VAS >0-3 cm) (n=58)	Moderate (VAS >3-7 cm) (n=154)	Severe (VAS >7-10 cm) (n=242)	*P* value[a]
Mean (SD) age, y	61.0 (15.4)	56.6 (14.6)	57.1 (14.6)	49.9 (14.6)	<.001
Female sex, No. (%)	180 (45.9)	26 (44.8)	63 (40.9)	131 (54.1)	.031
Pneumonia No. (%)	258 (92.1)	35 (87.5)	95 (88.8)	134 (77.5)	.036
As first symptom, No. (%)		12 (21.8)	24 (16.7)	42 (18.9)	.003
Recovery, No. (%)		31 (56.4)	65 (46.8)	96 (42.3)	.351
Median (IQR) recovery time, d		4 (4)	7 (5)	7 (5)	<.001
(*a*) Symptoms, No. (%)					
Rhinorrhea	11 (5.45)	3 (8.82)	6 (11.5)	11 (13.1)	.906
Sore throat	7 (3.47)	3 (8.82)	5 (9.62)	7 (8.33)	.939
Cough	139 (68.8)	26 (76.5)	34 (65.4)	58 (69.0)	.549
Dyspnea	38 (18.8)	6 (17.6)	8 (15.4)	12 (14.3)	.900
Fever	163 (80.7)	31 (91.2)	41 (78.8)	67 (79.8)	.280
(*b*) Comorbidities, No. (%)					
Respiratory	37 (22.6)	6 (20.7)	4 (13.3)	5 (8.93)	.278
Hypertension	77 (47.0)	14 (48.3)	13 (43.3)	17 (30.4)	.219
Cardiovascular disease	42 (25.6)	8 (27.6)	5 (16.7)	6 (10.7)	.132
Diabetes mellitus	29 (17.7)	6 (20.7)	5 (16.7)	6 (10.7)	.433
Obesity (BMI>30)	48 (54.5)	8 (20.0)	10 (25.0)	22 (55.0)	.329
Chronic kidney disease	15 (9.15)	2 (6.90)	4 (13.3)	3 (5.36)	.438
Neurological disease	17 (10.4)	3 (10.3)	0 (0.00)	2 (3.57)	.113
Immunosuppression	20 (12.2)	3 (10.3)	3 (10.0)	4 (7.14)	.757
Cancer	35 (21.3)	3 (10.3)	6 (20.0)	5 (8.93)	.365
(*c*) Blood biomarkers					
Median (IQR) C-reactive protein, mg/mL	18.4 (49.75)	22.2 (117.5)	18.5 (42.05)	11.0 (13.26)	.003
Median (IQR) D-dimer, µg/L	1690 (2658)	1152 (1830)	980 (1664)	975 (1192)	.915
Median (IQR) ferritin, µg/L	836 (1268)	1003 (840)	826 (1034)	640 (948)	.064
Median (IQR) lymphocyte count, 10^9 cells/L	950 (782)	665 (588)	1112 (756)	1203 (716)	<.001

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; VAS, visual analog scale.
[a]The *P* value was obtained based on severity of smell loss excluding the no loss of smell group.

3.3. Stratification by Severity of Loss of Smell

A total of 454 COVID-19–positive patients reported loss of smell, which was mild in 58 (12.8%), moderate in 154 (33.9%), and severe in 242 (53.3%). Compared with patients affected by mild loss of smell, those with severe loss of smell were younger (49.9 vs 56.6 years) and predominantly female (54.1% vs 44.8%) and less frequently had pneumonia (77.5% vs 87.5%). In addition, patients with severe loss of smell experienced this manifestation less frequently as a first symptom (18.9% vs 21.8%) and recovered later (7 vs 4 days) than those with mild loss (Table 3). However, no differences were found in the frequency of patients who had recovered their sense of smell. Regarding symptoms and comorbidities, no differences were found between the levels of severity of loss of smell. Concerning blood biomarkers, CRP, D-dimer, and ferritin values decreased, with a higher severity of loss of smell, although significant values were detected only for CRP (*P*=.003). Lymphocyte values increased with severity of loss of smell (*P*<.001) (Table 3).

3.4. Stratification by Severity of Loss of Taste

A total of 442 COVID-19–positive patients reported loss of taste; this was mild in 44 (10.0%), moderate in 164 (37.1%), and severe in 234 (52.9%). Stratification by severity of loss of smell revealed differences. Patients with severe loss of taste were younger (51.3 vs 56.2 years), with no differences by sex, and had similar pneumonia rates to those with mild loss of smell. In addition, no differences by severity were found in loss of taste as a first symptom and recovery rate. However, patients with severe loss of taste recovered later (7 vs 5 days) than those with mild loss. Once again, no differences were found in the frequency of the symptoms and comorbidities analyzed with respect to the different levels of severity of loss of taste. Concerning blood biomarkers, only CRP decreased significantly (*P*=.023), with a higher severity of loss of taste (Table 4).

3.5. Multivariate Analysis of Associated Factors

Logistic regression analysis was performed to investigate the characteristics associated with loss of smell and loss of

Table 4. Characteristics of COVID-19 Patients Stratified by Severity of Loss of Taste

Characteristics	No Loss of Taste (VAS 0 cm) (n=404)	Mild (VAS >0-3 cm) (n=42)	Moderate (VAS >3-7 cm) (n=127)	Severe (VAS >7-10 cm) (n=230)	*P* value[a]
Mean (SD) age, y	60.1 (15.9)	56.2 (14.8)	56.9 (14.5)	51.3 (14.7)	<.001
Female sex, No. (%)	186 (46.0)	17 (38.6)	73 (44.5)	124 (53.0)	.098
Pneumonia, No. (%)	262 (91.3)	21 (75.0)	93 (85.3)	146 (83.0)	.409
As first symptom, No. (%)		8 (22.2)	28 (21.9)	38 (18.4)	.311
Recovery, No. (%)		14 (42.4)	62 (48.4)	94 (44.1)	.789
Median (IQR) recovery time, d		5 (4)	6 (4.5)	7 (4)	<.001
(*a*) Symptoms, No. (%)					
Rhinorrhea	10 (4.61)	2 (9.52)	5 (10.0)	14 (16.7)	.544
Sore throat	7 (3.23)	2 (9.52)	6 (12.0)	7 (8.33)	.803
Cough	150 (69.1)	11 (52.4)	35 (70.0)	61 (72.6)	.197
Dyspnea	37 (17.1)	2 (9.52)	11 (22.0)	14 (16.7)	.481
Fever	173 (79.7)	14 (66.7)	42 (84.0)	73 (86.9)	.099
(*b*) Comorbidities No. (%)					
Respiratory	38 (21.5)	2 (18.2)	4 (12.9)	8 (13.3)	.834
Hypertension	82 (46.3)	5 (45.5)	12 (38.7)	22 (36.7)	.871
Cardiovascular disease	44 (24.9)	3 (27.3)	8 (25.8)	6 (10.0)	.070
Diabetes mellitus	30 (16.9)	1 (9.09)	5 (16.1)	10 (16.7)	1.000
Obesity (BMI>30)	56 (63.6)	3 (9.38)	7 (21.9)	22 (68.8)	.288
Chronic kidney disease	14 (7.91)	1 (9.09)	2 (6.45)	7 (11.7)	.884
Neurological disease	20 (11.3)	1 (9.09)	0 (0.00)	1 (1.67)	.295
Immunosuppression	19 (10.7)	0 (0.00)	4 (12.9)	7 (11.7)	.653
Cancer	36 (20.3)	1 (9.09)	5 (16.1)	7 (11.7)	.827
(*c*) Blood biomarkers					
Median (IQR) C-reactive protein, mg/mL	18.2 (44.67)	18.7 (124.24)	19.0 (62.7)	12.2 (19.59)	.023
Median (IQR) D-dimer, µg/L	1561 (2322)	960 (971)	1052 (1440)	1000 (1700)	.819
Median (IQR) ferritin, µg/L	830 (1175)	1142 (1245)	656 (1025)	791 (1266)	.395
Median (IQR) lymphocyte count, 10^9 cells/L	940 (770)	1039 (452)	1113 (890)	1146 (760)	.686

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; VAS, visual analog scale.
[a]The *P* value was obtained by severity of loss of taste excluding the no loss of taste group.

taste. Older age (>60 years) and hospital admission were associated with the loss of smell (Figure 2A). Compared with younger patients (<40 years), age >60 years was associated with a 63% reduced risk for loss of smell (OR, 0.37; 95%CI, 0.24-0.78), while the reduced risk for hospital admission was 47% (OR, 0.53; 95%CI, 0.37-0.77). Concerning blood biomarkers, an increase of 10 mg/mL in CRP was associated with a 3% reduced risk of loss of smell (OR, 0.29; 95%CI, 0.19-0.45). The crude analysis revealed a significant association between loss of smell and presence of pneumonia (OR, 0.40), rhinorrhea (OR, 3.32), sore throat (OR, 2.70), and respiratory comorbidities (OR, 0.51). However, the significance of these associations disappeared when the analysis was adjusted for age, sex, and hospital admission. No association with the loss of smell was observed for smoking habit, symptoms (cough, dyspnea, and fever), blood biomarkers, or comorbidities (Table 5).

As for loss of taste (Figure 2B), the following associations were found in the adjusted multivariate analysis: age >60 years (OR, 0.54; 95%CI, 0.35-0.82), hospital admission (OR, 0.61; 95%CI, 0.43-0.87), and rhinorrhea (OR, 2.57; 95%CI, 1.11-5.95) (Figure 1B). The crude analysis revealed a significant association between loss of taste and presence of pneumonia (OR, 0.47) and comorbid neurological diseases (OR, 0.16). However, the significance of these associations disappeared when the analysis was adjusted. No association with the loss of taste was observed for smoking habit, blood biomarkers, symptoms, or comorbidities (Table 6).

4. Discussion

Our study revealed several findings of interest. First, patients diagnosed with COVID-19 were older and evenly distributed with respect to sex, and their STD was at least 2-fold more common than in control patients (common cold/flu-like symptoms and 2 negative test results). Second, more than half of the COVID-19 patients presented loss of smell (53.7%) or taste (52.2%); in >90%, both senses were impaired. One in every 5 patients presented loss of smell (18.5%) or loss of taste (19.1%) as the first symptom of the disease. Third, hospitalized COVID-19 patients were older, predominantly

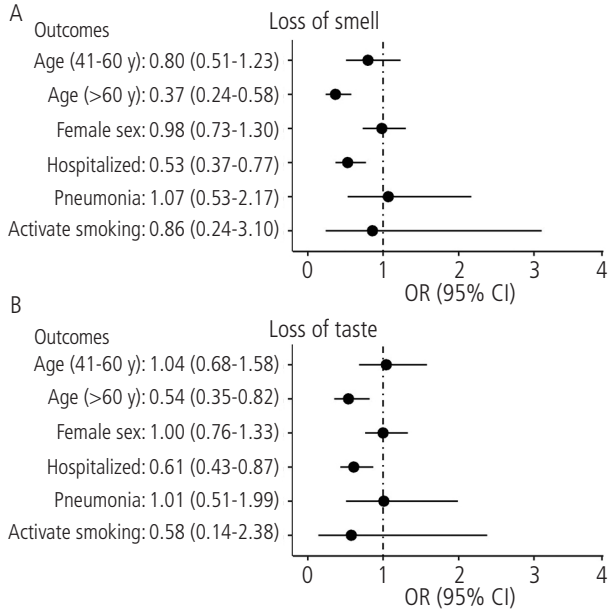

Figure 2. Association of factors (outcomes) with loss of smell (A) and loss of taste (B) in COVID-19 patients. Data for the multivariate analysis are expressed as the odds ratio (OR) and the error bars as the 95%CI. COVID-19 indicates coronavirus disease 2019.

male, with a higher rate of pneumonia. In addition, loss of taste or smell was less common and severe than in outpatients, although the recovery rate was higher. Fourth, 1 out of every 2 COVID-19 patients with STD experienced severe loss of smell and/or taste. Those with severe loss of smell were younger and predominantly female, were less likely to have pneumonia, and recovered later than patients with milder dysfunction. Fifth, the multivariate analysis revealed older age (>60 years) and being hospitalized to be associated with a better sense of smell and/or taste. In addition, increased CRP was also associated with a better sense of smell.

We found the frequencies of loss of smell (53.7%) and taste (52.2%) to be higher than those reported in the early observational studies from China and Iceland [16,21], although they were lower than those from a European multicenter study [17] and similar to those found by Menni et al [22]. In COVID-19–positive patients who reported loss of smell and taste, dysfunction was commonly moderate-severe rather than mild (87.2% and 90%, respectively). A recent meta-analysis showed a 52.7% pooled prevalence for loss of smell [18]. Studies based on validated instruments, such as the University of Pennsylvania Smell Identification Test (UPSIT) [23], the smell component of the National Health and Nutrition Examination Survey (NHANES), the short version of the Questionnaire of Olfactory Disorders–Negative Statements [17,24,25], and the COVID-19 Anosmia Reporting Tool [26,27], showed the prevalence of loss of smell to be 86.60% compared with 36.64% in studies based on nonvalidated instruments [18].

We also demonstrated that almost half of COVID-19–positive patients reported an improvement in STD at the time of the survey; in 90.6%, the improvement was observed in less than 2 weeks after infection. Hospitalized patients had a higher rate of recovery from STD, in parallel with the resolution of other COVID-19–related symptoms. Over time, such an improvement would suggest a competitive action of the virus against the receptors of the olfactory and gustatory cells or local inflammatory phenomena, rather than permanent damage of the olfactory neuroepithelium. Yan et al [28] suggest that outpatient and inpatient COVID-19 cases may follow different clinical courses. The authors hypothesize that ambulatory cases are perhaps partly the result of nasal-centric viral spread, whereas patients requiring hospitalization may be experiencing a more pulmonary-centric viral infection leading to an increased rate of respiratory failure and the need for hospital admission [28].

Furthermore, based on previous studies, and consistent with our results, sinonasal symptoms are less common in patients with COVID-19, thus arguing against the hypothesis that loss of smell is mainly related to postviral nasal obstruction or edema/inflammation [29].

Perception of flavor is perhaps the most intense multisensory sensation of our everyday life, and flavor is based on the combination of gustatory and olfactory stimuli. The 3 nerves associated with taste dysfunction are as follows: the facial nerve (cranial nerve VII), which provides fibers to the anterior two-thirds of the tongue; the glossopharyngeal nerve (cranial nerve IX), which provides fibers to the posterior third of the tongue; and the vagus nerve (cranial nerve X), which supplies the epiglottis region, from where the fibers then travel to the ventroposterior medial nucleus of the thalamus. Landis et al [30] described a significant association between impaired olfactory function (evaluated with Sniffin' Sticks) and decreased gustatory function quantified by chemical gustometry (taste strips). This association, which was also described by Migneault-Bouchard et al [31], could be explained by the interaction and partially common processing between both chemical senses.

In our study, longer recovery time was observed in patients with severe loss of smell and taste (VAS >7-10 cm). These results correlate with the literature on postinfectious smell dysfunction, where London et al [32] reported that microsmic patients were more than twice as likely to move into the normal range than anosmic patients, a finding also confirmed by Hummel et al [33] and Cavazzana et al [34], thus illustrating that higher/better initial smell scores using Sniffin' Sticks were associated with a higher probability of subsequent normosmia.

Our finding that STD was predominant in younger and nonhospitalized patients was similar to data reported by Lee et al [35]. The explanation of this demographic trend is not yet understood, considering that olfactory loss is more common in older individuals [36]. Further research should be performed based on more in-depth analysis of the etiology and pathogenesis of the loss of smell and taste in COVID-19.

As reported elsewhere [17,28,35], we found no association between STD and symptoms and comorbidities. Using blood biomarkers, Mao et al [16] retrospectively analyzed neurological symptoms in COVID-19 patients, whose symptoms were categorized into central, peripheral (including STD), and musculoskeletal. The authors found no association between the laboratory findings and peripheral neurological symptoms. We found a statistically significant association between increased CRP and a reduced risk of loss of smell.

Table 5. Crude (OR_c) and Adjusted (OR_{adj}) Multivariate Analysis of the Characteristics Associated With Loss of Smell in COVID-19 Patients

		OR_c	95%CI	*P* value	OR_{Adj}	95%CI	*P* value
(*a*) Demographics (n=846)							
Age, y	<40	1			1		
	41-60	0.67	0.44-1.03	.065	0.80	0.51-1.23	.304
	>60	0.29	0.19-0.45	<.001	0.37	0.24-0.58	<.001
Sex	Male	1			1		
	Female	1.11	0.84-1.45	.461	0.98	0.73-1.30	.870
Hospital admission	Nonhospitalized	1			1		
	Hospitalized	0.41	0.29-0.57	<.001	0.53	0.37-0.77	<.001
Pneumonia (n=600)	No	1			1		
	Yes	0.40	0.24-0.68	<.001	1.07	0.53-2.17	.842
(*b*) Symptoms (n=372)							
Rhinorrhea	No	1			1		
	Yes	2.32	1.08-4.98	.032	2.00	0.87-4.58	.101
Sore throat	No	1			1		
	Yes	2.70	1.07-6.78	.035	1.88	0.69-5.20	.219
Cough	No	1			1		
	Yes	1.03	0.66-1.60	.901	1.07	0.62-1.84	.806
Dyspnea	No	1			1		
	Yes	0.78	0.45-1.35	.371	0.70	0.38-1.27	.242
Fever	No	1			1		
	Yes	1.07	0.64-1.81	.792	1.89	0.90-3.94	.091
(*c*) Blood biomarkers[a,b] (n=353)							
C-reactive protein, mg/mL	10	0.970	0.944-0.997	.031	0.971	0.943-0.999	.045
D-dimer, µg/L	100	0.999	0.997-1.000	.278	0.999	0.997-1.001	.602
Ferritin, µg/L	100	0.987	0.969-1.000	.162	0.994	0.980-1.008	.392
Lymphocytes, $\times 10^9$ cells/L	100	1.011	0.994-1.028	.206	1.014	0.996-1.033	.120
(*d*) Comorbidities[a,c] (n=284)							
Smoker	No	1			1		
	Yes	0.85	0.30-2.40	.756	0.86	0.24-3.10	.813
Obesity (BMI>30)	No	1			1		
	Yes	1.48	0.87-2.53	.147	1.49	0.85-2.62	.169
Respiratory	No	1			1		
	Yes	0.51	0.27-0.99	.047	0.74	0.35-1.54	.419
Hypertension	No	1			1		
	Yes	0.70	0.43-1.14	.150	0.84	0.44-1.63	.614
Cardiovascular disease	No	1			1		
	Yes	0.57	0.31-1.05	.073	0.79	0.38-1.64	.519
Diabetes mellitus	No	1			1		
	Yes	0.81	0.42-1.55	.521	1.22	0.55-2.72	.620
Chronic kidney disease	No	1			1		
	Yes	0.84	0.36-2.00	.699	1.07	0.39-3.00	.889
Neurological disease	No	1			1		
	Yes	0.39	0.14-1.10	.075	0.57	0.19-1.74	.325
Immunosuppression	No	1			1		
	Yes	0.69	0.31-1.53	.355	0.87	0.33-2.32	.789
Cancer	No	1			1		
	Yes	0.51	0.26-1.00	.050	0.66	0.31-1.46	.311

Abbreviations: BMI, body mass index; OR_{Adj}, odds ratio adjusted for age, sex, and severity (hospitalized, nonhospitalized).
[a]All patients were hospitalized with pneumonia.
[b]OR_{Adj}: adjusted for age and sex.
[c]OR_{Adj}: adjusted for age, sex, and comorbidities.

Table 6. Crude (OR_c) and Adjusted (OR_{adj}) Multivariate Analysis of the Characteristics Associated With Loss of Taste in COVID-19 Patients

		OR_c	95%CI	*P* value	OR_{Adj}	95%CI	*P* value
(*a*) Demographics (n=846)							
Age, y	<40	1			1		
	41-60	0.90	0.60-1.35	.619	1.04	0.68-1.58	.864
	>60	0.44	0.29-0.65	<.001	0.54	0.35-0.82	.004
Sex	Male	1			1		
	Female	1.10	0.84-1.44	.489	1.00	0.76-1.33	.986
Hospital admission	Nonhospitalized	1			1		
	Hospitalized	0.51	0.36-0.70	<.001	0.61	0.43-0.87	.007
Pneumonia (n=600)	No	1			1		
	Yes	0.47	0.28-0.77	.003	1.01	0.51-1.99	.975
(*b*) Symptoms (n=372)							
Rhinorrhea	No	1			1		
	Yes	3.24	1.48-7.10	.003	2.57	1.11-5.95	.028
Sore throat	No	1			1		
	Yes	3.21	1.28-8.08	.013	2.30	0.88-6.50	.086
Cough	No	1			1		
	Yes	0.99	0.64-1.56	.985	0.78	0.46-1.33	.358
Dyspnea	No	1			1		
	Yes	1.03	0.59-1.77	.926	0.80	0.44-1.47	.473
Fever	No	1			1		
	Yes	1.26	0.73-2.16	.395	1.42	0.75-2.70	.279
(*c*) Blood biomarkers[a,b] (n=353)							
C-reactive protein, mg/mL	10	0.977	0.950-1.004	.099	0.980	0.952-1.028	.165
D-dimer, µg/L	100	0.999	0.998-1.000	.415	1.000	0.998-1.001	.737
Ferritin (µg/L)	100	0.991	0.974-1.028	.283	0.995	0.982-1.009	.512
Lymphocyte, $\times 10^9$ cells/L	100	0.996	0.984-1.008	.518	0.999	0.987-1.011	.847
(*d*) Comorbidities[a,c] (n=284)							
Smoker	No	1			1		
	Yes	0.56	0.18-1.79	.329	0.58	0.14-2.38	.447
Obesity (BMI>30)	No	1			1		
	Yes	1.14	0.66-1.98	.634	1.11	0.62-2.00	.725
Respiratory	No	1			1		
	Yes	0.58	0.30-1.14	.112	0.82	0.38-1.78	.612
Hypertension	No	1			1		
	Yes	0.72	0.44-1.18	.190	0.91	0.46-1.81	.791
Cardiovascular disease	No	1			1		
	Yes	0.60	0.32-1.13	.113	0.84	0.39-1.82	.660
Diabetes mellitus	No	1			1		
	Yes	0.91	0.47-1.77	.784	1.51	0.66-3.49	.332
Chronic kidney disease	No	1			1		
	Yes	1.27	0.54-2.96	.587	1.44	0.52-4.04	.484
Neurological disease	No	1			1		
	Yes	0.16	0.04-0.69	.014	0.22	0.04-1.02	.053
Immunosuppression	No	1			1		
	Yes	1.00	0.46-2.21	.990	1.36	0.52-3.61	.532
Cancer	No	1			1		
	Yes	0.57	0.29-1.14	.111	0.66	0.30-1.49	.321

Abbreviations: BMI, body mass index; OR_{Adj}, odds ratio adjusted for age, sex, and severity (hospitalized, nonhospitalized)
[a]All patients were hospitalized with pneumonia diagnosis.
[b]OR_{Adj}: adjusted for age and sex.
[c]OR_{Adj}: adjusted for age, sex, and comorbidities.

Since CRP is a proinflammatory marker, it is related to the severity of COVID-19. After categorizing the severity of the disease based on hospital admission, we can infer that the less severe the disease, the greater the loss of smell. Besides, a significant correlation between more severe loss of smell and decreased frequency of pneumonia was also observed. In contrast, Vaira et al [37] and Mao et al [16] did not find any correlation between chemosensory impairment and the severity of pneumonia.

Our study has 4 main strengths. First, RT-PCR confirmed COVID-19 in patients whose demographics, hospital admission status, and diagnosis of pneumonia were well documented. Second, we had a COVID-19–negative control group with common cold/flu-like symptoms who were matched by sex. Third, our approach, which was based on in-person interviews, ensured better comprehension of the questionnaire by the patients through emphasis of the difference between flavor and taste in order to avoid confusion. Finally, using the VAS for loss of smell and taste enabled patients to provide a self-reported ordinal quantitative assessment of their sensory dysfunction.

Our study is also subject to a series of limitations. First, as in many other studies, the suboptimal sensitivity of SARS-CoV-2 RT-PCR based on nasopharyngeal swabs might have led to misclassification and diagnostic bias. Second, RT-PCR for detection of respiratory viruses (eg, rhinovirus, influenza, and parainfluenza) was not applied in the control group. Third, given the unnecessary safety risk for physicians and the discomfort for patients due to their medical condition, no validated questionnaire or instrument to assess smell and taste was applied. Finally, the COVID-19 survey was applied at only 1 point related to its onset date, although further follow-up will be undertaken.

5. Conclusions

Loss of smell and taste are common in COVID-19, and at least twice as common as in controls. In COVID-19–positive patients, the STD was mainly present in young and nonhospitalized patients. According to severity by hospital admission status, hospitalized patients were older, with a lower frequency of STD, which recovered earlier than in outpatients (nonhospitalized). Analysis stratified by the severity of STD showed that more than half of the COVID-19–positive patients presented severe loss of smell or taste, and that both senses were impaired in >90%. Further studies will be needed to provide explanations for these chemosensory impairments and to elucidate the underlying pathogenic mechanisms.

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Conflicts of Interest

Isam Alobid has acted as a consultant for Roche, Novartis, Mylan, Menarini, and MSD. Joaquim Mullol has been a member of national and international advisory boards and received speaker's fees and funding for clinical trials and research projects from ALK, AstraZeneca, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mitsubishi-Tanabe, MSD, Mylan-MEDA Pharma, Novartis, Regeneron Pharmaceuticals, SANOFI-Genzyme, UCB Pharma, and Uriach Group. The remaining authors declare that they have no conflicts of interest.

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Isam Alobid
Joaquim Mullol

ENT Department, Hospital Clinic
C/ Villarroel 170
08035 Barcelona
Barcelona, Catalonia, Spain
E-mail: isamalobid@gmail.com
jmullol@clinic.cat