Smell and taste dysfunctions in COVID-19 are associated with younger age in ambulatory settings - a multicenter cross-sectional study

Short title: Smell and taste dysfunctions in COVID-19

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Abstract

Background: Since China's initial anecdotal reports of coronavirus disease 2019 (COVID-19), there have been a growing number of studies describing smell and/or taste dysfunction (STD).

Objective: The aim 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: A multicenter cross-sectional study on SARS-CoV-2 positive patients (n=846) and controls (n=143) from 15 Spanish Hospitals. Data of STD with an in-person survey was collected prospectively. STD severity was categorized by visual analogue scale. STD onset time, recovery rate, time to recovery, hospital admission, pneumonia diagnosis, comorbidities, smoking and symptoms were analyzed.

Results: STD were at least 2-fold more common in COVID-19-positive compared to controls. In COVID-19-positive, hospitalized patients were older, with lower frequency of STD and recovered earlier than out-patients. Stratified analysis by severity of STD showed that more than a half of COVID-19 subjects presented severe loss of smell (53.7%) or taste (52.2%), in >90% this impairment was of both senses. In the multivariate analysis, an older age (>60yo), being hospitalized and an increased level of C-reactive protein were factors associated with a better sense of smell and/or taste. COVID-19-positive patients reported improvement of smell (45.6%) and taste (46.1%) at the time of the survey, 90.6% in less than two weeks' post-infection.

Conclusion: STD is a common symptom in COVID-19, and mainly present in young and non-hospitalized patients. More studies are needed to evaluate the follow-up of the chemosensory impairment.

Key words: Smell loss. Taste loss. SARS-CoV-2. COVID-19. Hospital admission.

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

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Introduction

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

The most common symptoms were fever, fatigue, cough, dyspnea, and expectoration, while rhinorrhea or sore throat were less frequent [3]. Common laboratory findings include lymphocytopenia and increased values of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, and erythrocyte sedimentation rate (ESR) [4]. On chest X-ray or computed tomography (CT), bilateral lung involvement and pneumonia were common [3,4]. Reverse polymerase chain reaction (RT-PCR) is currently considered the Gold Standard test for SARS-CoV-2 infection diagnosis. It may be both performed from naso or oropharyngeal swabs [5,6].

Smell/flavor dysfunction in viral upper respiratory tract infections (URTI) is common [7-9]. Our team has demonstrated that two out of three patients with common cold or post-viral acute rhinosinusitis have some degree of smell impairment, this being mainly correlated with disease severity [8]. A follow-up of post-viral smell loss revealed that over 80% of patients reported subjective recovery after one year [10]. The role of real taste dysfunction (not retronasal smell loss) is less clear in common cold although it has been recently reported to be associated with COVID-19 [11].

The exact pathophysiology of post-viral olfactory dysfunction is not yet well understood. In COVID-19, angiotensin-converting enzyme 2 (ACE2) was identified as 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 may not be surprising for COVID-19 to affect the olfactory neuro-epithelium [13,14]. The expression and distribution of ACE2 remind us the SARS-CoV-2 may cause some neurologic manifestations through direct or indirect mechanisms [15].

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Since China's initial anecdotal reports [16], there have been a growing number of studies describing a wide frequency range of smell and/or taste dysfunction (STD), 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 of STD and their severity with demographic characteristics, hospital admission, symptoms, comorbidities, and blood biomarkers.

Materials and Methods

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 subjects.

Study design

A multicenter prospective cross-sectional study on SARS-CoV-2 positive patients and controls was performed from March 21st to April 18th, 2020. Controls were defined as patients having common cold/flu-like symptoms and two consecutive negative COVID-19 RT-PCR tests. Participants were included from 15 Spanish University Hospitals grouped by Autonomous Regions: *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).

Study Population

To be enrolled in the study, patients had to meet the following inclusion criteria: a) COVID-19 cases: patients of any gender, adults (≥ 18 years old), with

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suggestive symptoms of the disease and positive RT-PCR specific test; b) Controls: patients of both genders, adults (≥ 18 years old), with common cold/flu-like symptoms and two negative RT-PCR for COVID-19. All participants were able to be interviewed and answer 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 with appropriate personal protective equipment (PPE).

Outcomes

1. Assessment of olfactory and gustatory function.

A complete questionnaire exploring STD was created and performed in-person to all patients with COVID-19 positivity, either hospitalized or outpatient with appropriate PPE.

The questionnaire included 4 items: a) a smell loss visual analogue scale (VAS, 0-10cm, being 0 no smell loss and 10 maximum smell loss) focusing on smell and food/drink flavor; b) a taste loss VAS 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; c) a question about STD symptoms onset (days before or after the other COVID-19 symptoms); and d) a question about recovering from STD (durations in days of STD symptoms). Patients were carefully asked about the timeline of the onset, duration, and the eventual recovery of the chemosensory symptoms.–The VAS for sinonasal symptoms is currently being used in clinical practice, based on the EPOS guidelines, to classify chronic rhinosinusitis into mild (VAS >0-3), moderate (VAS >3-7) and severe (VAS>7-10) disease [20]. Using this criterion, we stratified patients according to smell loss VAS as normosmic-mild (VAS 0-3), moderate (VAS 4-6) and severe olfactory loss (VAS 7-10). (see: supplementary document)

Due to limitations related to the severity of the COVID-19, the contingency of the emergency, as well as physician and patient's safety, additional diagnostic methods such as nasal endoscopy, instrumental smell assessment, or chemical

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gustometry were not performed. Regarding a benefit-risk balance, their implementation was considered an unnecessary additional exposure time of physicians to COVID-19 patients, as well as an unnecessary safety risk and bother for patients due to their medical condition.

2. Demographics, symptoms, comorbidities, and blood biomarkers.

Demographics on gender, age, symptoms onset date, and clinical setting (ambulatory or hospital admission) were registered.

COVID-19 patients were stratified according to whether they were hospitalized or not as an indicator of severity of systemic involvement or pneumonia complication. Patients were asked about their symptoms (fever, rhinorrhea, sore throat, cough, and dyspnea) and blood biomarkers were analyzed, including C-Reactive protein (CRP) [mg/dL], ferritin [ng/dL], lymphocytes [10^9cells/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).

Statistical analysis

For the descriptive analysis, mean and standard deviation were calculated for the age. Moreover, median and the interquartile range to the rest of the continuous variables were calculated. The qualitative variables are expressed in absolute frequencies and percentages. The normality of the continuous variables was evaluated through the Shapiro-Wilk test with a significance level of $p = 0.01$.

Chi-square test and Fisher's exact test were used to compare categorical variables between COVID-19 patient's vs controls, and hospitalized vs non-hospitalized, and finally, for loss of smell and taste severity in the categorical variables. T-Student test or Mann-Whitney U test to comparison of continuous quantitative variables. Analysis of variance (ANOVA) and Kruskal-Wallis test were used in the quantitative continuous variables.

Logistic regression has been used to estimate the association (Odds ratio) between STD in COVID-19-positive patients, with independent variables. The

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models were built including several variables according to these groups: 1) age, gender and hospitalization, 2) pneumonia, 3) symptoms, 4) blood biomarkers, and 5) comorbidities. A significance level of $p<0.05$ was established. The data analysis was done using the program RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/., version 1.1.453.

Results

COVID-19 patients and controls

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

The frequencies of smell and taste loss were significantly higher among COVID-19-positive (53.7% and 52.2%, $p<0.001$) than in the control group (30.1% and 31.5%), respectively (Figure 1A). Simultaneous STD was more frequent in COVID-19-positive (47.2%) compared to control group (21.7%) ($p<0.001$). STD were at least 2-fold more common in COVID-19-positive than in the control group for either loss of smell (OR=2.69; CI95%= 1.84-3.97), loss of taste (OR=2.38; CI95%= 1.64-3.50) and both loss of smell and taste (OR=3.16; CI95%= 2.06-4.95). No differences were reported on recovery rate and recovery time. Both the loss of smell (median: 8.0 vs 7.0) and loss of taste (median: 8.0 vs 6.0, $p=0.005$) severity by VAS were scored higher by COVID-19-positive vs controls, this being only significant for the loss of taste (Figure 1B). No differences were observed on the recovery rate and time for either the loss of smell or taste.

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

Recovery rate of STD in COVID-19-positive was 45.5% (n=170) at the time of the survey, of them 90.6% (n=154) in less than 2 weeks, and 9.4% (n=16) in >2 weeks. On the other hand, 54.5% (n=204) patients were not recovered, 38.5% (n=144) still had general or respiratory symptoms, and 16% (n=60) remained only with STD.

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COVID-19 severity by hospital admission

Analysing the COVID-19-positive group (n=846) according to disease severity by hospital admission (Table 2), 649 patients were hospitalized [mean (SD) age= 60 (14.6) yo, 42.4% female] while 197 were in ambulatory setting [mean (SD) age= 46.5 (14.5) yo, 63.5% female]. In the hospitalized group, a higher incidence of pneumonia was observed compared to non-hospitalized patients (97.5% vs 41.6%, p<0.001). Regarding loss of smell, frequency (70.1% vs 48.7%) (Figure 1C) and severity (9.0 vs 7.0) (Figure 1D) were significantly higher (p<0.005) in non-hospitalized vs hospitalized patients, also with lower frequency of smell recovery among non-hospitalized (40.9% vs 47.6%, p<0.005). Similar results were observed concerning the loss of taste and its recovery. Concerning symptoms, hospitalized patients had significantly (p<0.01) more cough, fever, and dyspnoea.

Stratification by loss of smell severity

A total of 454 COVID-19-positive patients reported olfactory dysfunction, 58 (12.8%) had mild, 154 (33.9%) moderate, and 242 (53.3%) severe smell loss. The profile of patients with severe loss of smell was younger (49.9yo vs 56.6yo), predominantly female (54.1% vs 44.8%), and had less pneumonia (77.5% vs 87.5%) than those with mild loss of smell. In addition, patients with severe loss of smell manifested it less as a first symptom (18.9% vs 21.8%) and recovered later (7 vs 4 days), compared to those with mild loss (Table 3). However, no differences were found, in the frequency of smell-recovered patients. Regarding symptoms and comorbidities, no differences between different loss of smell severity levels were found. Concerning blood biomarkers: CRP, D-dimer and ferritin decreased with higher severity of loss of smell, this being significant only for CRP (P=0.003), while lymphocytes increased with loss of smell severity (p<0.001) (Table 3).

Stratification by loss of taste severity

A total of 442 COVID-19-positive patients reported gustatory dysfunction, 44 (10.0%) had mild, 164 (37.1%) moderate and 234 (52.9%) severe taste loss. Some differences were observed compared to findings by stratifying for loss of

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smell severity. The profile of patients with severe loss of taste was younger (51.3yo vs 56.2yo) with no differences by gender, and had similar pneumonia rates than those with mild loss of smell. In addition, no differences by severity were found in taste loss manifested as a first symptom and recovery-rate. However, patients with severe loss of taste recovered later (7 vs 5 days), compared to those with mild loss. Once more, no differences were found on the frequency of analysed symptoms and comorbidities between different loss of taste severity levels. Concerning blood biomarkers, only CRP showed a significant (p=0.023) decrease with higher severity of loss of taste (Table 4).

Multivariate analysis of associated factors

Concerning the characteristics associated with the loss of smell and the loss of taste, a logistic regression analysis was performed. Older age (>60yo) and hospital admission were found as associated factors with the loss of smell (Figure 2A). Compared to younger patients (<40yo), being >60 yo was associated with a 63% reduced risk for smell loss (OR=0.37; CI95%=0.24-0.78) while the reduced risk for hospital admission was 47% (OR=0.53; CI95%= 0.37-0.77). Concerning blood biomarkers, an increase of 10mg/mL in CRP was associated with a 3% (OR=0.29; CI95%=0.19-0.45) of reduced risk for smell loss. The presence of pneumonia (OR=0.40), symptoms such as rhinorrhea and sore throat (OR=3.32 and 2.70, respectively), and respiratory comorbidities (OR=0.51) were also significantly associated with smell loss in the crude analysis. However, the significance of these associations disappeared when the analysis was adjusted by age, gender, and hospital admission. No association with the loss of smell was observed for smoking habit and the other symptoms (cough, dyspnoea, and fever), blood biomarkers and patient's comorbidities (Table 5).

Regarding the logistic regression for the loss of taste (Figure 2B), the following associations were found in the adjusted multivariate analysis: age>60yo (OR=0.54; CI95%=0.35-0.82), hospital admission (OR=0.61; CI95%=0.43-0.87), and rhinorrhea (OR=2.57; CI95%=1.11-5.95) (Figure 1B). The presence of pneumonia (OR=0.47) and comorbid neurological diseases (OR=0.16) was also significantly associated with the loss of taste in the crude analysis. However, the significance of these associations disappeared when the analysis was adjusted.

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No association with the loss of taste was observed for smoking habit, blood biomarkers, and other symptoms and patient's comorbidities (Table 6).

Discussion.

The main findings of our study were: 1st) Subjects with diagnosed COVID-19 were older, with similar gender, and their olfactory and taste dysfunction was at least 2-fold more common than in control subjects (common cold/flu-like symptoms and 2 negative tests); 2nd) More than half of COVID-19 subjects presented loss of smell (53.7%) or taste (52.2%), in >90% this impairment was of both senses. One out of five subjects presented loss of smell (18.5%) or loss of taste (19.1%) as the first symptom of the disease; 3rd) COVID-19 hospitalized patients were older, predominantly men, with a higher rate of pneumonia, and had a lower frequency and severity, but a higher rate of recovery from the loss smell or loss of taste than COVID-19 outpatients (non-hospitalized); 4th) Among COVID-19 subjects with sensory dysfunction, one out of two had a severe loss of smell and/or taste. Subjects with severe loss of smell were younger, predominantly female, had a lower rate of pneumonia, and recovered later than patients with a milder dysfunction; 5th) In the multivariate analysis, an older age (>60yo), and being hospitalized were factors associated with a better sense of smell and/or taste. In addition, an increased level of PCR was a factor also associated with a better sense of smell.

In our study, the frequencies of loss of smell (53.7%) and taste (52.2%) were higher than those reported in the early anamnestic observational studies from China and Iceland [16,21], however lower than those from a European multicentric study [17], and similar to those found by Menni et al [22]. Of those COVID-19-positive patients who reported smell and taste loss, the dysfunction was commonly moderate-severe rather than mild (87.2% and 90% respectively). A recent meta-analysis showed 52.7% pooled prevalence of smell loss [18]. They demonstrated that studies using validated instruments including the University of Pennsylvania Smell Identification Test (UPSIT) [23], smell component of the National Health and Nutrition Examination Survey (NHANES), a short version of the Questionnaire of Olfactory Disorders–Negative Statements [17,24,25], and the COVID-19 Anosmia Reporting Tool [26,27]

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showed an 86.60% smell loss prevalence compared to 36.64% in studies which used non-validated instruments [18].

We have also demonstrated that almost half of COVID-19-positive patients reported improvement of STD at the time of the survey, among them, 90.6% in less than two weeks' post-infection. Hospitalized patients had more recovery rate of chemosensory disorders paralleling to resolution of other COVID-19-related symptoms. This improvement over time, would suggest a competitive action of the virus on the receptors of the olfactory and gustatory cells or local inflammatory phenomena, rather than permanent damage of the olfactory neuro-epithelium. Yan et al. [28] suggests that out and in-patient COVID-19 cases may follow different clinical courses. They hypothesize that perhaps ambulatory cases are in part the result of a nasal-centric viral spread, whereas patients requiring hospitalization may be experiencing a more pulmonary-centric viral infection leading to increased rate of respiratory failure and need for hospital admission [28].

On the other hand, based on previous studies, and consistent with our results, sinonasal symptoms are less common in COVID-19. This argues against the hypothesis that smell loss is mainly related to a post-viral nasal obstruction or edema/inflammation [29].

The perception of flavour is perhaps the most multisensory of our everyday experiences. Flavour involves the combination of gustatory and olfactory stimuli. Concerning taste dysfunction, three nerves associated with taste are 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 provides fibers to the epiglottis region, then fibers travel to the ventroposterior medial nucleus of the thalamus. previous studies by Landis et al. described a significant association between impaired olfactory function (evaluated with Sniffin' Sticks) with a decreased gustatory function quantified by chemical gustometry (taste strips) [30]. This association, also described by Migneault-Bouchard et al., could be explained by the interaction and a partially common processing between both chemical senses [31].

In our study, longer recovery time was observed in those patients with severe loss of smell and taste (VAS >7-10 cm). These results correlate with the

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literature on post-infectious smell dysfunction, where London et al. [32] reported that microsmic patients were more than twice as likely to improve into the normal range than anosmic patients, a finding also confirmed by Hummel et al. [33], and Cavazzana et al. [34], showing that higher/better initial smell scores using Sniffin' Sticks were associated with higher probability of later normosmia.
Our findings on STD being predominant in younger and non-hospitalized patients were similar to those 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 [36]. A greater analysis regarding the etiopathogenesis of the loss of smell and taste in COVID-19 infection will need further research.

As previously reported in other studies [17,28,35] we found no association between STD and symptoms and comorbidities. In blood biomarkers, Mao et al. [16] retrospectively analyzed neurological symptoms in COVID-19 patients, categorized into central, peripheral (including STD) and musculoskeletal symptoms, where no association was found between laboratory findings and peripheral neurological symptoms. We found a statistically significant association between increased CRP and a reduced risk of smell loss. CRP is a pro-inflammatory marker, and therefore, is related to the severity of COVID-19. According to our results, by categorizing the severity of the disease due to hospital admission, we can infer that the less severe the disease, the greater the loss of smell. Besides, a significant correlation between higher severity of smell loss and decreased rate of pneumonia diagnoses was also observed. Other studies, 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 both strengths and limitations.
Among our strengths were: 1) RT-PCR confirmed positive COVID-19 patients whose demographics, hospital admission status, and pneumonia diagnosis was well documented; 2) negative COVID-19 control group matched by gender with common cold/flu-like symptoms; 3) in-place personal interview using PPE allowing a better comprehension of the questionnaire by the patients, emphasizing the difference between flavor and taste in order to avoid confusion; 4) VAS scores for both smell and taste loss was performed, allowing

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a self-reported ordinal quantitative assessment of the sensory dysfunction. On the other hand, our study also had limitations**:** 1) as for many other studies, the suboptimal sensitivity of SARS-CoV-2 RT-PCR on nasopharyngeal swab might have led to misclassification and diagnostic bias; 2) lack of respiratory viruses RT-PCR test detection for the control group (rhinovirus, influenza, parainfluenza, among others); 3) Due to unnecessary safety risk for physicians and discomfort for patients due to their medical condition, no validated questionnaire, instrumental olfaction and gustatory assessment were considered; and 4) COVID-19 survey was measured at only one point related to its onset date although further follow-up will be performed.

CONCLUSIONS

Smell and taste dysfunction is a frequent symptom in COVID-19, at least 2-fold more common compared to controls. In COVID-19-positive the STD was mainly present in young and non-hospitalized patients. According to severity by hospital admission, hospitalized patients were older, with lower frequency of STD which recovered earlier than in out-patients (non-hospitalized). Stratified analysis by the severity of STD showed that more than half of COVID-19 subjects presented a severe loss of smell or taste, among them >90% reported an impairment in both smell and taste. Further studies will be needed to provide explanations for these chemosensory impairments as well as for the pathogenic mechanisms for both the loss of smell and loss of taste.

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Conflicts of Interest

- Isam Alobid: Consultant for Roche, Novartis, Mylan, Menarini, MSD
- Joaquim Mullol: member of national or international advisory boards, received speaker fees, or 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 other authors declare that they have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Frequency and severity of loss of smell or taste in COVID-19 subjects. A) Self-reported frequency of smell and taste loss in COVID-19 (+) vs controls; B) Self-reported severity by visual analogue scale (VAS, 0-10cm) of loss of smell and taste in COVID-19 (+) vs controls; C) Self-reported frequency of loss of smell and taste in COVID-19 hospitalized vs non-hospitalized subjects; and D) Self-reported severity by VAS of loss of smell and taste in COVID-19 (+) hospitalized vs non-hospitalized subjects.

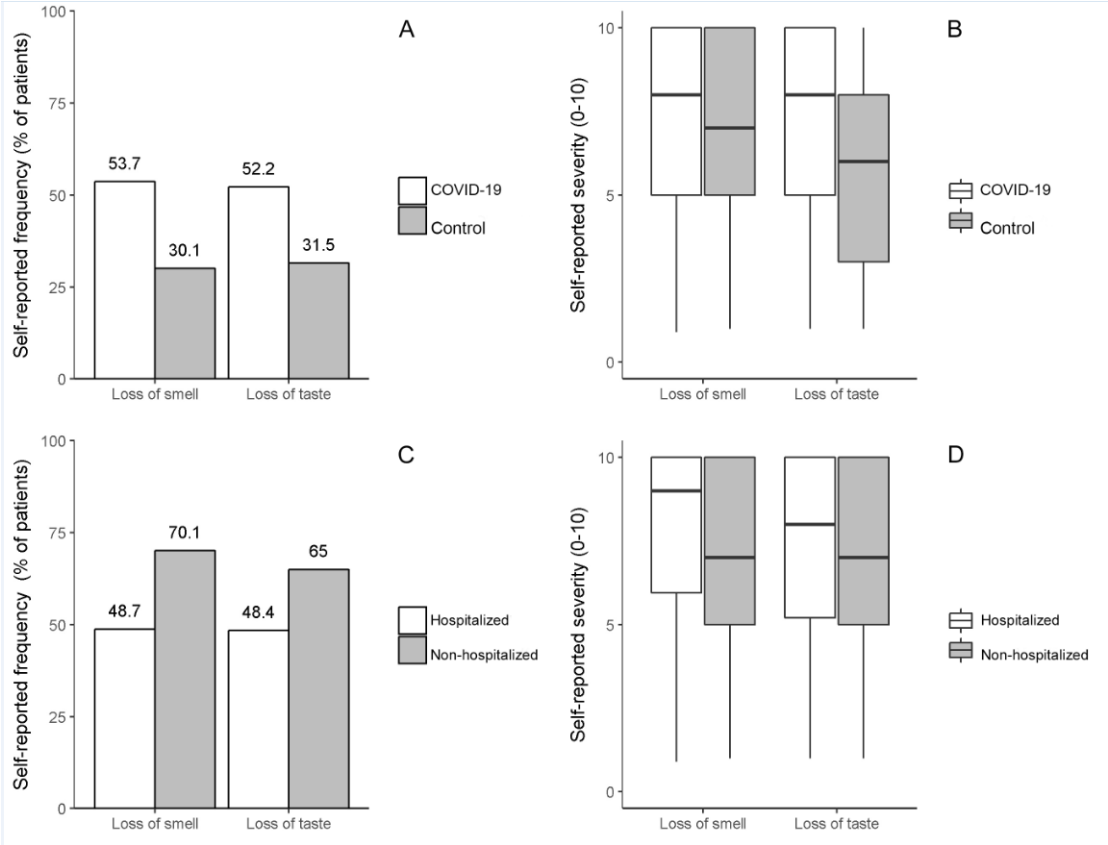

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Figure 2. Association of factors (outcomes) with the loss of smell (A), and the loss of taste (B) in COVID-19 subjects. Data of the multivariate multivariate are given by Odds Ratio (OR) and the error bars by 95% confidence interval.

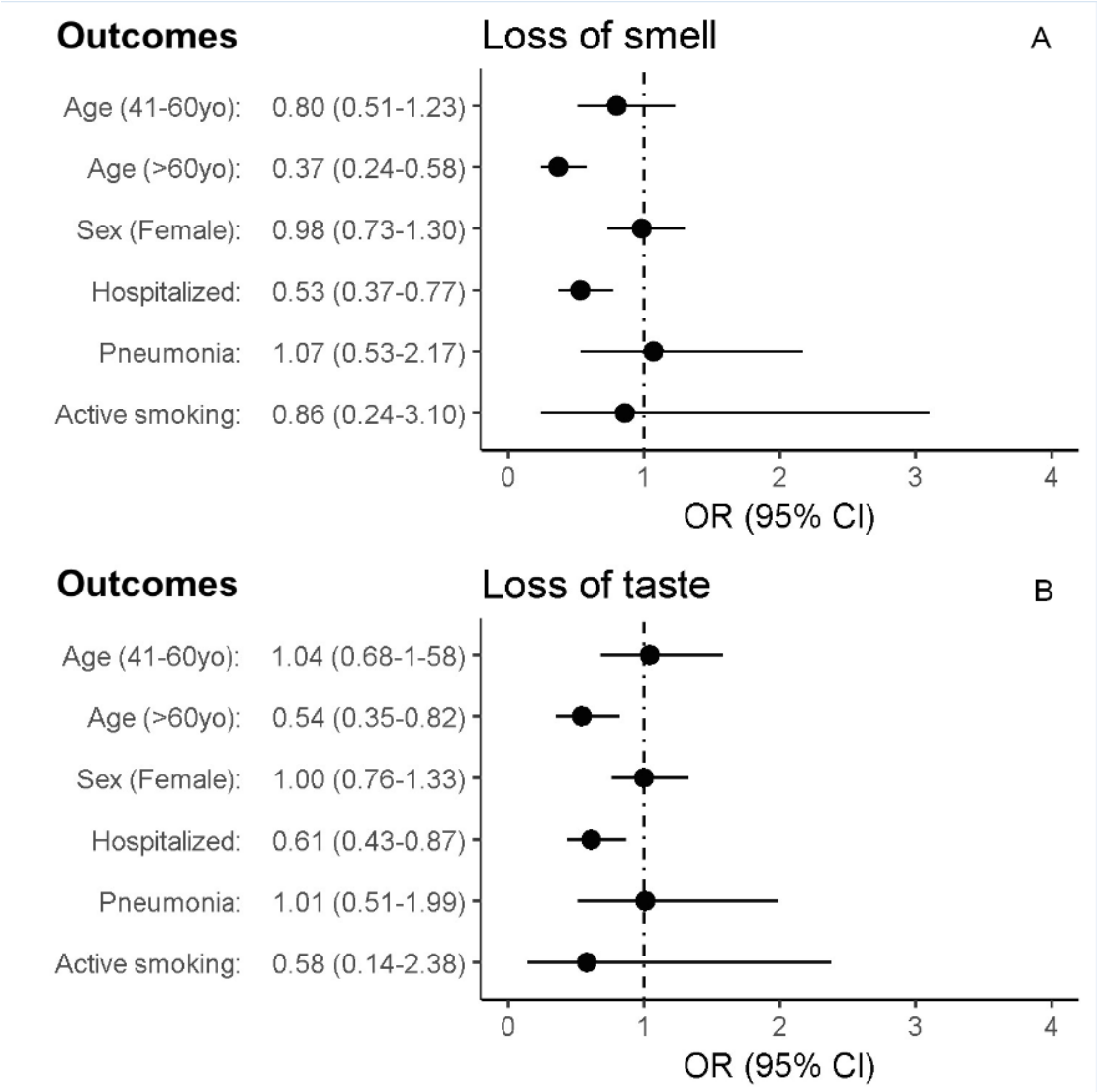

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Table 1. Characteristics of COVID-19 patients compared to controls.

Characteristics	Positive COVID-19 (n=846)	Negative COVID-19 (n=143)	*P* value
Age, years, media (SD)	56.8 (15.7)	53.5 (16.6)	0.028
Gender, female, N (%)	400 (47.3)	70 (49.0)	0.780
a) Loss of Smell			
Frequency, N (%)	454 (53.7)	43 (30.1)	<0.001
Severity, VAS (0-10cm), median [IQR]	8.0 [5.0]	7.0 [5.0]	0.526
Mild (>0-3cm), N (%)	58 (12.8)	9 (20.9)	0.316
Moderate (>3-7cm), N (%)	154 (33.9)	14 (32.6)	
Severe (>7-10cm), N (%)	242 (53.3)	20 (46.5)	
As first symptom, N (%)	78 (18.5)	6 (26.1)	0.425
Recovery, N (%)	192 (45.6)	10 (58.8)	0.189
Recovery time, days, median [IQR]	7.0 [6.0]	6.0 [2.0]	0.642
b) Loss of Taste			
Frequency, N (%)	442 (52.2)	45 (31.5)	<0.001
Severity, VAS (0-10cm), median [IQR]	8.0 [5.0]	6.0 [5.0]	0.005
Mild (0-3cm), N (%)	44 (9.95)	13 (28.9)	<0.001
Moderate (>3-7cm), N (%)	164 (37.1)	17 (37.8)	
Severe (>7-10cm), N (%)	234 (52.9)	15 (33.3)	
As first symptom, N (%)	78 (19.1)	6 (23.1)	0.694
Recovery, N (%)	189 (46.1)	13 (61.9)	0.308
Recovery time, days, median [IQR]	7.0 [5.0]	7.0 [2.0]	0.712

Abbreviations: COVID-19: coronavirus disease 2019; SD: standard deviation; VAS: visual analogue scale; IQR: interquartile range.

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Table 2. Characteristics of all patients according to severity by hospital admission (hospitalized and non-hospitalized) with confirmed COVID-19.

Characteristics	Hospitalized (n=649)	Non-hospitalized (n=197)	*P* value
Age, years, media (SD)	60.0 (14.6)	46.5 (14.5)	<0.001
Gender, female, N (%)	275 (42.4)	125 (63.5)	<0.001
Pneumonia, N (%)	475 (97.5)	47 (41.6)	<0.001
a) Loss of Smell			
Frequency, N (%)	316 (48.7)	138 (70.1)	<0.001
Severity, VAS (0-10cm), median [IQR]	7.0 [5.0]	9.0 [3.0]	<0.001
Mild (>0-3cm), N (%)	50 (15.8)	8 (5.80)	<0.001
Moderate (>3-7cm), N (%)	122 (38.6)	32 (23.2)	
Severe (>7-10cm), N (%)	144 (45.6)	98 (71.0)	
As first symptom, N (%)	57 (19.3)	21 (16.8)	0.079
Prior to other symptoms, days, median [IQR]	3.0 [2.0]	2.0 [3.5]	0.993
Recovery, N (%)	140 (47.6)	52 (40.9)	<0.001
Recovery time, days, median [IQR]	7.0 [6.0]	7.0 [5.0]	0.484
b) Loss of Taste			
Frequency, N (%)	314 (48.4)	128 (65.0)	<0.001
Severity, VAS (0-10cm), median [IQR]	7.0 [5.0]	9.0 [3.6]	<0.001
Mild (0-3cm), N (%)	36 (11.5)	8 (6.25)	0.003
Moderate (>3-7cm), N (%)	128 (40.8)	36 (28.1)	
Severe (>7-10cm), N (%)	150 (47.8)	84 (65.6)	
As first symptom, N (%)	58 (19.5)	20 (18.2)	0.360
Prior to other symptoms, days, median [IQR]	3.0 [2.0]	3.0 [3.5]	0.978
Recovery, N (%)	147 (49.3%)	42 (37.5%)	<0.001
Recovery time, days, median [IQR]	7.0 [5.0]	7.0 [6.0]	0.162
c) Symptoms, N (%)			
Rhinorrhea	31 (9.28)	0 (0.00)	0.058
Sore throat	19 (5.69)	3 (7.89)	0.481
Cough	252 (75.4)	5 (13.2)	<0.001
Dyspnoea	64 (19.2)	0 (0.00)	0.006
Fever	295 (88.3)	7 (18.4)	<0.001

Abbreviations: COVID-19: coronavirus disease 2019; SD: standard deviation; VAS: visual analogue scale; IQR: interquartile range.

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Table 3. Characteristics of COVID-19 patients stratified by severity of loss of smell.

Characteristics	Non-smell loss (VAS 0cm) (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*
Age, years, mean (SD)	61.0 (15.4)	56.6 (14.6)	57.1 (14.6)	49.9 (14.6)	<0.001
Gender, female, N (%)	180 (45.9)	26 (44.8)	63 (40.9)	131 (54.1)	0.031
Pneumonia N (%)	258 (92.1)	35 (87.5)	95 (88.8)	134 (77.5)	0.036
As first symptom, N (%)		12 (21.8)	24 (16.7)	42 (18.9)	0.003
Recovery, N (%)		31 (56.4)	65 (46.8)	96 (42.3)	0.351
Recovery time, days, median [IQR]		4 [4]	7 [5]	7 [5]	<0.001
a) Symptoms, N (%)					
Rhinorrhea	11 (5.45)	3 (8.82)	6 (11.5)	11 (13.1)	0.906
Sore throat	7 (3.47)	3 (8.82)	5 (9.62)	7 (8.33)	0.939
Cough	139 (68.8)	26 (76.5)	34 (65.4)	58 (69.0)	0.549
Dyspnoea	38 (18.8)	6 (17.6)	8 (15.4)	12 (14.3)	0.900
Fever	163 (80.7)	31 (91.2)	41 (78.8)	67 (79.8)	0.280
b) Comorbidities N (%)					
Respiratory	37 (22.6)	6 (20.7)	4 (13.3)	5 (8.93)	0.278
Hypertension	77 (47.0)	14 (48.3)	13 (43.3)	17 (30.4)	0.219
Cardiovascular disease	42 (25.6)	8 (27.6)	5 (16.7)	6 (10.7)	0.132
Diabetes mellitus	29 (17.7)	6 (20.7)	5 (16.7)	6 (10.7)	0.433
Obesity (BMI>30)	48 (54.5)	8 (20.0)	10 (25.0)	22 (55.0)	0.329
Chronic kidney disease	15 (9.15)	2 (6.90)	4 (13.3)	3 (5.36)	0.438
Neurological disease	17 (10.4)	3 (10.3)	0 (0.00)	2 (3.57)	0.113
Immunosuppression	20 (12.2)	3 (10.3)	3 (10.0)	4 (7.14)	0.757
Cancer	35 (21.3)	3 (10.3)	6 (20.0)	5 (8.93)	0.365
c) Blood biomarkers					
C-reactive protein (mg/mL), median [IQR]	18.4 [49.75]	22.2 [117.5]	18.5 [42.05]	11.0 [13.26]	0.003
D-dimer (µg/L), median [IQR]	1690 [2658]	1152 [1830]	980 [1664]	975 [1192]	0.915
Ferritin (µg/L), median [IQR]	836 [1268]	1003 [840]	826 [1034]	640 [948]	0.064
Lymphocyte count (10^9cells/L), median [IQR]	950 [782]	665 [588]	1112 [756]	1203 [716]	<0.001

Abbreviations: COVID-19: coronavirus disease 2019; SD: standard deviation; VAS: visual analogue scale; IQR: interquartile range; BMI: body mass index.
* The p-value was obtained by severity of smell loss excluding the non-smell loss group.

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Table 4. Characteristics of COVID-19 patients stratified by severity of taste loss.

Characteristics	No taste loss (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*
Age, years, media (SD)	60.1 (15.9)	56.2 (14.8)	56.9 (14.5)	51.3 (14.7)	<0.001
Gender, female, N (%)	186 (46.0)	17 (38.6%)	73 (44.5%)	124 (53.0%)	0.098
Pneumonia N (%)	262 (91.3)	21 (75.0)	93 (85.3)	146 (83.0)	0.409
As first symptom, N (%)		8 (22.2)	28 (21.9)	38 (18.4)	0.311
Recovery, N (%)		14 (42.4)	62 (48.4)	94 (44.1)	0.789
Recovery time, days [IQR]		5 [4]	6 [4.5]	7 [4]	<0.001
a) Symptoms, N (%)					
Rhinorrhea	10 (4.61)	2 (9.52)	5 (10.0)	14 (16.7)	0.544
Sore throat	7 (3.23)	2 (9.52)	6 (12.0)	7 (8.33)	0.803
Cough	150 (69.1)	11 (52.4)	35 (70.0)	61 (72.6)	0.197
Dyspnoea	37 (17.1)	2 (9.52)	11 (22.0)	14 (16.7)	0.481
Fever	173 (79.7)	14 (66.7)	42 (84.0)	73 (86.9)	0.099
b) Comorbidities N (%)					
Respiratory	38 (21.5)	2 (18.2)	4 (12.9)	8 (13.3)	0.834
Hypertension	82 (46.3)	5 (45.5)	12 (38.7)	22 (36.7)	0.871
Cardiovascular disease	44 (24.9)	3 (27.3)	8 (25.8)	6 (10.0)	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)	0.288
Chronic kidney disease	14 (7.91)	1 (9.09)	2 (6.45)	7 (11.7)	0.884
Neurological disease	20 (11.3)	1 (9.09)	0 (0.00)	1 (1.67)	0.295
Immunosuppression	19 (10.7)	0 (0.00)	4 (12.9)	7 (11.7)	0.653
Cancer	36 (20.3)	1 (9.09)	5 (16.1)	7 (11.7)	0.827
c) Blood biomarkers					
C-reactive protein (mg/mL), median [IQR]	18.2 [44.67]	18.7 [124.24]	19.0 [62.7]	12.2 [19.59]	0.023
D-dimer (µg/L), median [IQR]	1561 [2322]	960 [971]	1052 [1440]	1000 [1700]	0.819
Ferritin (µg/L), median [IQR]	830 [1175]	1142 [1245]	656 [1025]	791 [1266]	0.395
Lymphocyte count (10^9cells/L), median [IQR]	940 [770]	1039 [452]	1113 [890]	1146 [760]	0.686

Abbreviations: COVID-19: coronavirus disease 2019; SD: standard deviation; VAS: visual analogue scale; IQR: interquartile range; BMI: body mass index.
*The p-value was obtained by severity of taste loss excluding the no taste loss group

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Table 5. Crude (OR_c) and adjusted (OR_{adj}) multivariate analysis on the characteristics associated to Loss of Smell in COVID-19 patients.

		OR_c	CI95%	p-value	OR_{Adj}	CI95%	p-value
a) Demographics (n=846)							
Age	<40	1			1		
	41-60	0.67	(0.44-1.03)	0.065	0.80	(0.51-1.23)	0.304
	>60	0.29	(0.19-0.45)	<0.001	0.37	(0.24-0.58)	<0.001
Sex	Male	1			1		
	Female	1.11	(0.84-1.45)	0.461	0.98	(0.73-1.30)	0.870
Hospital admission	Non-hospitalized	1			1		
	Hospitalized	0.41	(0.29-0.57)	<0.001	0.53	(0.37-0.77)	<0.001
Pneumonia (n=600)	No	1			1		
	Yes	0.40	(0.24-0.68)	<0.001	1.07	(0.53-2.17)	0.842
b) Symptoms (n=372)							
Rhinorrhea	No	1			1		
	Yes	2.32	(1.08-4.98)	0.032	2.00	(0.87-4.58)	0.101
Sore throat	No	1			1		
	Yes	2.70	(1.07-6.78)	0.035	1.88	(0.69-5.20)	0.219
Cough	No	1			1		
	Yes	1.03	(0.66-1.60)	0.901	1.07	(0.62-1.84)	0.806
Dyspnoea	No	1			1		
	Yes	0.78	(0.45-1.35)	0.371	0.70	(0.38-1.27)	0.242
Fever	No	1			1		
	Yes	1.07	(0.64-1.81)	0.792	1.89	(0.90-3.94)	0.091
c) Blood biomarkers $^{\alpha, \beta}$ (n= 353)							
C-reactive protein (mg/mL)	10 mg/mL	0.970	(0.944-0.997)	0.031	0.971	(0.943-0.999)	0.045
D-dimer (µg/L)	100 µg/L	0.999	(0.997-1.000)	0.278	0.999	(0.997-1.001)	0.602
Ferritin (µg/L)	100 µg/L	0.987	(0.969-1.000)	0.162	0.994	(0.980-1.008)	0.392
Lymphocyte (10^9 cells/L)	100 cells/L	1.011	(0.994-1.028)	0.206	1.014	(0.996-1.033)	0.120
d) Comorbidities $^{\alpha, \delta}$ (n=284)							
Smoker	No	1			1		
	Yes	0.85	(0.30-2.40)	0.756	0.86	(0.24-3.10)	0.813
Obesity (BMI>30)	No	1			1		
	Yes	1.48	(0.87-2.53)	0.147	1.49	(0.85-2.62)	0.169
Respiratory	No	1			1		
	Yes	0.51	(0.27-0.99)	0.047	0.74	(0.35-1.54)	0.419
Hypertension	No	1			1		
	Yes	0.70	(0.43-1.14)	0.150	0.84	(0.44-1.63)	0.614
Cardiovascular disease	No	1			1		
	Yes	0.57	(0.31-1.05)	0.073	0.79	(0.38-1.64)	0.519
Diabetes mellitus	No	1			1		
	Yes	0.81	(0.42-1.55)	0.521	1.22	(0.55-2.72)	0.620
Chronic kidney disease	No	1			1		
	Yes	0.84	(0.36-2.00)	0.699	1.07	(0.39-3.00)	0.889
Neurological disease	No	1			1		
	Yes	0.39	(0.14-1.10)	0.075	0.57	(0.19-1.74)	0.325
Immunosupression	No	1			1		
	Yes	0.69	(0.31-1.53)	0.355	0.87	(0.33-2.32)	0.789
Cancer	No	1			1		
	Yes	0.51	(0.26-1.00)	0.050	0.66	(0.31-1.46)	0.311

OR_{Adj}: adjusted by age, gender and severity (hospitalized, non-hospitalized); α: All patients were hospitalized with pneumonia diagnosis. β: OR_{Adj} adjusted by age and gender; δ: OR_{Adj}: adjusted by age, gender and comorbidities; BMI: body mass index.

Table 6. Crude (OR_c) and adjusted (OR_{adj}) multivariate analysis on the characteristics associated to Loss of Taste in COVID-19 patients.

		OR_c	CI95%	p-value	OR_{Adj}	CI95%	p-value
a) Demographics (n=846)							
Age	<40	1			1		
	41-60	0.90	(0.60-1.35)	0.619	1.04	(0.68-1.58)	0.864
	>60	0.44	(0.29-0.65)	<0.001	0.54	(0.35-0.82)	0.004
Sex	Male	1			1		
	Female	1.10	(0.84-1.44)	0.489	1.00	(0.76-1.33)	0.986
Hospital admission	Non-hospitalized	1			1		
	Hospitalized	0.51	(0.36-0.70)	<0.001	0.61	(0.43-0.87)	0.007
Pneumonia (n=600)	No	1			1		
	Yes	0.47	(0.28-0.77)	0.003	1.01	(0.51-1.99)	0.975
b) Symptoms (n=372)							
Rhinorrhea	No	1			1		
	Yes	3.24	(1.48-7.10)	0.003	2.57	(1.11-5.95)	0.028
Sore throat	No	1			1		
	Yes	3.21	(1.28-8.08)	0.013	2.30	(0.88-6.50)	0.086
Cough	No	1			1		
	Yes	0.99	(0.64-1.56)	0.985	0.78	(0.46-1.33)	0.358
Dyspnoea	No	1			1		
	Yes	1.03	(0.59-1.77)	0.926	0.80	(0.44-1.47)	0.473
Fever	No	1			1		
	Yes	1.26	(0.73-2.16)	0.395	1.42	(0.75-2.70)	0.279
c) Blood biomarkers $^{\alpha, \beta}$ (n= 353)							
C-reactive protein (mg/mL)	10 mg/mL	0.977	(0.950-1.004)	0.099	0.980	(0.952-1.028)	0.165
D-dimer (µg/L)	100 µg/L	0.999	(0.998-1.000)	0.415	1.000	(0.998-1.001)	0.737
Ferritin (µg/L)	100 µg/L	0.991	(0.974-1.028)	0.283	0.995	(0.982-1.009)	0.512
Lymphocyte (10^9 cells/L)	100 cells/L	0.996	(0.984-1.008)	0.518	0.999	(0.987-1.011)	0.847
d) Comorbidities $^{\alpha, \delta}$ (n=284)							
Smoker	No	1			1		
	Yes	0.56	(0.18-1.79)	0.329	0.58	(0.14-2.38)	0.447
Obesity (BMI>30)	No	1			1		
	Yes	1.14	(0.66-1.98)	0.634	1.11	(0.62-2.00)	0.725
Respiratory	No	1			1		
	Yes	0.58	(0.30-1.14)	0.112	0.82	(0.38-1.78)	0.612
Hypertension	No	1			1		
	Yes	0.72	(0.44-1.18)	0.190	0.91	(0.46-1.81)	0.791
Cardiovascular disease	No	1			1		
	Yes	0.60	(0.32-1.13)	0.113	0.84	(0.39-1.82)	0.660
Diabetes mellitus	No	1			1		
	Yes	0.91	(0.47-1.77)	0.784	1.51	(0.66-3.49)	0.332
Chronic kidney disease	No	1			1		
	Yes	1.27	(0.54-2.96)	0.587	1.44	(0.52-4.04)	0.484
Neurological disease	No	1			1		
	Yes	0.16	(0.04-0.69)	0.014	0.22	(0.04-1.02)	0.053
Immunosuppression	No	1			1		
	Yes	1.00	(0.46-2.21)	0.990	1.36	(0.52-3.61)	0.532
Cancer	No	1			1		
	Yes	0.57	(0.29-1.14)	0.111	0.66	(0.30-1.49)	0.321

OR_{Adj}: adjusted by age, gender and severity (hospitalized, non-hospitalized); α: All patients were hospitalized with pneumonia diagnosis. β: OR_{Adj} adjusted by age and gender; δ: OR_{Adj}: adjusted by age, gender and comorbidities; BMI: body mass index.

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