

Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients

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Abstract. Lechien JR, Chiesa-Estomba CM, Beckers E, Mustin V, Ducarme M, Journe F, Marchant A, Jouffe L, Barillari MR, Cammaroto G, Circiu MP, Hans S, Saussez S (COVID-19 Task Force of the Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS), Marseille, France; University of Mons (UMons), Mons, Belgium; Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France; Université Libre de Bruxelles, Brussels, Belgium; Hospital Universitario Donostia, San Sebastian, Spain; Clinique de l'Europe, Brussels, Belgium; EpiCURA Hospital, Hornu; Université libre de Bruxelles, Brussels, Belgium; Bayesia, Changé, France; University of Naples SUN, Naples; and Forli Hospital, Forli, Italy). Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients (Brief Report). *J Intern Med*, 2021; <https://doi.org/10.1111/joim.13209>

Objective. To investigate prevalence and recovery of olfactory dysfunction (OD) in COVID-19 patients according to the disease severity.

Methods. From 22 March to 3 June 2020, 2581 COVID-19 patients were identified from 18 European hospitals. Epidemiological and clinical data

were extracted at baseline and within the 2-month post-infection.

Results. The prevalence of OD was significantly higher in mild form (85.9%) compared with moderate-to-critical forms (4.5–6.9%; $P = 0.001$). Of the 1916 patients with OD, 1363 completed the evaluations (71.1%). A total of 328 patients (24.1%) did not subjectively recover olfaction 60 days after the onset of the dysfunction. The mean duration of self-reported OD was 21.6 ± 17.9 days. Objective olfactory evaluations identified hyposmia/anosmia in 54.7% and 36.6% of mild and moderate-to-critical forms, respectively ($P = 0.001$). At 60 days and 6 months, 15.3% and 4.7% of anosmic/hyposmic patients did not objectively recover olfaction, respectively. The higher baseline severity of objective olfactory evaluations was strongly predictive of persistent OD ($P < 0.001$).

Conclusion. OD is more prevalent in mild COVID-19 forms than in moderate-to-critical forms. OD disappeared in 95% of patients regarding objective olfactory evaluations at 6 months.

Keywords: anosmia, COVID-19, olfactory, recovery, SARS-CoV-2, smell.

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Introduction

As of 11 November 2020, there have been 50 810 753 confirmed cases of coronavirus disease 2019 (COVID-19) worldwide, with 1 263 844 confirmed deaths [1]. The clinical picture of the infection may vary regarding the disease severity and

usually includes general, otolaryngological and neurological symptoms [2, 3]. The olfactory dysfunction (OD) is one of the most prevalent symptoms [2]. The prevalence of OD may vary regarding the clinical setting, with rates of total loss of smell as high as 70% in patients with mild COVID-19 form [2, 4, 5]. The prevalence of OD in moderate-to-critical COVID-19 forms was poorly investigated [6, 7]. Moreover, there is, to date, a paucity of studies prospectively studying the recovery rates of smell sense in COVID-19 patients [8, 9].

The aim of this study is to investigate both prevalence and recovery of OD in COVID-19 patients through subjective and objective clinical tools.

Methods

Five European local ethics committees approved the study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303, CHUC-P20/30-24/03-B325-2020; J.Bordet Institute:CE3137). The electronic informed consent was obtained.

Subjects and setting

From 22 March to 3 June 2020, ambulatory and hospitalized patients with laboratory-confirmed diagnosis of COVID-19 (nasal swabs-RT-PCR) were consequently identified from 18 European hospitals. The definition of mild, moderate, severe and critical patients was based on the COVID-19 Disease Severity Scoring of World Health Organization [10].

Mild patients were defined as patients without evidence of viral pneumonia or hypoxia and were commonly home-managed and followed. Moderate COVID-19 patients had clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no sign of severe pneumonia (including $SpO_2 \geq 90\%$ on room air). Severe COVID-19 patients were defined as individuals with clinical signs of pneumonia plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or $SpO_2 < 90\%$ on room air. According to the centre and the availability of local healthcare resource, moderate and severe patients were home-managed (moderate) or hospitalized in non-intensive care units (ICU) vs. ICU. Patients with critical disease had acute respiratory distress syndrome (ARDS), sepsis or septic shock and were hospitalized in ICU. Patients with OD were followed to assess the recovery olfactory rates and the duration of OD.

Epidemiological and clinical outcomes

Epidemiological (gender, age, ethnicity) and clinical data (comorbidities and symptoms) were collected with a standardized online questionnaire at the end of the disease (defined as the general symptom resolution) or at the hospital discharge. Both patients (home-managed) and physicians (hospitalized patients) may fulfil the questionnaire.

The following admission outcomes were collected from the hospitalized patients: O₂ saturation, chest computed tomography findings and biology, including blood formula, liver, renal, heart functions, inflammatory molecules and ionogram. The 1-month serology (IgG) has been realized in patients who benefited from objective olfactory evaluations.

For patients who completed the study, olfactory and gustatory questions were based on the smell and taste component of the National Health and Nutrition Examination Survey [11, 12].

A subset of patients (EpiCURA Hospital, Belgium & Foch Hospital, Paris, France) benefited from objective olfactory tests within the 2 (mild, moderate) or 3 (severe to critical) weeks of the onset of the olfactory disease. Olfactory evaluations were made at 30 days, 60 days and 6 months. Olfactory objective evaluations consisted of Sniffin-Sticks tests (Medisense, Groningen, Netherlands), which is a standardized and validated psychophysical olfactory evaluation using 16 smell pens. The patient had to choose the adequate term describing the smell between 4 given options [11]. The total score ranges from 0 (no olfaction) to 16 (perfect olfaction). Regarding results, three categories were defined as follows: normosmia (score between 12 and 16), hyposmia (score between 9 and 11) and anosmia (score < 9) [13]. Patients with hyposmia or anosmia were invited to attend for repeated evaluation with Sniffin-Sticks until scores returned to normal levels. Patients who benefited from psychophysical olfactory evaluation also fulfilled the French version of the sino-nasal outcome tool-22 (SNOT-22) [14]. More details about the data collection, inclusion and exclusion criteria are available in the flow chart (Fig. 1).

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows

(SPSS-v22,0; IBM Corp, Armonk, NY, USA). The outcome comparison between severity patient groups and the evolution of olfactory evaluations through the follow-up period were made through Kruskal–Wallis test, Mann–Whitney U test, Wilcoxon rank test and chi-square test. The relationship between epidemiological, clinical and olfactory outcomes was analysed through multivariate analysis. According to the WHO classification, the statistics were realized considering 3 groups: mild, moderate and severe-to-critical patients.

Results

A total of 2581 ambulatory and hospitalized COVID-19 patients were included. Patients fulfilled the baseline evaluations, including 2194 (85.0%), 110 (4.3%) and 277 (10.7%) patients with mild, moderate and severe-to-critical COVID-19, respectively. There were 1624 females (62.9%). The proportion of female was higher in mild patient group compared with other groups ($P = 0.001$, Table 1). The following ethnicities were represented: Caucasian (83.6%), South American (11.6%), Asian (1.2%), North African (1.2%), Black African (0.7%) and mixing/other (1.5%). The epidemiological and clinical features of patients are reported in Tables 1 and 2, and Appendix 1.

Prevalence of olfactory dysfunction

Amongst the 2581 patients, 1916 reported self-reported OD (74.2%). The prevalence of self-reported OD was 85.9%, 4.5% and 6.9% in mild, moderate and severe-to-critical patients, respectively ($P = 0.001$). The clinical presentation significantly varied between mild and moderate-to-critical patient groups. Patients with moderate-to-critical COVID-19 were older than patients with mild COVID-19 ($P = 0.001$). Moderate-to-critical forms had higher prevalence of the following comorbidities: hypertension, diabetes, gastric disorders, renal, respiratory, heart, liver and neurological disorders ($P < 0.05$). Amongst the usual symptoms, OD was more prevalent in mild form compared with moderate-to-severe forms ($P = 0.001$). Severe and critical COVID-19 patients had more frequently cough (severe and critical), dyspnoea and fever than the others ($P < 0.05$) (Table 1).

Evolution of subjective olfactory dysfunction

Amongst the patients with OD, 1363 (71.1%) completed the follow-up subjective evaluations

(Fig. 1). The high majority of these patients had mild COVID-19 form (98.0%). Their clinical and olfactory features are described in Appendix 1. The most prevalent comorbidities were hypertension (8.4%), asthma (6.5%) and gastroesophageal disorders (5.0%). According to our clinical tools (National Health and Nutrition Examination Survey and SNOT-22), the most prevalent symptoms of patients were asthenia, headache and rhinorrhea. OD consisted of self-reported total loss of smell in 81.6% of patients, whilst 18.4% of patients reported partial loss of smell. The mean duration of COVID-19 symptoms (excluding OD) was 13.8 ± 6.1 days. The OD developed after the other symptoms in 44.7% of cases and disappeared within the month following the onset of OD in 54.3% of patients. Dysgeusia, defined as the impairment of salty, sweet, bitter and sour, was reported by 55.9% of patients, whereas 83.9% of patients reported aroma perception dysfunction (Appendix 2). A total of 328 patients (24.5%) did not subjectively recover olfaction 60 days after the onset of the dysfunction. The mean duration of self-reported OD was 21.6 ± 17.9 days.

Prevalence and evolution of objective olfactory dysfunction

Amongst the 2581 patients, 233 patients completed objective olfactory evaluations. There were 52 patients with moderate-to-critical COVID-19 and 181 patients with mild form of the disease (77.7%). Self-reported anosmia, cacosmia, phantosmia and aroma dysfunction were significantly more prevalent in mild than moderate-to-critical COVID-19 forms ($P < 0.02$; Appendix 3). The mean values of the Sniffin-Sticks tests were significantly lower in mild patient group compared with moderate-to-critical patient group ($P = 0.001$; Appendix 3). Moreover, the prevalence of objective olfactory dysfunction was significantly higher in mild forms compared with moderate-to-critical forms (36.6 vs. 54.7; $P = 0.001$).

The baseline mean value of Sniffin-Sticks tests of anosmic and hyposmic patients ($N = 118$; 7.6 ± 3.0) significantly improved after 30 (10.6 ± 3.7) and 60 days (11.3 ± 3.5) of follow-up ($P = 0.001$). At the end of the first follow-up period (60 days), 18 anosmic/hyposmic patients did not objectively fully recover olfaction (15.3%). At 6 months, there were 6 and 5 remained anosmic and hyposmic patients, representing a 6-month recovery rate of 95.3%.

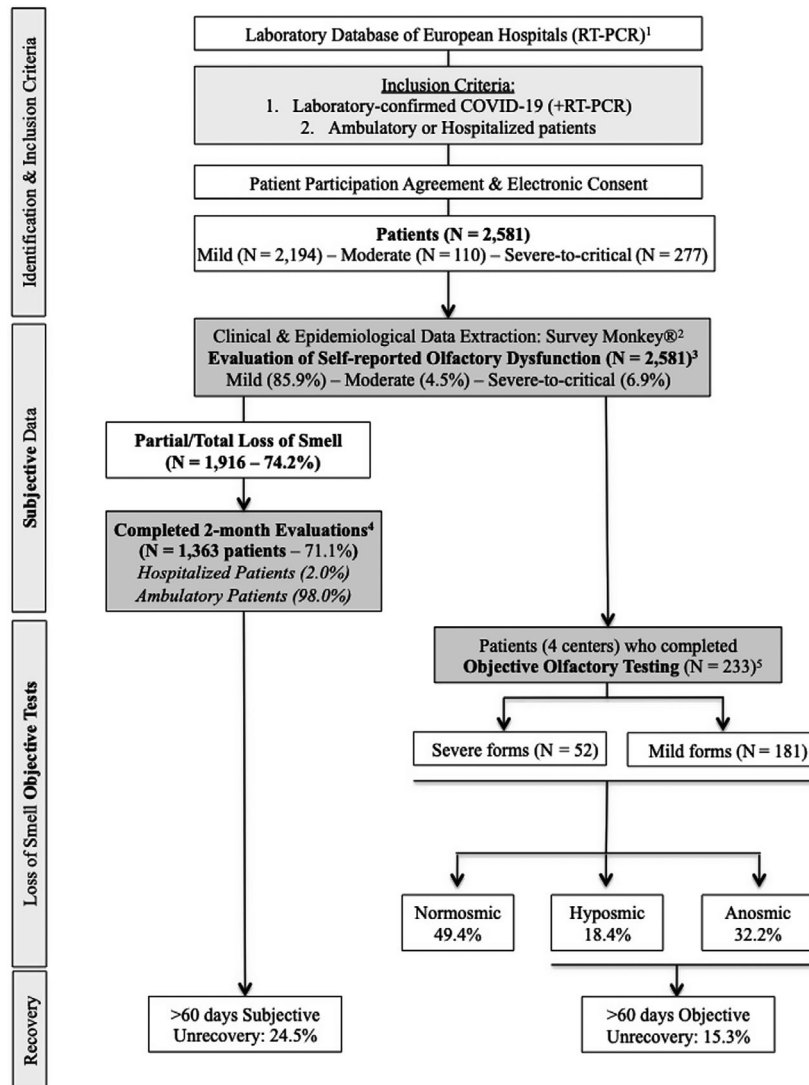


Fig. 1 Flow Chart. ¹The diagnosis tests of ambulatory and hospitalized patients were centralized in Hospital Laboratories, allowing the identification of patients with a positive diagnosis. ²Physicians directly completed patient information on an online questionnaire for hospitalized patients whilst ambulatory patients fulfilled the evaluation at home (home-managed patients). ³The first objective of the study was to investigate the prevalence of olfactory dysfunction according to the severity of the disease (N = 2581). ⁴The second objective of the study was to investigate the recovery of olfaction, which was made on 1363 patients who completed the evaluations. To be included, patients had to be followed over the 60 days post-COVID-19 to assess (potential) occurrence and evolution of olfactory dysfunction. ⁵The third objective of the study was to objectively assess the olfactory dysfunction in a subset of patients of the 2581 included patients. COVID-19 = coronavirus disease 2019; RT-PCR = reverse transcription polymerase chain reaction.

Clinical and objective olfactory associations

Amongst the cohort of 2581 patients, there was no significant association between clinical data (biology, CT-scan findings) and the development of OD.

Amongst the cohort of 233 patients, individuals with fever exhibited a significantly higher level of IgG ($r_s = 0.521$; $P = 0.001$). The Sniffin-Sticks test value was positively associated with the patient age ($r_s = 0.246$; $P = 0.001$). There was no significant association between the following outcomes: nasal

Table 1. Epidemiological and clinical characteristics of patients

Characteristics	All patients <i>N</i> = 2581	Mild <i>N</i> = 2194	Moderate <i>N</i> = 110	Severe and critical <i>N</i> = 277
Age (y - Mean; SD)	44.5 ± 16.4	41.9 ± 13.0	68.8 ± 16.1	71.9 ± 13.7
Gender (F/M)	1624/957	1455/739	52/58	117/160
Comorbidities				
Hypertension	414 (16.0)	173 (7.9)	61 (55.5)	180 (65.0)
Current Smoker	351 (13.6)	281 (12.8)	18 (16.4)	52 (18.8)
Asthma	170 (6.6)	137 (6.2)	11 (10.0)	22 (7.9)
Diabetes	148 (5.7)	41 (1.9)	27 (24.5)	80 (28.9)
Reflux or gastric ulcer	120 (4.6)	87 (4.0)	12 (10.9)	21 (7.6)
Heart problems	102 (4.0)	40 (1.8)	13 (11.8)	49 (17.7)
Kidney Insufficiency	57 (2.2)	10 (0.5)	8 (7.3)	39 (14.1)
Neurological Disease	67 (2.6)	14 (0.6)	10 (9.1)	43 (15.5)
Respiratory insufficiency	65 (2.5)	11 (0.5)	11 (10.0)	43 (15.5)
Liver Insufficiency	34 (1.3)	17 (0.8)	6 (5.5)	11 (4.0)
Symptoms (<i>N</i> - %)				
Olfactory dysfunction	1916 (74.2)	1884 (85.9)	5 (4.5)	27 (6.9)
Cough and sticky mucus/phlegm	1545 (59.9)	1266 (57.7)	52 (47.3)	227 (81.9)
Arthralgia and myalgia	1400 (54.2)	1340 (61.0)	14 (12.7)	46 (16.6)
Asthenia, anorexia or confusion	1351 (52.3)	1042 (47.5)	57 (51.8)	252 (91.0)
Dyspnoea	1293 (50.1)	995 (45.4)	67 (61.0)	231 (83.4)
Gustatory dysfunction	1182 (45.8)	1178 (53.7)	2 (1.8)	2 (0.7)
Fever (>38°C)	1188 (46.0)	880 (40.1)	62 (56.4)	246 (88.8)

F/M, female/male; *N*, number; SD, standard deviation.

symptom severity, the occurrence of self-reported OD and the result of the objective olfactory testing. The higher baseline severity of olfactory loss measured using the Sniffin-Sticks was strongly predictive of 2-month persistent loss ($P < 0.001$). The level of IgG was positively correlated with the Sniffin-Sticks test in the entire cohort ($r_s = 0.395$; $P = 0.003$).

Discussion

Loss of smell is a key symptom of the coronavirus disease 2019, which may be isolated symptom or associated with other general and otolaryngological symptoms. The majority of studies that investigated OD in COVID-19 included mild patients [2, 4, 11, 15-17], which raised the issue of the specificity and the predictive value of OD on the severity of the infection. The prognostic value of OD in COVID-19 was poorly investigated [18, 19].

In this study, we observed that both self-reported and objective ODs were more prevalent in mild

patients compared with individuals presenting moderate-to-critical COVID-19. Vaira *et al.* recently observed that anosmia and hyposmia accounted for 70% of COVID-19 mild-to-moderate patients [5]. However, they only observed a trend of significant differences between severe and mild forms regarding the objective olfactory disorder. In the study of Moein *et al.*, 60 COVID-19 hospitalized and home-managed patients benefited from objective olfactory evaluations [20]. Using a different anosmia definition (microsmia), the authors reported a prevalence of objective OD in 98% of patients. Although a low number of hospitalized patients ($N = 6$), the study findings support a higher prevalence of OD in mild patients (45%) compared with severe patients (10%) [20]. The comparison with these two studies is however limited because authors did not classify the patients according to the WHO classification and they used different olfactory tests.

The main hypothesis underlying the higher prevalence of anosmia in mild COVID-19 would consist

Table 2. General and olfactory subjective outcomes of COVID-19 patients

Characteristics	All Patients (N = 1363)
Age (y - Mean; SD)	41.9 ± 13.0
Gender (F/M)	885/478
Current Smoker	156 (11.4)
History of seasonal allergy	286 (21.0)
General Symptoms (N - %)	
Asthenia	1176 (86.3)
Headache	952 (69.9)
Myalgia	861 (63.2)
Anorexia	762 (55.9)
Cough	715 (52.5)
Arthralgia	631 (46.3)
Fever (>38°C)	584 (42.9)
Diarrhoea	565 (41.5)
Dyspnoea	505 (37.1)
Abdominal pain	362 (26.6)
Nausea, vomiting	322 (23.6)
Sticky mucus/phlegm	280 (20.5)
Ear, nose and throat Symptoms (N - %)	
Self-reported anosmia	1112 (81.6)
Rhinorrhoea	878 (64.4)
Nasal obstruction	846 (62.1)
Taste dysfunction	762 (55.9)
Postnasal drip	715 (52.5)
Sore throat	661 (48.5)
Face pain/heaviness	656 (48.1)
Ear pain	531 (39.0)
Dysphonia	525 (38.5)
Dysphagia	325 (23.8)
Self-reported hyposmia	251 (18.4)
Aroma sense dysfunction (retro-olfaction)	
Total loss of aroma perception sense	225 (16.5)
Partial loss of aroma	777 (57.0)
Distortion	142 (10.4)
No problem	136 (10.0)
Missing Data	83 (6.1)
Smell dysfunction	
Cacosmia	921 (67.6)
Phantosmia	224 (16.4)

Table 2 (Continued)

Characteristics	All Patients (N = 1363)
Onset of smell dysfunction N = 1339	
Before the other symptoms	225 (16.8)
Concomitant with other symptoms	439 (32.8)
After the other symptoms	599 (44.7)
Did not remember/Missing data	76 (5.7)
Smell dysfunction duration	
1-4 days	157 (11.7)
5-8 days	213 (15.9)
9-14 days	172 (12.8)
15-30 days	186 (13.9)
31-45 days	152 (11.4)
45-60 days	131 (9.8)
Unresolved	328 (24.5)
Mean duration (Mean, SD, days)	21.6 ± 17.9

F/M, female/male; N, number; SD, standard deviation.

of differences in the immune response to the infection in mild and moderate-to-critical patients [21]. In this hypothesis, patients with mild COVID-19 could have a better local immunological response through a higher production of IgA, which could limit the virus spread into the organism. The limited virus spread in the host body could therefore be associated with a mild clinical form of the disease. Due to the local inflammatory reaction and the well-demonstrated olfactory cell expression of angiotensin-converting enzyme-2 (ACE2) and TMPRSS2 [22, 23], the patients with mild disease could have stronger impairment of olfactory cells. In addition, we observed that severe and critical patients had a significantly higher level of IgG than mild patients, which may corroborate some findings of the literature [24]. However, this hypothesis requires additional studies involving immunological sera, saliva and nasal secretion analyses.

According to our analysis, young patients could have a higher rate of anosmia compared with elderly individuals. Similar findings have been reported in the study of Speth *et al.* who investigated self-reported OD in 103 COVID-19 patients [25]. Although a significant *P*-value, we need to remain cautious in the interpretation of these

results because the correlation coefficient is low ($r_s = 0.246$).

The high prevalence of OD in COVID-19 patients supports the need for primary care, ear, nose and throat (ENT) and neurology physicians to be able to counsel patients regarding the likelihood of recovery, and to identify those at risk of persistent OD, such that therapeutic strategies can be targeted appropriately. Considering both subjective and objective data, we may suggest that the 60-day recovery rate ranges from 75% to 85%. Interestingly, we may identify several profiles of OD severity because over a third of patients reported smell recovery within the 14 days following the development of OD, whilst one third did not recover within the 45 days. Typically, OD occurring as part of the common cold is related to nasal congestion, rhinorrhoea and olfactory cleft oedema and lasts 2–3 weeks. The high prevalence of nasal symptoms could partly explain the occurrence of short OD in some patients who rapidly recovered olfaction once the nasal symptoms disappeared. However, for patients with mid-to-long-term or persistent OD, the pathophysiological mechanisms underlying the development of OD could be more complex. According to recent findings [22, 26, 27], the OD could be additionally associated with injury of the olfactory neuroepithelial and the virus spread into the olfactory bulb where sustentorial cells and stem neurons may express ACE2 and TMPRSS2. Because the expression of ACE2 and TMPRSS2 varies between individuals [28], the long duration of OD in some patients could be due to higher protein expression and more extensive injuries of the olfactory cells. The neurogenesis of the olfactory cells is possible but may take several months [29]. The neural hypothesis of OD related to COVID-19 infection is supported by the lack of significant association between olfactory evaluation results and nasal complaints. Moreover, post-viral anosmia was observed in some infections related to viruses of the *Coronaviridae* family [30].

In sum, the mechanisms underlying the OD development could associate olfactory cleft congestion in short-term anosmic patients, injury of the olfactory neuroepithelium and virus spread into the olfactory bulb in mid-to-long-term anosmic patients. Future studies are needed to confirm these hypotheses.

The present study has several strengths and limitations. The main strength is the high number of

included patients, which allows to confirm the higher prevalence of OD in mild over moderate-to-critical patients. The data collected in this large cohort allowed us to evaluate the 2-month subjective and objective recovery rate of smell sense. The main limitations are the lack of clinical olfactory examination or imaging at the onset of the disease to assess the olfactory cleft and the olfactory bulb. These observations could provide useful information to better understand the pathophysiological mechanisms underlying the development of anosmia. However, performing nasal fibre-optic examination during the pandemic was prohibited. Moreover, the taste evaluations reported low rates of taste dysfunction in hospitalized patients. Many severe-to-critical patients had nasogastric feeding tube, which, additionally to the delay to assess taste function, may bias the assessment of taste dysfunction. Another limitation is related to the delay (2 to 3 weeks) between the OD onset and the realization of the olfactory evaluations. This delay was particularly long in hospitalized patients who had to be able to undergo olfactory evaluations. Although this possibility is not supported by patient-reported symptoms, the delay between the onset of symptoms and the objective olfactory testing may underestimate the incidence of olfactory dysfunction.

Conclusion

OD is a prevalent disorder in COVID-19 patients with a higher prevalence in patients with mild forms of the disease. At the 2 months of follow-up, 75% to 85% of patients recovered olfaction according to subjective and objective olfactory evaluations. Future studies are needed to determine the long-term recovery rate of COVID-19 patients.

Conflict of interest

The authors have no conflicts of interest.

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Author contribution

Eline beckers: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal). **Vincent Mustin:** Conceptualization (equal); Data curation (equal); Formal analysis

(equal); Funding acquisition (equal); Resources (equal). **Morgane Ducarme:** Resources (equal); Supervision (equal); Validation (equal); Writing-review & editing (equal). **Fabrice Journée:** Data curation (equal); Resources (equal); Software (equal). **Arnaud Marchant:** Supervision (equal); Validation (equal); Visualization (equal). **Marta Circiu:** Data curation (equal); Methodology (equal); Project administration (equal).

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APPENDIX 1

Table A1. Imaging and biological features of moderate-to-critical patients

Clinical features	Moderate N = 110	Severe-to-critical N = 277
Chest CT-scan findings (Lung Involvement)		
Typical COVID-19 pneumonia	67 (60.9)	157 (56.7)
Suspicion	33 (30.0)	69 (29.9)
Negative	10 (9.1)	51 (18.4)
Biology admission features		
Blood formula		
Haemoglobin (g dL ⁻¹)	13.2 ± 2.3	13.0 ± 2.2
Neutrophils (10 ³ per µL)	6.1 ± 3.8	7.1 ± 4.7
Lymphocytes (10 ³ per µL)	1.2 ± 0.7	1.0 ± 1.0
Platelets (10 ³ per µL)	247.3 ± 104.9	223.7 ± 104.7
Liver function		
GOT	47.0 ± 47.2	106.6 ± 593.8
GPT	38.1 ± 42.4	57.8 ± 250.9
GGT	80.4 ± 129.0	81.4 ± 91.8
Alkaline phosphatase	98.3 ± 90.4	92.0 ± 62.4
Total Bilirubin (mg dL ⁻¹)	0.8 ± 1.6	0.6 ± 0.5
Heart biology		
Troponin	16.8 ± 38.7	45.1 ± 132.3
CPK	255.9 ± 598.5	482.5 ± 1772.4
Renal function		
Creatinin (mg dL ⁻¹)	1.2 ± 1.0	1.6 ± 1.6
Urea (mg dL ⁻¹)	45.1 ± 33.4	59.0 ± 40.2
LDH (UI L ⁻¹)	315.3 ± 141.8	453.0 ± 667.1
Inflammatory molecules/other		
CRP (mg L ⁻¹)	68.8 ± 66.1	115.9 ± 93.9
D-Dimer (µg L ⁻¹)	276.3 ± 705.2	695.3 ± 1543.4
Ionogram		
Na ⁺ (mmol L ⁻¹)	135.6 ± 14.0	137.7 ± 5.5
K ⁺ (mmol L ⁻¹)	4.0 ± 0.8	4.1 ± 0.8
Cl ⁻ (mmol L ⁻¹)	96.3 ± 10.5	97.0 ± 8.4
Parameters (admission)		
Temperature (°C)	37.2 ± 1.0	37.4 ± 1.1
Systolic Blood Pressure	145.3 ± 108.8	134.4 ± 26.1
Diastolic Blood Pressure	76.2 ± 14.4	75.0 ± 15.4
Heart rate	88.6 ± 18.1	91.1 ± 19.7
O ₂ saturation (blood gases)	95.0 ± 2.3	93.7 ± 5.6
Second hospitalization (N, %)	9 (8.2)	24 (8.7)

CPK, creatine phosphokinase; CRP, C-reactive protein; CT, computed tomography; COVID-19, coronavirus disease 2019; GGT, gamma-GT; GOT, GPT, transaminases; LDH, lactate dehydrogenase; ICU, intensive care unit; SD, standard deviation.

APPENDIX 2

Table A2. Clinical characteristics of patients who benefited from objective olfactory evaluations

Characteristics	All patients with objective evaluation (N = 233)	Patient with mild COVID-19 form (N = 181)	Patient with MC COVID-19 form (N = 52)	Differences Mild vs MC P-value
Age (y - Mean; SD)	46.0 ± 14.3	42.4 ± 12.7	59.0 ± 12.7	0.001
Gender (F/M)	154/79	126/55	28/24	0.035
Current Smoker	15 (6.4)	14 (7.7)	1 (1.9)	NS
History of seasonal allergy	41 (17.6)	28 (15.5)	13 (25.0)	NS
Comorbidities				
Hypothyroidism	21 (9.0)	10 (5.5)	11 (21.2)	0.001
Hypertension	30 (12.9)	13 (7.2)	17 (32.7)	0.001
Asthma	20 (8.6)	12 (6.6)	8 (15.4)	NS
Reflux	30 (12.9)	20 (11.0)	10 (19.2)	NS
Depression	2 (0.9)	1 (0.6)	1 (1.9)	NS
Diabetes	19 (8.2)	7 (3.9)	12 (23.1)	0.001
Heart problems	13 (5.6)	5 (2.8)	8 (15.4)	0.002
Liver Insufficiency	3 (1.3)	2 (1.1)	1 (1.9)	NS
Kidney Insufficiency	3 (1.3)	0 (0)	3 (5.8)	0.012
Respiratory insufficiency	2 (0.9)	1 (0.6)	1 (1.9)	NS
Neurological Disease	2 (0.9)	0 (0)	2 (3.8)	NS
General Symptoms (N - %)				
Asthenia	183 (78.5)	137 (75.7)	46 (88.5)	0.001
Headache	147 (63.1)	114 (63.0)	33 (63.5)	NS
Myalgia	131 (56.2)	96 (53.0)	35 (67.3)	0.001
Anorexia	131 (56.2)	85 (47.0)	46 (88.5)	0.001
Cough	130 (55.8)	91 (50.3)	39 (75.0)	0.001
Arthralgia	104 (44.6)	77 (42.5)	27 (51.9)	0.035
Fever (>38C)	109 (46.8)	62 (34.3)	47 (90.4)	0.001
Diarrhoea	105 (45.1)	73 (40.3)	32 (61.5)	0.001
Dyspnoea	106 (45.5)	64 (35.4)	42 (80.8)	0.001
Abdominal pain	78 (33.5)	59 (32.6)	19 (36.5)	NS
Nausea, vomiting	74 (31.8)	50 (27.6)	24 (46.2)	0.001
Sticky mucus/phlegm	87 (37.3)	65 (35.9)	22 (42.3)	NS
Ear, nose and throat Symptoms (N - %)				
Self-reported anosmia	91 (39.1)	77 (42.5)	14 (26.9)	0.008
Rhinorrhoea	128 (54.9)	94 (51.9)	34 (65.4)	0.018
Nasal obstruction	134 (57.5)	105 (58.0)	29 (55.8)	NS
Taste dysfunction	51 (21.9)	42 (23.2)	9 (17.3)	NS
Postnasal drip	111 (47.6)	90 (49.7)	21 (40.4)	NS
Sore throat	82 (35.2)	62 (34.3)	20 (38.5)	NS
Face pain/heaviness	77 (33.0)	64 (35.4)	13 (25.0)	NS

Table A2. (Continued)

Characteristics	All patients with objective evaluation (N = 233)	Patient with mild COVID-19 form (N = 181)	Patient with MC COVID-19 form (N = 52)	Differences Mild vs MC P-value
Ear pain	81 (34.8)	69 (38.1)	12 (23.1)	NS
Dysphonia	91 (39.1)	67 (37.0)	24 (46.2)	0.019
Dysphagia	63 (27.0)	45 (24.9)	18 (34.6)	0.001
Self-reported hyposmia	66 (28.3)	53 (29.3)	13 (25.0)	0.008

Because some patients were in critical condition (intubated), 33.3% of severe patients did not remember or could not determine the time of the onset of olfactory dysfunction.

MC, moderate-to-critical; NS, nonsignificant; SD, standard deviation.

APPENDIX 3

Table A3. Olfactory outcomes of patients who benefited from objective olfactory evaluations

Characteristics	All patients with objective evaluation (N = 233)	Patient with mild COVID-19 Form (N = 181)	Patient with MC COVID-19 form (N = 52)	differences Mild vs MC P-value
SNOT-22 (Mean, SD)	33.5 ± 20.6	32.9 ± 20.4	35.3 ± 21.4	NS
Aroma sense dysfunction (retro-olfaction)				
Total loss of aroma perception sense	44 (18.9)	39 (21.5)	5 (9.6)	0.001
Partial loss of aroma	48 (20.6)	44 (24.3)	4 (7.7)	0.001
Distortion	18 (7.7)	16 (8.8)	2 (3.8)	0.001
Smell Dysfunction				
Cacosmia	115 (49.4)	108 (59.7)	7 (13.5)	0.005
Phantosmia	33 (14.2)	31 (17.1)	2 (3.8)	0.019
Onset of smell dysfunction				
Before the other symptoms	25 (15.9)	23 (17.7)	2 (7.4)	NS
Concomitant with other symptoms	51 (32.5)	43 (33.1)	8 (29.6)	
After the other symptoms	72 (45.9)	64 (49.2)	8 (29.6)	
Did not remember/Cannot determine ^a	9 (5.7)	0 (0)	9 (33.3)	
Objective Olfactory Tests				
Anosmia	75 (32.2)	63 (34.8)	12 (23.1)	0.001
Hyposmia	43 (18.4)	36 (19.9)	7 (13.5)	
Normosmia	115 (49.4)	82 (45.3)	33 (63.5)	
Sniffin-Sticks Test (Mean, SD)	10.5 ± 3.7	9.9 ± 3.7	12.3 ± 3.2	0.001
Serology (IgG level)	91.3 ± 84.2	54.5 ± 41.4	168.2 ± 75.1	0.001

MC, moderate-to-critical; NS, nonsignificant; SD, standard deviation; SNOT-22, sino-nasal outcome-22 questionnaire.

^aBecause some patients were in critical condition (intubated), 33.3% of severe patients did not remember or could not determine the time of the onset of olfactory dysfunction.