Prevalence and Recovery of Olfactory Dysfunction in 1,363 patients with coronavirus disease 2019: A Multicenter Longitudinal Study.

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Abstract

Olfactory dysfunction (OD) is a key symptom of coronavirus disease 2019 (COVID-19). Currently, a few data are available about the recovery of OD after the infection resolution. In this study, we investigated both prevalence and recovery rate of OD with subjective and objective clinical tools in 2,581 patients. First, our data showed that the prevalence of OD was significantly higher in mild form (85.9%) compared with moderate-to-critical forms (4.5-9.7%; p=0.001). Second, focusing on patients with OD who completed the 2-month follow-up period (N=1,363), we observed that 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. Third, the objective olfactory evaluations performed on a subset of patients (N=233) reported hyposmia or anosmia in 54.7% and 36.6% of mild and moderate-to-critical forms, respectively (p=0.001). At the end of follow-up, 15.3% of anosmic/hyposmic patients did not objectively recover olfaction. The higher baseline severity of objective olfactory evaluations was strongly predictive of persistent OD (p<0.001). OD disappeared in 75% to 85% of patients regarding self-reported or objective olfactory evaluations.

Introduction

As of June 24th 2020, there have been 9 million confirmed cases of coronavirus disease 2019 (COVID-19) worldwide, with 469,587 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. Moreover, there is, to date, a paucity of studies prospectively studying the recovery rates of smell sense in COVID-19 patients.

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 & Setting

From March 22, to June 3, 2020, 2,581 ambulatory and hospitalized patients with laboratory-confirmed diagnosis of COVID-19 (nasal swabs-RT-PCR) were consequently identified from 18 European hospitals. Among them, 1,916 patients reported subjective OD (74.9%), defined as partial of total loss of smell. The

definition of mild, moderate, severe and critical patients was based on the COVID-19 Disease Severity Scoring of World Healthy Organization.[6] 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, dyspnea, fast breathing) but no sign of severe pneumonia (including SpO2 ≥ 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 SpO2 < 90% on room air. According to the center and the availability of local healthcare resource, moderate and severe patients were home-managed (moderate) or hospitalized in non-intensive care units (ICU) *versus* 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 fulfill the questionnaire. For patient who completed the study, olfactory and gustatory questions were based on the smell and taste component of the National Health and Nutrition Examination Survey (Appendix 1).[7,8]

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 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.[7] The total score ranges from 0 (no olfaction) to 16 (perfect olfaction). Regarding results, three categories were defined: normosmia (score between 12–16), hyposmia (score between 9–11) and anosmia (score < 9).[9] 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 sinonasal outcome tool-22 (SNOT-22).[10] More details about the data collection, inclusion and exclusion criteria are available in the flow chart (Fig. 1).

Biology and Imaging Findings

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.

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, Mann-Whitney U test, Wilcoxon Rank test and Chi-square. The relationship between epidemiological, clinical and olfactory outcomes was analyzed 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 2,581 patients fulfilled the baseline evaluations, including 2,194 (85.0%), 110 (4.3%) and 277 (10.7%) patients with mild, moderate, severe-to-critical COVID-19, respectively. There were 1,624 females (62.9%). The proportion of female was higher in mild patient group compared to 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.

Table 1
Epidemiological & Clinical Characteristics of Patients.

Characteristics	All Patients	Mild	Moderate	Severe & Critical
	N = 2,581	N = 2,194	N = 110	N = 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 Insuffisiency	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 insuffisiency	65 (2.5)	11 (0.5)	11 (10.0)	43 (15.5)
Liver Insuffisiency	34 (1.3)	17 (0.8)	6 (5.5)	11 (4.0)
Symptoms (N - %)				
Olfactory dysfunction	1916 (74.2)	1884 (85.9)	5 (4.5)	27 (9.7)
Cough & sticky mucus/phlegm	1545 (59.9)	1266 (57.7)	52 (47.3)	227 (81.9)
Arthralgia & 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)
Dyspnea	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 (> 38C°)	1188 (46.0)	880 (40.1)	62 (56.4)	246 (88.8)

Table 1 footnotes: Abbreviations: F/M=female/male; N=number; SD=standard deviation.

Table 2
Imaging and Biological Features of Moderate-to-critical Patients.

	Moderate	**Severe-to-critical**
Clinical Features	N = 110	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		
Hemoglobin (g/dL)	13.2 ± 2.3	13.0 ± 2.2
Neutrophils (10^3/µl)	6.1 ± 3.8	7.1 ± 4.7
Lymphocytes (10^3/µl)	1.2 ± 0.7	1.0 ± 1.0
Patelets (10^3/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
Alkalin phosphatase	98.3 ± 90.4	92.0 ± 62.4
Total Bilirubin (mg/dL)	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)	*1.2 ± 1.0*	1.6 ± 1.6
Urea (mg/dL)	*45.1 ± 33.4*	59.0 ± 40.2
LDH (UI/L)	315.3 ± 141.8	453.0 ± 667.1
Inflammatory Molecules/other		
CRP (mg/L)	68.8 ± 66.1	115.9 ± 93.9

	Moderate	Severe-to-critical
D-Dimer (µg/L)	276.3 ± 705.2	695.3 ± 1543.4
Ionogram		
Na+ (mmol/L)	135.6 ± 14.0	137.7 ± 5.5
K+ (mmol/L)	4.0 ± 0.8	4.1 ± 0.8
Cl- (mmol/L)	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
O2 saturation (blood gases)	95.0 ± 2.3	93.7 ± 5.6
Second hospitalization (N, %)	9 (8.2)	24 (8.7)

Table 2 footnotes: Abbreviations: CPK=creatin 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.

Prevalence of Olfactory Dysfunction

Among the 2,581 patients, 1,916 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 ($p < 0.05$). Among 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), dyspnea and fever than the others ($p < 0.05$) (Table 1).

Evolution of Subjective Olfactory Dysfunction

Among the patients with OD, 1,363 (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 Table 3. The most prevalent comorbities 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, while 18.4% of patients reported partial loss of smell (Table 3). 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 (Table 3). 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.

Table 3

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 (> 38C°)	584 (42.9)
Diarrhea	565 (41.5)
Dyspnea	505 (37.1)
Abdominal pain	362 (26.6)
Nausea, vomiting	322 (23.6)
Sticky mucus/phlegm	280 (20.5)
Ear, nose and throat Sympotms (N - %)	
Self-reported anosmia	1112 (81.6)
Rhinorrhea	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)

Characteristics	All Patients (N = 1363)
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)
Onset of Smell Dysfunction	N = 1339
Before the other symptoms	225 (16.8)
Concomittant 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

Table 3 footnotes: Abbreviations: F/M=female/male; N=number; SD=standard deviation.

Prevalence and Evolution of Objective Olfactory Dysfunction

Among the 2,581 patients, 233 patients completed objective olfactory evaluations (Table 4). 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 ($p < 0.02$). The mean values of the Sniffin'Sticks tests were significantly lower in mild patient group compared with moderate-to-critical patient group ($p = 0.001$; Table 5). Moreover, the prevalence of objective olfactory dysfunction was significantly higher in mild forms compared with moderate-to-critical forms (36.6 *versus* 54.7; $p = 0.001$).

Table 4

Clinical Characteristics of Patients who benefited from Objective Olfactory Evaluations.

Characteristics	All patients with	Patient with Mild	Patient with MC	Differences
	Objective Evaluation	COVID-19 Form	COVID-19 Form	Mild vs MC
	(N = 233)	(N = 181)	(N = 52)	*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 (15.5à	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 Insuffisiency	3 (1.3)	2 (1.1)	1 (1.9)	NS
Kidney Insuffisiency	3 (1.3)	0 (0)	3 (5.8)	0.012
Respiratory insuffisiency	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

Characteristics	All patients with	Patient with Mild	Patient with MC	Differences
	Objective Evaluation	COVID-19 Form	COVID-19 Form	Mild vs MC
Diarrhea	105 (45.1)	73 (40.3)	32 (61.5)	0.001
Dyspnea	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 Sympotms (N - %)				
Self-reported anosmia	91 (39.1)	77 (42.5)	14 (26.9)	0.008
Rhinorrhea	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
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

Table 4 footnotes: *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. Abbreviations: MC=moderate-to-critical; NS=non significant; SD= standard deviation.

Table 5
Olfactory Outcomes of Patients who benefited from Objective Olfactory Evaluations.

Characteristics	All patients with	Patient with Mild	Patient with MC	Differences
	Objective Evaluation	COVID-19 Form	COVID-19 Form	Mild vs MC
	(N = 233)	(N = 181)	(N = 52)	*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	157	N = 130	N = 27	
Before the other symptoms	25 (15.9)	23 (17.7)	2 (7.4)	NS
Concomittant 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*	9 (5.7)	0 (0)	9 (33.3)	
Objective Olfactory Tests		N = 181	N = 52	
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

Table 5 footnotes: *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. Abbreviations:

MC=moderate-to-critical; NS=non significant; SD= standard deviation; SNOT-22= sino-nasal outcome-22 questionnaire.

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 follow-up, 18 anosmic/hyposmic patients did not objectively fully recover olfaction (15.3%).

Clinical and Objective Olfactory Associations

Among the cohort of 2,581 patients, there were no significant association between clinical data (biology, CT-scan findings) and the development of OD.

Among 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 nasal symptom severities; 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,[2,4,7,11–13] which raised the issue of the specificity and the predictive value of OD on the severity of the infection.

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.[14] 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%).[14] 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 of differences in the immune response to the infection in mild and moderate-to-critical patients. 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 Angiontensin Coverting Enzyme-2 (ACE2) and TMPRSS2,[15,16] 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.[17] 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.[18] Although a significant p-value, we need to remain cautious in the interpretation of this results for two reasons. On the one hand, the association is significant but exhibited a low correlation coefficient (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 75–85%. 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, while one third did not recover within the 45 days. Typically, OD occurring as part of the common cold is related to nasal congestion, rhinorrhea, olfactory cleft edema 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,[15,19] the OD could be additionally associated with injury of the olfactory neuroepithelial and a virus spread into the olfactory bulb where sustentorial cells and; in some patients, stem neurons express ACE2 and TMPRSS2. Because the expression of ACE2 and TMPRSS2 varies between individuals,[20] 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.[21] 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.[22]

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 terms 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 fiberoptic 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 follow-up, 75–85% 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.

Declarations

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Figures

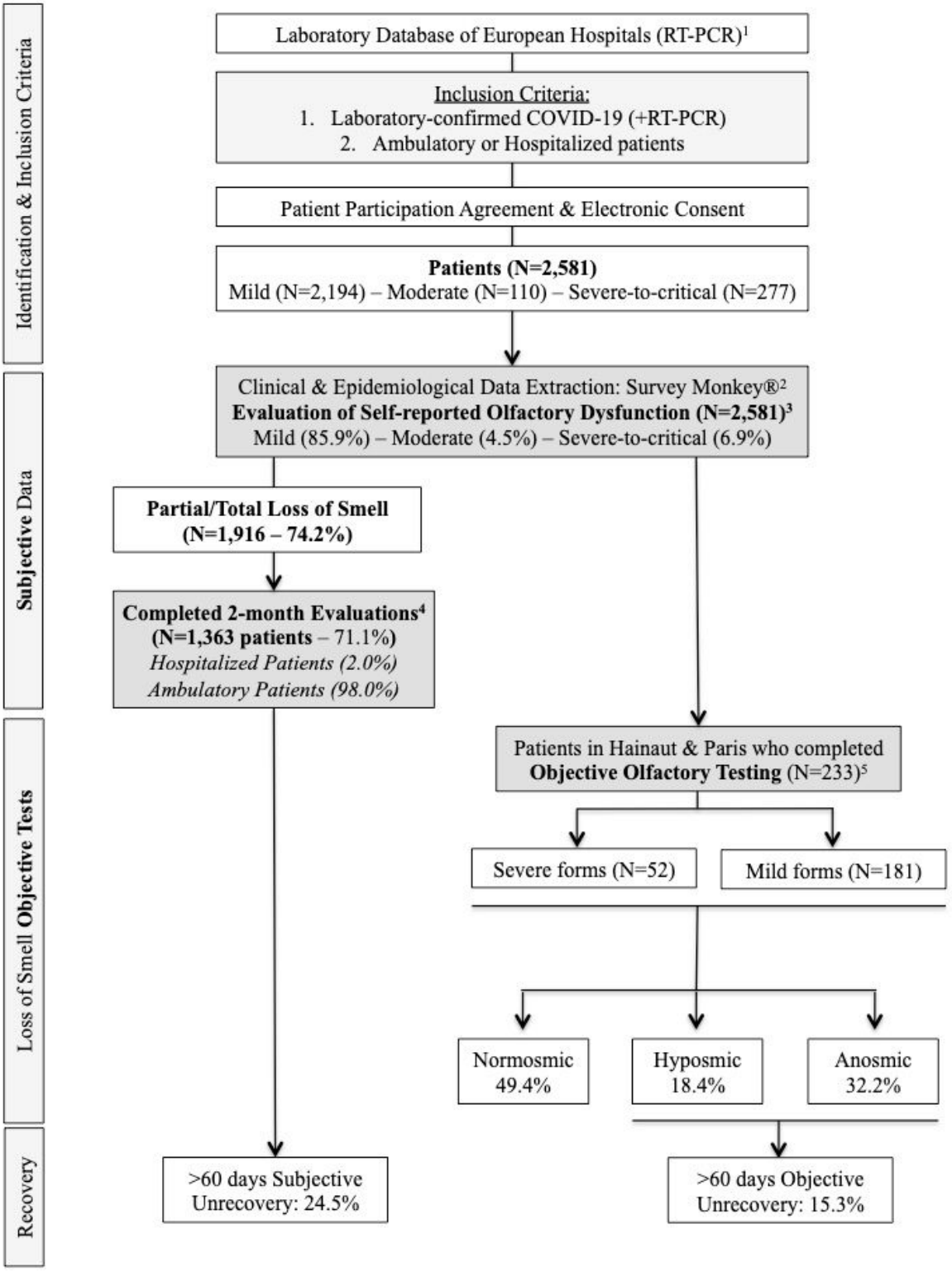

Figure 1

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 while 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=2,581).

4The second objective of the study was to investigate the recovery of olfaction, which was made on 1,363 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 2,581 included patients. Abbreviations: COVID-19= coronavirus disease 2019; RT-PCR= reverse transcription polymerase chain reaction.