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Prevalence and 24-month recovery of olfactory dysfunction in COVID-19 patients: A multicentre prospective study

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Objective. To investigate the prevalence and recovery of olfactory dysfunction (OD) in COVID-19 patients 24 months after the infection.

Methods. From 22 March 2020 to 5 June 2022, 251 COVID-19 patients were followed in three European medical centres. Olfactory function was assessed with subjective patient-reported outcome questionnaires and odour identification tests at baseline, 6, 12, 18 and 24 months postinfection. The predictive values of epidemiological and clinical data were investigated with multivariate analysis.

Results. One hundred and seventy-one patients completed the evaluations. The odour identification test revealed that 123 patients (50.8%) had OD at baseline. The prevalence of persistent psychophysical abnormalities at 6, 12, 18 and 24 months post-COVID-19 was 24.2%, 17.9%, 5.8% and 2.9%, respectively ($p = 0.001$). Parosmia occurred in 40 patients (23.4%) and lasted 60 ± 119 days. At 2 years, 51 patients (29.8%) self reported that their olfaction was unnormalised. Older patients had better odour identification evaluations at baseline ($p < 0.001$) but those with OD reported lower odour identification test scores at the end of the follow-up. Parosmia occurred more frequently in young patients. The olfactory training was significantly associated with higher values of Sniffin' Sticks tests at 18 months postinfection ($r_s = 0.678$; $p < 0.001$).

Conclusion. Two years post-COVID-19, 29.8% of patients reported persistent OD, but only 2.9% had abnormal identification psychophysical evaluations.

Keywords: anosmia, coronavirus, COVID-19, hyposmia, olfactory, otolaryngology, recovery, rhinology, SARS-CoV-2, serology, smell

Introduction

As of 5 June 2022, there were 528,816,317 cases of coronavirus disease 2019 (COVID-19) worldwide, including 6,294,969 deaths [1]. Olfactory dysfunction (OD) is one of the most common symptoms of COVID-19, accounting for 30%–86% of cases [2, 3]. The development of OD may be associated with olfactory cleft oedema and injuries of the olfactory neuroepithelium [4–7]. Although most patients recover the sense of smell within a few weeks, several authors have reported a significant rate of long-term OD [8–10]. Only a few authors have investigated the prevalence of OD 1 year after infection with objective methods [11–13], and there are no studies with 2-year follow-up. Long follow-up is essential to obtain a reliable estimate of the prevalence of persistent OD. Indeed, over the past decades, it has been found that spontaneous olfaction recoveries may occur between 1 and 2 years post viral infections [14, 15]. Furthermore, there

was no prospective study with repeated evaluations over a long follow-up time.

In the present study, we investigated the prevalence and predictive factors of persistent OD in COVID-19 patients of the first European wave 2 years after the infection.

Methods

The local ethics committee approved the study protocol (EpiCURA-2020-2303). Electronic informed consent was obtained.

Setting and patients

From 22 March 2020 to 3 June 2020, 251 patients with laboratory-confirmed diagnosis of COVID-19 (reverse transcription polymerase chain reaction) were included in the present study. Patients were recruited from three general hospitals (EpiCURA Hospital [Baudour, Belgium], CHU Saint-Pierre [Brussels, Belgium] and Foch Hospital [Paris, France]). The disease severity of patients was defined as mild, moderate, severe or critical according to the COVID-19 Disease Severity Scoring of World Health Organization [16]. Mild cases did not have viral pneumonia or hypoxia and were commonly home managed and followed. Moderate COVID-19 patients had clinical signs of pneumonia (e.g., fever, cough, dyspnea, fast breathing) but no sign of severe pneumonia (including $SpO_2 \geq 90\%$ on room air). Cases were defined as severe if they presented with clinical signs of pneumonia associated with one of the following outcomes: respiratory rate >30 breaths/min, severe respiratory distress or $SpO_2 < 90\%$ on room air. Individuals with critical disease had acute respiratory distress syndrome, sepsis or septic shock and were hospitalised in the intensive care unit.

Patients with OD before the infection (e.g., postviral, post-traumatic, nasal polyposis) and those who had a second COVID-19 infection throughout the follow-up were excluded. The OD term was defined as a patient self-reported OD, which may include subjective partial or total loss of smell or modified odours. Patients were not treated with topical or oral corticosteroids. Note that at each follow-up consultation, patients were carefully examined to exclude otolaryngological conditions that may influence the olfactory function (i.e., rhinitis, rhinosinusitis or any nasal disorders). In cases of acute nasal disorders, the evaluation was delayed.

Epidemiological and clinical data

Epidemiological and clinical data were collected with a standardised online questionnaire at the end of the disease, which was defined as general symptom resolution or at hospital discharge. The details of the prospective data collection have been described in previous studies [17, 18]. The following epidemiological and clinical outcomes were considered: age, gender, ethnicity, comorbidities and tobacco consumption. The prevalence and severity of patients were investigated with the COVID-19 Symptom Index, which is a 26-item patient-reported outcome questionnaire assessing common COVID-19 symptoms [19]. With the exception of the loss of smell and taste, the symptom severity was assessed as 0 (no symptom), 1 (mild symptom), 2 (moderate symptom), 3 (severe symptom) and 4 (very severe symptom). The olfactory function was instead self assessed as unchanged (score 0), partially lost (score 1) or completely lost (score 2). The total COVID-19 Symptom Index score ranges from 0 to 100. The nasal symptoms were assessed with the French version of the Sinonasal Outcome Tool 22 (SNOT-22) [20].

Olfactory evaluations

The olfactory and gustatory questions were described in the smell and taste component of the National Health and Nutrition Examination Survey [21]. The impact of OD on quality of life was evaluated with the French version of the short version of Questionnaire of Olfactory Disorders—Negative Statements (QOD-NS), which is a seven-item patient-reported outcomes questionnaire assessing the impact of smell changes on quality of life [22]. The total scale ranged from 0 (important impact on quality of life) to 21 (no impact on quality of life).

All patients underwent odour identification test evaluations with the Sniffin' Sticks tests (Medisense, Groningen, The Netherlands) to identify OD. The assessment of olfactory function was performed at baseline, within 2 weeks of the onset of OD. The olfactory evaluations were repeated for anosmic or hyposmic patients at 6, 12, 18 and 24 months postinfection until scores returned to the normal range. Sniffin' Sticks tests are a standardised and validated psychophysical olfactory evaluation (odour identification) using 16 smell pens. The individual had to identify the adequate term describing the smell between four given options [23]. The identification score ranges from 0

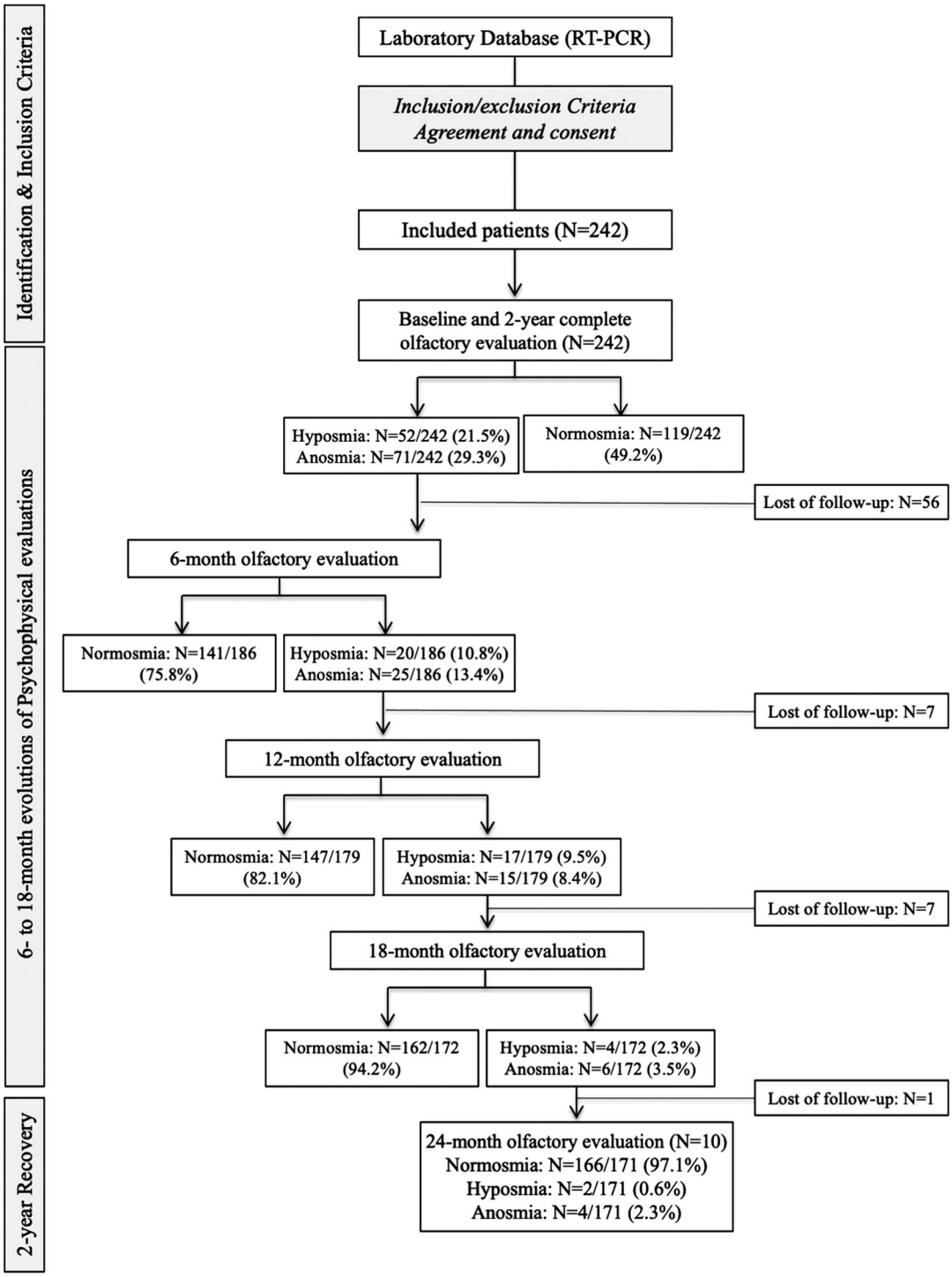

Fig. 1 *Flow chart. The percentages of hyposmia, anosmia and normosmia patients were calculated among patients who completed all evaluations. Abbreviations: COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription polymerase chain reaction.*

(no olfaction) to 16 (perfect olfaction). Depending on the score obtained, patients can be classified into the following categories: normosmia (score between 12 and 16), hyposmia (score between 9 and 11) and anosmia (score <9) [23]. At the end of the follow-up period (2 years), all patients were surveyed about their self perception of smell sense. They had to determine whether their olfaction was normalised or not.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, v23.0; IBM Corp, Armonk, NY, USA). The evolution of odour identification test scores was studied with the Wilcoxon signed-rank test. The relationship between epidemiological, clinical and olfactory outcomes was analysed with multivariate analysis.

Results

A total of 242 patients were enrolled in the study. Nine patients were excluded because they had another cause of OD or suffered from a second episode of COVID-19 during the follow-up. Seventy-one patients were lost during the study period and were, therefore, excluded from the analyses. There were no significant differences in the epidemiological and clinical features between dropout patients (mean age = 44.6 ± 18.6 years old; 44 females [62%]) and those who completed the evaluations. The study included 171 patients who completed the evaluations (Fig. 1). Among them, 130 patients had mild-to-moderate COVID-19 forms, while 41 individuals had severe-to-critical COVID-19. The mean age was 45.0 ± 12.0 years old. There were 120 females (70%) and 51 males (30%). The following ethnicities were included: Caucasian (93%), African (4%), South American (2%) and Asian (1%). The most common comorbidities included hypertension (13%), reflux (13%), asthma (9%) and allergy (9%) (Table 1). The prevalence of general symptoms is reported in Table 2. The mean COVID-19 Symptom Index was 16.0 ± 13.5.

Table 1. *Epidemiological and clinical characteristics of patients*

Characteristics	Patients *N*, 171
Age (years—mean, SD)	45.0 ± 12.0
Gender (F/M)	120/51
Ethnicity	
Caucasian	159 (93)
African	6 (4)
East Asian	2 (1)
South American	4 (2)
Comorbidities	
Hypertension	23 (13)
Current smoker	14 (8)
Asthma	15 (9)
Diabetes	13 (7)
Reflux disease	23 (13)
Heart problems	6 (4)
Kidney insufficiency	0 (0)
Neurological disease	1 (1)
Respiratory insufficiency	0 (0)
Liver insufficiency	1 (1)
Thyroid disorder	13 (8)
Rhinitis	11 (6)
Active allergy	15 (9)
Auto-immune disease	1 (1)

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

Prevalence and evolution of OD

At baseline, 128 patients (75%) self reported partial or total loss of smell (Table 3). Dysgeusia, which was defined as the impairment of salty, sweet, bitter and sour, was reported in 65% of cases (Table 2). According to the questions of the National Health and Nutrition Examination Survey, 112 (65%) individuals reported flavour dysfunction (i.e., total or partial loss or distortion of flavour). OD mainly occurred after the other COVID-19 symptoms (Table 3). The mean scores of SNOT-22 and the short version of QOD-NS are reported in Table 3. The baseline mean score of identification for Sniffin' Sticks tests was 10.5 ± 3.7. Note that the dropout patients reported a mean score of identification for Sniffin' Sticks tests of 7.0 ± 3.0, which did not significantly differ from the group of patients who completed the follow-up assessments.

According to the thresholds of identification for Sniffin' Sticks tests, the prevalence of OD was 50.8% at baseline. Precisely, there were 52 (21.5%) and 71 (29.3%) patients with hyposmia and anosmia, respectively. The prevalence of anosmia

Table 2. *General symptoms of patients*

Characteristics	*N* (%)	M (SD)
COVID-19 Symptom Index outcomes (*N*, %)		
Fever (>38°C)	77 (45)	0.8 ± 1.3
Asthenia	135 (79)	2.0 ± 1.5
Cough	96 (56)	1.0 ± 1.3
Chest pain	68 (40)	0.6 ± 1.1
Anorexia	93 (54)	1.2 ± 1.6
Arthralgia	74 (43)	0.7 ± 1.3
Myalgia	99 (58)	1.0 ± 1.3
Headache	111 (65)	1.2 ± 1.3
Diarrhoea	78 (46)	0.7 ± 1.1
Abdominal pain	61 (36)	0.4 ± 0.8
Nausea, vomiting	57 (33)	0.4 ± 0.9
Conjunctivitis	61 (36)	0.4 ± 0.8
Urticaria	45 (26)	0.2 ± 0.7
Dyspnea	82 (48)	0.8 ± 1.2
Sticky mucus/phlegm	64 (37)	0.4 ± 1.0
Nasal obstruction	101 (59)	0.8 ± 1.0
Rhinorrhoea	97 (57)	0.7 ± 1.0
Nasal burning	54 (32)	0.6 ± 1.0
Throat pain	63 (37)	0.4 ± 0.8
Ear pain	62 (36)	0.3 ± 0.7
Face pain/heaviness	57 (33)	0.3 ± 0.7
Dysphagia	46 (27)	0.2 ± 0.8
Dysphonia	69 (40)	0.5 ± 1.0
Tongue burning	18 (11)	0.3 ± 0.7
Self-reported total loss of smell	128 (75)	1.6 ± 1.8
Taste dysfunction	112 (65)	0.9 ± 1.1
COVID-19 Symptom Index	-	16.0 ± 13.5

Abbreviations: COVID-19, coronavirus disease 2019; M, mean; N, number; SD, standard deviation.

Table 3. *Olfactory outcomes*

Short version of QOD-NS	M (SD)
1. Feeling of social isolation	2.1 ± 0.8
2. Problem performing daily-life activities	2.0 ± 0.9
3. Anger related to sensory changes	1.9 ± 1.0
4. Less visits to the restaurant	1.7 ± 1.2
5. Less eating	1.6 ± 1.1
6. Difficulty relaxing	2.1 ± 0.8
7. Worrying about never getting used to olfactory changes	1.3 ± 1.1
Short version of QOD-NS	10.2 ± 6.6
SNOT-22 total score	32.9 ± 21.6
Flavour dysfunction (retro-olfaction)	
Total loss of flavour perception	47 (27)
Partial loss of flavour perception	42 (25)
Distortion	23 (13)
No problem	57 (33)
Missing data	2 (1.2)
Baseline smell dysfunction	
Parosmia	66 (38.6)
Phantosmia	33 (19.3)
Onset of smell dysfunction	
Before the other symptoms	25 (15)
Concurrent with other symptoms	52 (30)
After the other symptoms	73 (43)
Did not remember/missing data	21 (12)

Abbreviations: M, mean; QOD-NS, Questionnaire of Olfactory Disorders—Negative Statements; SD, standard deviation; SNOT-22, Sinonasal Outcome Tool 22.

significantly decreased to 13.4%, 8.4%, 3.5% and 2.3% after 6, 12, 18 and 24 months, respectively, post-COVID-19 ($p = 0.001$). The hyposmia prevalence significantly decreased throughout follow-up to reach 0.6% of patients at 2 years. According to Sniffin' Sticks tests, 97.1% of patients were considered normosmic at 2 years (Fig. 1). Patients completed an olfactory training protocol [16] until complete recovery of smell (twice daily training with daily-life odours or essential oils). The mean duration of olfactory training was 16.1 ± 19.11 weeks. The mean delay of patient-reported recovery of sense of smell was 23.4 ± 23.9 weeks. Phantosmia occurred in 28 patients (16.4%) and lasted 79.0 ± 181 days. Forty patients (23.4%) reported parosmia throughout the 2-year follow-up period, which lasted 60 ± 119 days. At the end of the follow-up, 23 patients (13.4%) reported that they were able to smell something (an odour) but were not able to identify the odour (for example, vanilla). At the end of the follow-up period (2 years), 51 patients (29.8%) self reported that their olfaction was still unnormalised.

Clinical and objective olfactory associations

The multivariate analysis reported significant positive associations between age and the following outcomes: baseline odour identification test evaluations ($r_s = 0.244$; $p < 0.001$) and the short version of the QOD-NS ($r_s = 0.228$; $p = 0.005$). The association between age and odour identification test evaluations was significant and negative 2 years post infection ($r_s = -0.380$;

$p = 0.019$), meaning that older patients with persistent OD had lower odour identification test evaluations at the end of the follow-up. Moreover, age was negatively associated with the occurrence of parosmia ($r_s = -0.259$; $p = 0.019$) during the follow-up period. The result of the baseline Sniffin' Sticks tests was predictive of the 6- ($r_s = 0.579$; $p < 0.001$) and 12-month ($r_s = 0.465$; $p = 0.013$) Sniffin' Sticks tests. The olfactory training was significantly associated with higher values of Sniffin' Sticks tests at 18 months post infection ($r_s = 0.678$; $p < 0.001$). There was a significant positive association between the duration of olfactory training and the value of the 18-month Sniffin' Sticks tests ($r_s = 0.552$; $p = 0.001$). According to the low number of patients with OD at 24 months post-COVID-19, the association analysis between 24-month odour identification test evaluations and outcomes was not performed. Regarding comorbidities, the presence of hypertension was associated with a lower risk of parosmia throughout the follow-up period ($p = 0.026$).

Discussion

The recovery process of olfactory function may vary from one patient to another. Before the pandemic, it was commonly suggested that the recovery of patients with 2-year postviral OD persistence remains uncertain [14, 15]. To the best of our knowledge, the present study is the first to report the 2-year recovery rate of COVID-19 patients with OD.

According to identification psychophysical olfactory evaluations, the prevalence of OD significantly decreased from 50.8% (baseline) to 18.7% (1 year) and 3.5% (2 years). The persistence of OD and related abnormal psychophysical tests more than 1-year post-COVID-19 was supported in the study by Ferreli et al., who reported 15.1% and 13.1% of persistent OD at 12 and 18 months post-COVID-19 according to a self-reported smell score [24]. In the study by Fortunato et al., 70% of patients still had OD 1-year post-COVID-19 [25], while Boscolo-Rizzo et al. observed 46% of abnormal psychophysical tests after a median of 401 days post-COVID-19 [12]. Among the patients with psychophysical olfactory disorders, these authors reported 7% of anosmic patients 1 year post infection. The lower rate of 1-year psychophysical testing abnormalities in the present study was probably related to the use of the odour identification test only, while Boscolo-Rizzo et al. used full threshold, discrimination and identification (TDI) assessment. The odour identification part of the TDI consists of a screening tool and may be associated with limited test–retest reliability. Indeed, in the Spanish validation of Sniffin' Sticks olfactory test (TDI), Delgado-Losada et al. reported a moderate test–retest reliability value of the identification test ($r_s = 0.69$) using Pearson and intraclass coefficient correlation [26], while Haehner et al. reported a value of 0.88 [27]. Similar limited reliability of the identification test was found in children and adolescent populations with an intraclass correlation coefficient of 0.83 in the study by Marino-Sanchez et al. [28].

In the present study, we observed that parosmia occurred in 40 patients (23.4%) and lasted a mean of 60 days, which corroborated the findings of Ferreli et al., who reported 23.1% of parosmia at 18 months post-COVID-19 [24]. The multivariate analysis reported that older patients had OD less frequently than young patients. A higher proportion of OD in young compared with older COVID-19 patients was reported in another study [29]. The lower odour identification tests of older subjects at 2 years were an original observation, which was not yet reported in COVID-19-related OD. However, it is known that older patients exhibit more pronounced olfactory loss [30] and more general disturbance of olfactory function [31] than the young. Thus, our 2-year age-related results may highlight more potential baseline differences in olfactory function between young and old individuals than differences in the recovery process [31].

Olfactory training is commonly proposed to patients with postviral loss of smell. In this study, we observed that the adherence to an olfactory training protocol was significantly associated with higher values of Sniffin' Sticks test scores at 18 months post infection. The efficacy of olfactory training in COVID-19 patients was supported by a recent meta-analysis, but this paper only included studies investigating short-term recovery (<1 year) [32]. The present paper may suggest a positive impact of olfactory training over the mid-to-long term, but future controlled studies are needed. The lack of use of the TDI test (48 pens) is the main limitation of the present study. Indeed, TDI provides identification, threshold and discrimination data to the physician who has more details about the characteristics of the smell disorder compared with only an identification test. TDI was not used because the realisation of psychophysical olfactory

evaluations was difficult at the time of the pandemic according to the patient consultation restrictions in the hospitals of our country. The lack of use of TDI may probably support the poor agreement between subjective and psychophysical identification evaluations. In addition to the use of incomplete olfactory testing, the lack of evaluation of all participants at all time points may result in a selection bias associated with a positive outcome. Indeed, it is conceivable that some patients with significant improvement in Sniffin' Sticks tests may develop some delayed OD, such as parosmia [33]. Future studies are needed to follow all patients throughout the follow-up period, including those who reported normalisation of smell sense. Note that the low number of dropout patients due to re-infection is probably related to the high vaccine cover in our region and the decreased risk of re-infection in vaccinated individuals. The legal requirement to wear a mask in our region may be an additional factor. Another explanation should be the decrease in the severity of the disease presentation and the related lack of screening tests for patients. Indeed, COVID-19 related to Omicron variants is characterised by less symptom severity and a lower proportion of OD compared with wild, alpha or delta variant forms [34]. The lower proportion of OD, which remains a typical symptom of the disease, and the low severity of the disease may lead to a reduction of self screening and, therefore, detection of second re-infection in some patients. Interestingly, the lower rate of OD in variants was supported by the recent study by Hintschich et al., who reported that the wild SARS-CoV-2 type was associated with a higher prevalence of hyposmia (73%) according to patient self reports and psychophysical testing compared with alpha (41%) or delta (48%) variants [35]. These observations were corroborated in the study by Boscolo-Rizzo et al., where the prevalence of OD in patients who were infected with the Omicron variant was above 30% [34].

The quarantine/infection-related restrictions limited us in the realisation of nasofibroscopy and imaging at the time of inclusion. The smell function evaluation had to be rapid and the contact between physicians and patients too. The high number of patients who were lost by follow-up is an additional weakness because we cannot state whether these patients recovered or not. Another limitation is related to the delay (1–2 weeks) between the OD onset and the realisation of the olfactory evaluations. This delay was particularly long in hospitalised patients who had to be able to undergo olfactory psychophysical evaluations. The delay between the onset of symptoms and the objective olfactory testing may underestimate the incidence of OD. The use of the same identification test throughout the study may be associated with a memory effect. However, to avoid this bias, we never gave the answer of odour testing to patients, which reduces the risk of bias. Another potential limitation is the recruitment of patients from three different hospitals. Indeed, the prevalence of OD and the patient features may vary from one region to another. The high number of patients who completed the evaluation is the main strength of our study. Nowadays, there are no similar studies assessing the olfactory function at several time points (6, 12, 18 and 24 months).

Conclusion

According to the method of assessment, the 2-year post-COVID-19 prevalence of OD ranged from 2.9% to 29.8% of patients. Future studies are needed to evaluate whether OD may resolve beyond the 2-year time point.

Conflict of interest

The authors have no conflict of interest.

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