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ORIGINAL CONTRIBUTION

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Prevalence of smell and taste dysfunction in different clinical severity groups of COVID-19 patients*

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Abstract

Background: Studies on the long-term prevalence of smell and taste impairment concerned with severe disease in the acute phase of COVID-19 are limited. The aim of our study was to assess and compare psychophysical testing and self-reported smell and taste disturbances and recovery between three patient groups suffering from critical, severe, or mild COVID-19 in a follow-up at six-months after the acute phase.

Methodology: The prospective controlled study of 227 participants comprised 72 intensive-care-unit-treated (ICU-treated), 53 pulmonology- or infectious-diseases-ward-treated (WARD-treated), and 48 home-isolated patients (HOME) with preceding COVID-19, and 54 individuals with no history of COVID-19 (CONTROL). All participants visited a follow-up clinic for a sense-of-smell screening and underwent Magnetic Resonance Imaging (MRI) of the brain, olfactory bulbs and sinonasal area at six months after acute disease. Before the follow-up visit, the participants received a questionnaire concerning smell and taste function. We sent a supplementary questionnaire including questions about phantosmia and parosmia and taste recovery at a median of 502.5 days after the acute phase.

Results: We found no statistically significant differences between the groups in the incidence of smell and taste dysfunction, recovery, or the occurrence of parosmia or phantosmia. There were no statistically significant differences in semi-objective smell performance across the different study groups and controls. The olfactory bulb volume was normal in all patients and controls. Mucosal thickening in paranasal sinuses was rare.

Conclusions: We found no difference in a six-month follow-up in the subjective or semi-objective senses of smell and taste between three severity groups of COVID-19 and controls.

Key words: COVID-19, smell dysfunction, different clinical severity groups, olfactory bulb volume, Sniffin' Sticks Test

Introduction

Impaired sense of smell/taste is one of the most prevalent symptoms reported by patients after COVID-19 [(1)]. Self-reported resolution of smell dysfunction occurs in most patients within two weeks of infection [(2)], but recent studies have demonstrated that in 7% of patients, anosmia persisted longer than one year, and in 2.5% of patients, two years after onset of COVID-19 [(3,4)]. In a two-year follow-up study, 88.2% of patients reported complete recovery in COVID-19-related smell and taste dysfunction [(4)]. These patients were mildly symptomatic in the acute phase of COVID-19. Parosmia, phantosmia, and dysgeusia are also reported in patients with mild or moderate infection [(5)]. Studies of long-term prevalence of smell and taste impairment have been published concerning patients with mild or moderate disease in

the acute phase of COVID-19, but to the best of our knowledge, data on patients with severe acute disease are insufficient.

The aim of our study was to assess and compare psychophysical testing and self-reported smell and taste disturbances and recovery between three patient groups suffering from critical, severe, or mild COVID-19 in a six-month follow-up and compare their results with non-covid controls. We also aimed to assess post-acute findings of Magnetic Resonance Imaging (MRI) of the olfactory bulbs and sinonasal area.

Patients and methods

We use the STROBE (strengthening the reporting of observational studies) guideline checklist for reporting our results. We carried out this study at Helsinki University Hospital in Helsinki, Finland. We recruited adult patients that had been treated in the Helsinki University Hospital intensive care units (ICU) to an ICU group (= critical COVID-19) and those treated in pulmonology or infectious diseases wards to a WARD group (= severe COVID-19). Patients included in this study had been receiving treatment between March 2020 and December 2020. We also recruited a group of home-isolated patients to a HOME group (= mild COVID-19) and persons without history of SARS-CoV-2 infection to a CONTROL group. Inclusion criteria were 1) a positive test for SARS-CoV-2 (for ICU, WARD, and HOME groups) by real-time polymerase chain reaction or positive antibody test, 2) age 18 or older, and 3) fluent in the Finnish language. Due to a concomitant study assessing neuropsychological recovery, we excluded patients with a diagnosis of a severe neurological or psychiatric comorbidity, severe impairment in hearing or vision, or developmental disability. We also excluded pregnant or lactating patients and, concerning the MRI, patients with contraindications for MRI (e.g. severe claustrophobia, cardiac pacemaker, or ferromagnetic fixation material in the body). Eligible ICU- and ward-treated patients were recruited by mailed invitation after hospital discharge or were directly contacted at the pulmonology or infectious diseases wards or follow-up clinic, and the home-isolated patients and non-covid controls were recruited via media announcements. In addition to the inclusion criteria used for ICU, WARD and HOME groups, the participants in the CONTROL group were only included if they had no history of COVID-19. All participants gave their written informed consent to participate in the study. The participants were treated according to the Declaration of Helsinki and its latest amendments throughout the study. The study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (HUS/1949/2020).

We collected data on clinical features and comorbidities from patient medical records.

All participants visited a follow-up clinic for a sense-of-smell screening. The timing of the visit was at a minimum of six months after hospital discharge for ICU and WARD patients, or, for HOME patients, a positive SARS-CoV-2 test. Before the follow-up visit the participants received a questionnaire concerning smell and taste function before COVID-19, possible post-COVID-19 dysfunction, and smell recovery at six months after COVID-19 (Supplement 1). We sent a complementary questionnaire including questions about eventual phantosmia and parosmia and taste recovery (Supplement 2).

Questionnaires

In the first questionnaire we asked whether patients had experienced dysfunction in sense of smell and/or taste (sweet, salty, sour, bitter) before COVID-19, post-COVID-19, and six months after recovery from COVID-19, and whether smell dysfunction had recovered by six months. We used a modified version of the National Health and Nutrition Examination Survey (NHANES 2013-2014: Taste & Smell Data Documentation, Codebook, and Frequencies (cdc.gov) [6]. The questionnaires were sent to the patients of the ICU, WARD, and HOME group.

Since many patients mentioned in the free-text space of the questionnaire that they had had symptoms typical of parosmia or phantosmia, we subsequently sent a complementary questionnaire to participants in autumn 2021, which included questions about eventual phantosmia and parosmia and taste recovery.

Smell test

We performed a semi-objective smell assessment on all study subjects using the Sniffin' Sticks Screening 12 Test (SST-12). SST-12 is based on a 16-item odour smell test with Sniffin' Sticks [7,8]. It is used for screening of smell dysfunction in clinical practice. There are 12 common odours and identification is performed by naming the odour from multiple-choice lists of four alternative odours. The test result is the sum of the correctly identified odours. Scores from 0 to 6 indicate anosmia, 7–10 hyposmia and 11–12 normosmia. We performed the test for each nostril separately. For analyses, we used the result from the better nostril in cases where patients attained different scores between nostrils. If the patient's sense of smell was reduced at 6 months, we advised the patient to start smell training [9].

MRI

The subjects underwent MRI of the brain, olfactory bulbs, and sinonasal area at six months after acute disease. We performed all imaging with a Philips Ingenia 3T (Philips Healthcare, Best, Netherlands) scanner and a 32-channel head coil. We assessed the olfactory bulbs from a coronal-fat-suppressed T2-weighted Turbo Spin Echo (TE 80 ms, TR 4200 ms, in-plane resolution 0.5 x 0.6 mm, slice thickness 2 mm, 48 slices, TSE-factor 15, and SENSE parallel imaging factor 1.5), and we acquired an axial heavily T2-weighted 3D DRIVE sequence (TE 120 ms, TR 2000 ms, in-plane

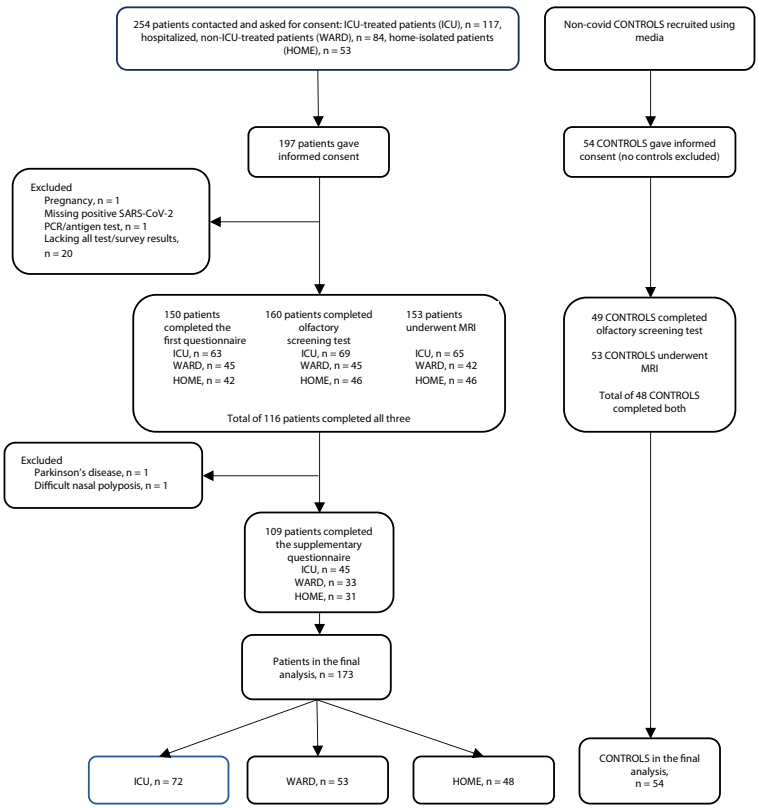

Figure 1. Flow chart showing the number of subjects included in the final analyses of three different clinical severity groups of COVID-19 and the control group. MRI = Magnetic Resonance Imaging.

resolution 0.4 x 0.55 mm, acquired slice thickness 1 mm, 100 slices, TSE factor 56, and compressed sensing 4.5) for assessing the olfactory bulb.

We performed the volumetry with 3D Slicer [9,10]. We coregistered the T2-weighted fat-suppressed images with the T2-weighted 3D DRIVE images by using General registration "BRAINS" [11]. We performed manual segmentation with the Editor module [9,10] with the T2-weighted 3D DRIVE as the main volume, but we used the T2-weighted fat-saturated sequence as support. We obtained the volume with the Label statistic module [9,10]. We visually evaluated the mucosal thickening of upper nasal cavities (superior meatuses), ethmoidal cells, and other sinuses using T2-weighted fat-saturated axial and coronal sequences, with a thickening more than very mild considered to be a positive finding. Two neuroradiologists, one of whom was specialized in analysing otorhinolaryngology images, performed the analyses.

Statistical methods

We used a convenience sample of participants with no a priori power calculation. We reported categorical variables as numbers and percentages and continuous variables as medians and interquartile ranges. We compared categorical variables between groups using either a Chi-squared test or Fisher–Freeman–Halton Exact test, when appropriate. We compared continuous variables between groups using a Mann–Whitney U-test. We used Spearman´s correlation for assessing correlations. We considered $p < 0.05$ to be statistically significant. We performed the analyses using SPSS version 28 for Windows (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Altogether, we included 173 participants with preceding COVID-19: 72 in the ICU, 53 in the WARD, and 48 in the HOME groups, and 54 individuals in the CONTROL group. Figure 1 shows the study flow chart.

Patient characteristics and past medical history of all COVID-19 patients and non-COVID-19 controls are summarized in Table 1. The median length of hospitalization was 20 (IQR 14–28) days for the ICU group, and eight (IQR 5–11.5) days for the WARD group. Patients in the ICU group had more comorbidities than patients in other groups.

The median time from hospital discharge (ICU and WARD patients) or positive SARS-CoV-2 test (HOME patients) to receiving a response to the first questionnaire was 200 (IQR 184.5–211) days. The median time from COVID-19 diagnosis to receiving a response to the supplementary questionnaire was 502.5 (IQR 478–521) days.

Table 1. Patient characteristics in three different clinical severity groups of COVID-19 patients and in the control group.

	ICU	WARD	HOME	CONTROL	p-value	All
Number of participants	72	53	48	54		227
Gender					0.002	
Female, n (%)	29 (40.3)	35 (66.0)	34 (70.8)	26 (48.1)		124 (54.6)
Age, years					< 0.001	
Mean ± SD	58.3 ± 11.7	56.6 ± 9.8	45.3 ± 13.4	55.3 ± 12.6		54.4 ± 12.8
Range	25-80	30-74	19-77	22-77		19-80
BMI, kg/m^2					< 0.001	
Mean ± SD	30.4 ± 5.5	28.5 ± 4.3	26.6 ± 4.1	NA		29.0 ± 5.0
Hypertension, n (%)	40 (55.6)	16 (30.2)	8 (19.0)	11 (22.0)	< 0.001	75 (34.6)
Dyslipidemia, n (%)	23 (31.9)	10 (18.9)	4 (9.5)	7 (14.0)	0.019	44 (20.3)
Heart disease*, n (%)	13 (18.1)	2 (3.8)	5 (11.9)	2 (4.0)	0.026	22 (10.1)
Diabetes, n (%)	17 (23.6)	5 (9.4)	2 (4.8)	1 (2.0)	< 0.001	25 (11.5)
Rheumatic disease, n (%)	8 (11.1)	0 (0.0)	0 (0.0)	1 (2.0)	0.004	9 (4.1)
Cancer, n (%)						
Remission	2 (2.8)	1 (1.9)	2 (4.8)	1 (2.0)	0.845	6 (2.8)
Active treatment	5 (6.9)	2 (3.8)	0 (0.0)	0 (0.0)	0.104	7 (3.2)
Pulmonary disease, n (%)						
Asthma	9 (12.5)	15 (28.3)	3 (7.1)	3 (6.0)	0.007	30 (13.8)
COPD**	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	0.148	2 (0.9)
Sleep apnoea	11 (15.3)	3 (5.7)	2 (4.8)	1 (2.0)	0.050	17 (7.8)
Neurological disease, previous stroke or TIA***, n (%)	1 (1.4)	1 (1.9)	2 (4.8)	1 (2.0)	0.731	5 (2.3)

*Includes coronary artery disease, heart arrhythmias (i.e. chronic atrial fibrillation), heart failure, dilated cardiomyopathy, **Chronic Obstructive Pulmonary Disease, ***Transcient Ischemic Attac.

Sense of smell

At six months after recovery from COVID-19 with or without disturbance in their sense of smell during or after the entire illness 52.4% (33/63) in the ICU group, 42.2 % (19/45) in the WARD group and 52.4% (22/42) in the HOME group reported normal smell function. Smell function recovery and frequencies of parosmia and phantosmia are summarized in Table 2. Olfactory disturbance included either loss or deterioration of the sense of smell with possibly associated parosmia or phantosmia, or parosmia and/or phantosmia alone. We found no statistically significant differences between the groups in the incidence of smell dysfunction, recovery, or the occurrence of parosmia or phantosmia. Parosmia (63.2% (12/19) in the ICU group, 92.9% (13/14) in the WARD group and 73.3% (11/15) in the HOME group, $p = 0.02$) and phantosmia (80% (12/15) in the ICU group, 86.7% (13/15) in the WARD group and 86.7% (13/15) in the HOME group, $p < 0.01$) was more common in females in all patient groups.

Timing of parosmia and phantosmia varied between patients. According to answers in the supplementary questionnaire for patients experiencing either parosmia or phantosmia, 33.3% (7/21) in the ICU group, 65.0% (13/20) in the WARD group, and 55.0% (11/20) in the HOME group experienced parosmia and/or phantosmia during the first three months after COVID-19 diagnosis ($p = 0.172$). One patient reported parosmia after 18 months of acute infection without preceding smell symptoms.

Sense of taste

Frequencies of taste dysfunction (ageusia or hypogeusia) and recovery are summarized in Table 3. We found no statistically significant differences between the groups in the incidence of taste dysfunction and recovery. In the questionnaire 38.1% (24/63) in the ICU group, 60% (27/45) in the WARD group and 57.1% (24/42) in the HOME group reported having taste dysfunction after COVID-19. One WARD patient experienced dysgeusia (metal taste) without impaired ability to taste sweet, salty, bitter, or sour.

Of the patients reporting COVID-19-related taste disturbances in the first questionnaire, 8.3% (2/24) in the ICU group, 3.7% (1/27) in the WARD group, and no one in the HOME group reported persistent taste dysfunction in the supplementary questionnaire.

Table 2. Reported smell dysfunction, recovery, and prevalence of parosmia and phantosmia in three different clinical severity groups of COVID-19 patients during follow-up.

	ICU, n = 72	WARD, n = 53	HOME, n = 48	p-value	All, n = 173
Patients who completed the first questionnaire, n (at median time 200 days)	63	45	42		150
Patients who completed the supplementary questionnaire, n (at median time 502.5 days)	45	33	31		109
Problems with smell function after COVID-19 diagnosis (n = 150)				0.424	
Normal smell function, n (%)	25 (39.7)	12 (26.7)	11 (26.2)		48 (32.0)
Smell dysfunction, n (%)	36 (57.1)	30 (66.7)	30 (71.4)		96 (64.0)
Smell function unknown, n (%)	2 (3.2)	3 (6.7)	1 (2.4)		6 (4.0)
Prevalence of parosmia (n = 150), n (%)	19 (30.2)	14 (31.1)	15 (35.7)	0.945	48 (32.0)
Prevalence of parosmia in patients with smell dysfunction, (n = 96), n (%)	19 (52.8)	14 (46.7)	15 (50.0)	0.973	48 (50.0)
of which females, n (%)	12 (63.2)	13 (92.9	11 (73.3)	0.163	36 (75.0)
Prevalence of phantosmia (n = 150), n (%)	15 (23.8)	15 (33.3)	15 (35.7)	0.545	45 (30.0)
Prevalence of phantosmia in patients with smell dysfunction (n = 96), n (%)	15 (41.7)	15 (50.0)	15 (50.0)	0.885	45 (46.9)
of which females, n (%)	12 (80.0)	13 (86.7	13 (86.7)	1.000	38 (84.4)
Parosmia and phantosmia combined in patients with smell dysfunction (n = 96), n (%)	13 (36.1)	9 (30.0)	10 (33.3)	0.588	32 (33.3)
Smell function recovery in patients with COVID-19 (n = 96), time of first questionnaire Smell function normalized, n (%)	8 (22.2)	7 (23.3)	11 (36.7)	0.080	26 (27.1)
Smell function recovery in patients with COVID-19 (n = 96), time of second questionnaire Smell function normalized, n (%)	16 (44.4)	11 (36.7)	14 (46.7)	0.367	41 (42.7)

Smell test

The SST-12 odour identification test was completed by 209 participants (69/72 in the ICU group, 45/53 in the WARD group, 46/48 in the HOME group, and 49/54 in the CONTROL group). Prevalences of anosmia, hyposmia and normosmia in the different patient groups are presented in Table 4. There were no statistically significant differences in semi-objective smell performance across the different groups. Correlation of the Sniffin´Stick test result with age was statistically significant only in the CONTROL group (Spearman correlation coefficient -0.497, p< 0.001). We assessed the SST-12 result and its relation to the 10th percentile of healthy subjects [7] and found no statistically significant difference when comparing the patients with and without subjective impairment (associated parosmia or phantosmia, or parosmia and/or phantosmia alone) of smell performance.

MRI

Altogether, 90.3% (65/72) of patients in the ICU group, 79.2% (42/53) in the WARD group, 95.8% (46/48) in the HOME group, and 98.1% (53/54) in the CONTROL group underwent MRI. Except for one unilateral scar/atrophy in the olfactory bulb of a COVID-19 patient with perifocal frontobasal traumatic brain contusion, the olfactory bulb volume was normal in all patients and controls. Olfactory cleft opacification was seen in 4.6% of patients (3/65) in the ICU group, 9.5% (4/42) in the WARD group, 2.2% (1/46) in the HOME group, and 3.8% (2/53) in the CONTROL group. Mucosal thickening in ethmoidal, maxillary, frontal, and sphenoidal sinuses was rare, but statistically, the least mucosal thickening in ethmoidal sinuses was observed in the HOME group ($p < 0.037$). A summary of the MRI findings is provided in Table 5.

Discussion

In this observational study, comparing smell and taste disturbances with recovery between critical, severe, and mild COVID-19 patients, we found no statistically significant differences between the different severity groups in any assessment.

Table 3. Reported taste dysfunction and recovery in three different clinical severity groups of COVID-19 patients during follow-up.

	ICU, n = 72	WARD, n = 53	HOME, n = 48	p-value	All, n = 173
Patients who completed the first questionnaire, n (at median time 200 days)	63	45	42		150
Patients who completed the supplementary questionnaire, n (at median time 502.5 days)	45	33	31		109
Taste dysfunction during the 12 months before COVID-19 diagnosis (n = 150), n (%)				0.836	
Yes, n (%)	2 (3.2)	2 (4.4)	2 (4.8)		6 (4.0)
No, n (%)	58 (92.1)	42 (93.3)	39 (92.9)		139 (92.7)
Unknown, n (%)	3 (4.8)	1 (2.2)	1 (2.4)		5 (3.3)
Taste dysfunction after COVID-19 diagnosis, first questionnaire, n (%)				0.095	
Yes, n (%)	20 (31.7)	20 (44.4)	23 (54.8)		63 (42.0)
No, n (%)	42 (66.7)	23 (51.1)	18 (42.9)		83 (55.3)
Unknown, n (%)	1 (1.6)	2 (4.4)	1 (2.4)		4 (2.7)
Taste dysfunction after COVID-19 diagnosis, both questionnaires combined*, n (%)				0.058	
Yes, n (%)	24 (38.1)	27 (60.0)	24 (57.1)		75 (50.0)
No, n (%)	38 (60.3)	16 (35.6)	17 (40.5)		71 (47.3)
Unknown, n (%)	1 (1.6)	2 (4.4)	1 (2.4)		4 (2.7)
Recovery of taste function by the follow-up (n = 75)**, n (%)				0.368	
Recovered, n (%)	15 (62.5)	21 (77.8)	15 (62.5)		51 (68.0)
Not recovered, n (%)	2 (8.3)	1 (3.7)	0 (0.0)		3 (4.0)
Unknown, n (%)	7 (29.2)	5 (18.5)	9 (37.5)		21 (28.0)

*Twelve patients reported taste dysfunction only in the supplementary questionnaire (ICU n = 4, WARD n = 7, HOME n = 1), **Out of those patients who reported basic taste dysfunction in either questionnaire combined.

Comparing post-acute findings in MRI of the olfactory bulbs between critical, severe, and mild COVID-19 patients and non-covid controls, we found no statistically significant differences between the groups. When comparing post-acute findings of mucosal thickening in sinuses, there was, statistically, the least mucosal thickening in the ethmoidal sinuses of HOME group patients. Mucosal thickening of paranasal sinuses was rare in all groups.

We found no differences in the frequency of self-reported smell dysfunction or its recovery between the three patient groups. Smell function recovery was reported by 44.4%, 36.7%, and 46.7% of patients in the ICU group, WARD group, and HOME group, respectively. In another six-month follow-up study of 56 COVID-19 patients, 64.3% subjectively reported loss of smell at the time of COVID-19 diagnosis, but after six months, 69.6% reported normal smell function and 64.3% of patients were normosmic, as tested by the University of Pennsylvania Smell Identification Test (UPSIT) [12]. That study included six former ICU patients (11%) and three (5%) hospitalized non-ICU patients, and the analysis of smell test scores revealed no significant differences between ICU, hospitalized, and out-patients, but the ICU and hospitalized groups were small. In one other six-month follow-up of patients with self-reported loss of smell during the COVID-19 pandemic, 40.7% of patients reported full smell function recovery [13]. Our results are in line with these studies. In a systematic review and meta-analysis on self-reported alteration of smell or taste in 3563 COVID-19 patients, the prevalence of smell or taste dysfunction was 47% [1]. Severely symptomatic patients in the acute phase reported less smell dysfunction (31% prevalence) than those with mild to moderate symptoms (67% prevalence) [1]. In our study, we found no statistically significant differences between the different severity groups.

In our study the prevalence of parosmia in those patients with smell problems was about 50% in each group. The prevalence is slightly higher in our study than the 43.1% prevalence of parosmia in patients with smell loss in the Hopkins et al. study [13].

A prospective study of 1031 COVID-19 patients with mild to moderate disease revealed anosmia in 67.9% of cases, hyposmia in 30%, parosmia in 28.4%, and phantosmia in 18% [5]. After six months, a follow-up showed complete recovery occurred in 66% of cases and partial recovery in 22.1% of cases. In our

Table 4. Sniffin' Sticks Screening 12 Test results in three different clinical severity groups of COVID-19 patients at six months after acute disease and in the control group.

	ICU	WARD	HOME	CONTROL	All
Normosmia (11-12), n (%) mean score ± SD	27 (39.1) 11.30 ± 0.47	19 (42.2) 11.26 ± 0.45	28 (60.9) 11.54 ± 0.51	26 (53.1) 11.35 ± 0.49	100 (47.8) 11.37 ± 0.49
Hyposmia (7-10), n (%) mean score ± SD	38 (55.1) 9.24 ± 0.85	24 (53.3) 9.33 ± 0.82	15 (32.6) 9.13 ± 0.92	22 (44.9) 8.95 ± 1.17	99 (47.4) 9.18 ± 0.93
Anosmia (0-6), n (%) mean score ± SD	4 (5.8) 5.00 ± 1.41	2 (4.4) 3.50 ± 2.12	3 (6.5) 5.67 ± 0.58	1 (2.0) 5.00 ± 0.00	10 (4.8) 4.90 ± 1.37

p = 0.214, Scoring as follows: normosmia 11–12, hyposmia 7–10, anosmia ≤ 6.

Table 5. MRI findings – olfactory bulb and mucosal assessment in three different clinical severity groups of COVID-19 patients at six months after acute disease and in the control group.

	ICU n = 72	WARD n = 53	HOME n = 48	CONTROL n = 54	p-value	All n = 227
Patients who underwent the MRI, n	65	42	46	53		206 (n = 197 in olfactory bulb analysis)
Olfactory bulb volume, mean ± SD (mm^3)	65 ± 20	64 ± 21	65 ± 20	74 ± 21	0.067	68 ± 21
Excluded (n) *	6	2	1			9
Olfactory cleft opacification, n (%)	3 (4.6)	4 (9.5)	1 (2.2)	2 (3.8)	0.471	10 (4.9)
Mucosal thickening in ethmoidal sinuses, n (%)	7 (10.8)	8 (19.0)	1 (2.2)	10 (18.9)	0.026	26 (12.6)
Mucosal thickening in maxillary, frontal, and sphenoidal sinuses, n (%)	7 (10.8)	6 (14.3)	1 (2.2)	4 (7.5)	0.191	18 (8.7)

study, the prevalence of parosmia was on average 32% among all COVID-19 patients with or without smell problems, and this is similar to the 28.4% prevalence in the Teaima et al. study [5]. The prevalence of phantosmia among all patients with or without smell problems in our study was slightly higher than the 18% prevalence in the Teaima et al. study [5]. The prevalence of parosmia and phantosmia in females has been higher in some earlier studies, too [14-16].

In many studies, the self-rated disturbance of smell and taste have been considered in combination. The reliability of differentiating disturbances in the perception of basic taste and finer flavours has been questioned [17,18]. However, in our study, the recovery of taste was much better than that recovery of smell, suggesting that patients are able to differentiate between these two chemosensitive qualities. In the follow-up, taste dysfunction persisted in only a few patients. In another six-month follow-up study, the ability of patients to differentiate between sweet, salty, sour, and bitter tastes also improved from 60% to 97.2% [13].

Based on the SST-12 tests we conducted in our study, 5.8% of patients in the ICU, 4.4% in the WARD, 6.5% in the HOME, and 2% in the CONTROL group could be classified as functional anosmic. The mean hyposmia score (score 7–10) was over 9 in all patient groups and controls. The SST-12 test has been shown to be quick and reliable in screening large populations of post-COVID- 19 patients for smell dysfunction, especially in identifying anosmic patients [18]. Furthermore, in our study, the SST-12 test detected anosmic patients. In our study, prevalence of normosmia based on the SST-12 test was mostly seen in the HOME group (60%), who were younger than participants in other groups. It is known that there is a decrease in subjects' ability to identify odours after the age of 60.9 years [7].

In our study, MRI showed the olfactory bulb to be of normal volume in every patient except one with a history of trauma. Opacification of the olfactory cleft was uncommon. Detection of abnormalities in imaging may be time-dependent, which may explain the low frequency of such findings in our study [20]. According to a case report, resolution of olfactory bulb findings is rapid [21]. In a systematic review of imaging studies, opacification of the olfactory cleft with normal olfactory bulb morphology and signal intensity were the most common imaging findings in early (< 1 month from onset of anosmia) and late (> 1 month from onset of anosmia) COVID-19-induced smell dysfunction, while paranasal sinuses were normal in most cases [22]. Olfactory cleft opacification was detected in most anosmic patients with COVID-19 compared to the normal olfactory cleft in normosmic

controls, with resolution of olfactory cleft opacification correlating with improved sense of smell [22]. However, MRI also showed, similarly, that the olfactory cleft was normal in most cases with COVID-19-induced anosmia [23].

Causes of COVID-19-related anosmia are still unclear. ACE2 receptor expression levels are significantly high in the olfactory epithelium. Inflammation in this area can be one of the main reasons for the cause of anosmia. Although the olfactory neurons do not have ACE2 receptors, inflammation may propagate to these cells or stem cells through supported cells and cause damage to the olfactory bulb and central brain systems, hence resulting in anosmia [23].

Our study was conducted during the first and second waves of the pandemic when no typing of the virus variant was available, but when the Wuhan and, subsequently, Delta variants dominated. These results may not be generalizable to later variants [24].

The main strength of our study is that the study includes semi-objective and self-reported smell and taste disturbances and recovery according to the severity of acute disease in a long-term follow-up, as well as the comparison of these results with those of non-covid controls.
There are some limitations that need to be discussed. Smell and taste loss was first reported at the time of questionnaires, and recall bias cannot be ruled out and may differ between the groups. The sample size was small with no a priori power calculation, and type 2 error cannot be excluded. The response rate to the questionnaires was moderate, and we did not send the questionnaire to non-covid controls. We cannot exclude selection bias and volunteer bias. The CONTROL group did not undergo laboratory testing to rule out history of SARS-CoV-2 infection and thus we cannot rule out subclinical infection during the study. However, at that stage (during the 1st and 2nd wave), the disease was still not largely disseminated in the general population. The groups were composed differently, considering sex, age, and number of comorbidities. In the HOME group, there were proportionally more females than in the other groups. Such a female predominance was also found in the study of Giacomelli et al. [25], but this could reflect either gender differences in completing voluntary questionnaires or the risk of severe disease [25].

Conclusions

We found no differences in a six-month follow-up completed with supplementary questionnaire at 502.5 days in the subjective or semi-objective senses of smell and taste between three severity groups of COVID-19 and non-covid controls. At six months, MRI showed olfactory bulb volume to be normal in every patient and non-covid control.

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Authorship contribution

Concept and design: SV, JM, and JH. Collection of the data: IT and JH. Analysis and interpretation of the data: SV, IT, JM, LK, KG, AL, and JH. Statistical analysis of the data: IT, LK, JH. Drafting of the manuscript: SV. Critical revision of the manuscript for important intellectual content: IT, JM, LK, KG, AL, and JH. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

All participants gave their written informed consent to participate in the study. The participants were treated according to the Declaration of Helsinki and its latest amendments throughout the study. The study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (HUS/1949/2020).
All participants gave their written informed consent to participate in the study and for publication.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to data being comprised of patient protected health information but are available from the corresponding author on reasonable request.

Conflict of interest

AL reports consultancy for Viatris, Sanofi Pharma, and Novartis, all uninvolved in the submitted work.

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SUPPLEMENTARY MATERIAL

SUPPLEMENT 1

Date:
Patient's name or the research number of the patient:

7 questions concerning sense of smell and taste

Survey implementation: [ ] The research subject read and answered questions independently. [ ] The researcher or close relative read the questions and marked the research subject's answers. [ ] The researcher/next of kin marked the verbally given answers.
Carefully read each question and tick the appropriate answer option.

The next questions are about your (/your next of kin's) sense of smell.
During the 12 months before getting COVID-19 did you (/your next of kin) have a problem with your (/his/her) ability to smell, either as not being able to smell things or things not smelling the way they are supposed to?

	Option	Cross
1	Yes	
2	No	
9	I don't know	

1. How would you (/your next of kin) rate your (his/her) ability to smell now as compared to when you were (/he was/she was) 25 years old? Is it better, worse, or is there no change?

	Option	Cross
1	Better now	
2	Worse now	
3	No change	
9	Do not wish to answer	

2. After getting COVID-19, have you (/has he/has she) had a problem with your (/his/her) ability to smell, either as not being able to smell things or things not smelling the way they are supposed to?

	Option	Cross	
1	Yes		
2	No		Go to question 5
9	I don't know		Go to question 5

3. Is the problem with your ability to smell always there or does it come and go?

	Option	Cross
1	Yes	
2	No	
9	I don't know	

The next questions are about your (/your next of kin's) sense of taste.
4. During the 12 months before getting COVID-19 did you (/he/she) have a problem with your (/his/her) ability to taste sweet, sour, salty, or bitter foods and drinks?

	Option	Cross
1	Yes	
2	No	
9	I don't know	

5. After getting COVID-19 did you (/he/she) have a problem with your (/his/her) ability to ability to taste sweet, sour, salty, or bitter foods and drinks?

	Option	Cross
1	Yes	
2	No	
9	I don't know	

6. If your sense of smell had already deteriorated before you were diagnosed with COVID-19, do you know what caused it?

	Option	Cross
1	I have been diagnosed with polyps in the nose.	
2	I have had a serious injury to the head area (blow to the head area, fracture in the head or face area).	
3	The sense of smell worsened already with a previous flu.	
4	Other reason (in the space for extra comments below the table, enter what).	
5	The cause is unknown, although I have visited the doctor and have been in examinations.	
6	I don't know	

Free space for extra comments:

SUPPLEMENT 2

Dear Research patient!

You previously participated in a RECOVID study, in connection with which you answered questions about changes in your sense of smell, and you are also likely to have had your sense of smell tested during your visit. More information has since emerged on changes in senses of smell and taste associated with COVID-19 infection. We would like to ask you a few more supplementary questions so you can map out in more detail possible changes to these senses and your recovery from them. In addition to questions related to smell and taste, we also ask for some background information. Responding to the survey is voluntary.

Questions:

Weight: _____
Height: _____

1. The deterioration of sense of smell also affects sense of taste, causing the finer nuances of flavours to be eliminated. However, through the taste buds, we sense the basic tastes: sweet, salty, sour, and bitter. Since your COVID-19 diagnosis, have you (or your next of kin) had trouble tasting sweet, sour, salty, or bitter tastes in food or drinks?

1 There hasn't been any problem tasting the basic tastes during the whole period.
2 Basic tastes have been restored.
3 Basic tastes have not been restored.
4 The basic tastes are still there, but the finer flavours are still missing.
9 I can't say.

2. Have you experienced any distortion to your sense of smell, i.e. have the smells smelled normal (coffee smells like coffee, etc.)?

1 There has been no distortion to my sense of smell.
2 There has been distortion to my sense of smell.
9 I can't say.

3. Have you sensed fake odours, i.e. have you smelled odours that don't really exist and that others don't smell?

1 There have been no fake smells.
2 There have been fake smells.
9 I can't say.

4. If you have experienced distortion to your sense of smell or false smells, at what point did this appear?

At _____ months

5. When the distortion to sense of smell or the false smells appeared, then what was the general situation with the sense of smell?

1 The sense of smell was otherwise functioning normally.
2 The sense of smell was otherwise poor.
3 I couldn't smell anything other than these distorted or fake smells.
9 I can't say/I don't remember.

6. The sense of smell problem...
1 ...has now disappeared.
2 ...still bothers me.
9 I can't say.

7. If you wish, you can provide us with more information about your symptoms below: