RHINOLOGY

Psychophysical evaluation of chemosensory functions 5 weeks after olfactory loss due to COVID-19: a prospective cohort study on 72 patients

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Abstract

Purpose To evaluate the evolution of chemosensation via extended psychophysical testing in patients who suffered from sudden chemosensory loss due to coronavirus disease 2019 (COVID-19). Additionally, this study sought to determine whether odor threshold testing provided additional information on olfactory loss due to COVID-19 compared to the more common odor identification testing.

Methods Prospective cohort study of patients with sudden chemosensory loss since February 2020 and confirmed COVID-19 infection via RT-PCR or serology testing. Olfactory function was tested extensively using the "Sniffin Sticks" test battery. In addition, we screened gustatory perception and nasal cooling sensations using psychophysical tests.

Results Seventy-two patients completed the study. After a mean of 37 days, 37% of patients showed olfactory dysfunction, 7% were dysgeusic, and 48% showed signs of low sensitivity for cooling sensation. A longer duration of anosmia before smell improvement was correlated with lower olfactory function at 5 weeks. Odor threshold detection was more affected by COVID-19 compared to odor identification.

Conclusion Five weeks after developing sudden chemosensory loss due to COVID-19, a high proportion of patients were dysosmic and showed signs of low nasal cooling sensitivity, whereas most of them had normal taste function. SARS-CoV-2 affected mainly odor thresholds, possibly suggesting that the major cause of loss of smell lies at the level of the olfactory neuroepithelium, rather than in the central nervous system.

Keywords Chemosensory loss · Psychophysical test · COVID-19 · SARS-CoV-2

Introduction

Since the outbreak of the coronavirus disease 2019 (COVID-19) in December 2019 in China, sudden chemosensory loss (SCL) as a presenting clinical symptom was slow to emerge. Mao et al. [1] reported smell and taste impairment in only 12 out of 214 hospitalized patients between January and mid-February. In contrast, as the disease progressed in Europe, reports of SCL accumulated rapidly with most of them based on surveys [2, 3]. Only a limited number of preliminary quantitative studies started evaluating olfactory and gustatory dysfunction (e.g., [4, 5]). Most of these studies relied solely on screening tests based on odor identification tasks because they are very easy to administer. However, it has been hypothesized that odor detection thresholds represent the function of the peripheral olfactory system to a higher degree than the central nervous processing of olfactory information. Although central nervous damage has also been described, respiratory viruses are expected to produce major damage at the level of the olfactory epithelium [6, 7]. Hence, evaluating detection thresholds may provide specific information on the olfactory loss due to SARS-CoV-2. Moreover, so far studies focused almost entirely on smell

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and taste and did not investigate the potential loss of trigeminal chemosensation (TCS). Although much less studied than olfaction and gustation, TCS plays a major role in daily life conveying sensations such as airflow, cooling, tingling, burning, or stinging.

As of today, evolution of SCL due to COVID-19 has not been investigated yet by extended psychophysical testing. In this prospective cohort study, we sought to evaluate the evolution of the chemosensory modalities after SCL. We also sought to determine whether testing odor threshold detection provides additional information regarding olfactory loss due to COVID-19 compared to odor identification.

Materials and methods

Study design, setting, and participants

This prospective cohort study was conducted between February 1 and May 30, 2020. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Adult patients with SCL since February 2020 were recruited via public call from our institution. RT-PCR analysis on nasopharyngeal swab or serologic testing for IgG antibodies were performed depending on the date of onset of SCL, ≤ 14 days or > 14 days respectively. Eligible patients were asked to come to the clinic for psychophysical testing at least 2 weeks after the onset of their symptoms. This was necessary to minimize the risk of transmission for our study personnel as psychophysical testing is a 30-min procedure requiring close proximity and access to nostrils and mouth of the participant.

Study population data

Patient demographics, including age, sex, body mass index, and known respiratory allergies were collected. A second questionnaire focused on chemosensory loss: date of onset, duration of anosmia (i.e., the interval between date of onset and beginning of recovery), self-assessment of complete recovery (yes/no), presence of parosmia and/or phantosmia. During patient interview, close-ended questions concerning trigeminal chemosensation were asked and included absent lacrimation while cutting onions, loss of nasal cooling sensation while inhaling eucalyptol/menthol, loss of nasal or oral burning/tingling sensation while eating spicy food, mustard, or wasabi.

Psychophysical measurements

Orthonasal olfactory function was tested using the extended "Sniffin' Sticks" test battery (Burghart GmbH, Wedel, Germany) based on odor-containing felt tips. Three olfactory tasks were performed: threshold detection (T), discrimination (D), and identification (I). These scores ranged from 1 to 16 (T) or 0 to 16 (D and I). The total olfactory score (TDI score) is the sum of all three subtests and range from 1 to 48. Normative data were used to establish that TDI scores of > 30.5, $16–30.5$, and < 16 indicated normosmia, hyposmia, and (functional) anosmia, respectively [8]. Odor threshold (T score) was evaluated following the single-staircase technique with three-alternative forced choice from 16 triplets of stepwise dilutions. In each triplet, two pens were odorless and one was impregnated with n-butanol (cheese-like smell) that the participant had to identify. The final score was the mean of the last four turning points in the staircase. The odor discrimination task (D score) consisted of the identification of the pen that smelled different than two other pens with identical odor. A total of 16 triplets of pens were administered. Finally, for the identification task (I score), the participant was asked to identify each of 16 pens with common odors using a four-alternative forced choice.

To screen for intranasal trigeminal dysfunction, the patient was asked to identify the one pen among the 16 scents that produced a cooling sensation as one of them contained levomenthol. Screening of taste function was assessed with taste strips for the four basic tastes (sweet, salty, bitter, and sour) at suprathreshold concentrations (Burghart GmbH, Wedel, Germany). Participants were asked to identify the correct taste (four-alternative forced choice). Scores ranged from 0 to 4. Scores of ≥ 3, 2, and ≤ 1 were interpreted as normogeusia, hypogeusia, and ageusia, respectively, (adapted from [9]).

Statistical analysis

The relationship between clinical data and chemosensory scores was analyzed using Spearman correlation for scale data and Fisher's exact test for categorical data. Comparisons of continuous variables were performed using Kruskal–Wallis H test for three independent groups. Analysis of variance by ranks between the three olfactory task scores were done using Friedman test and post hoc pairwise comparisons with degrees of freedom adjusted according to Bonferroni. Individual Wilcoxon Signed Rank Test (using Bonferroni adjusted alpha value) was used for post hoc comparisons between related samples. All analyses were performed using the Statistical Package for the Social Sciences for Mac OS (SPSS version 25; IBM Corp, Armonk, NY, USA).

Results

A total of 72 patients were enrolled and completed the study (Fig. 1): 25 patients had a positive RT-PCR analysis on nasopharyngeal swab and 47 had developed IgG antibodies for

SARS-CoV-2. Characteristics of study participants are summarized in Table 1.

Olfaction

After a mean of 37 days after SCL, 6 patients were anosmic (8%), 21 were hyposmic (29%), and 45 were normosmic (63%) with TDI scores (mean $\pm$ SD) of 9.8 ± 4.4, 25.7 ± 3.7, and 37.8 ± 3.9, respectively, (Fig. 2 and Table 2). Only 3 patients (4%) considered to have fully recovered their sense of smell, all in the normosmic group. Duration of anosmia was significantly correlated with olfactory subgroup (Table 2). Post hoc comparison showed statistical differences between normosmic and hyposmic groups ($p = 0.001$), and normosmic and anosmic groups ($p = 0.035$) but not between anosmic and hyposmic groups.

Threshold, discrimination, and identification task scores are shown in Table 2. The results of the Friedman test indicated that there was a statistically significant difference in

Table 1 Characteristics of study patients

Characteristic	All patients ($N = 72$)
Age	
Mean $\pm$ SD, years old	38.9 ± 12.4
Gender	
Female, N (%)	49 (68.1)
Male, N (%)	23 (31.9)
BMI	
Mean $\pm$ SD, kg/m^2	24.0 ± 4.3
Allergic patients, N (%)	11 (15.3)
Duration of anosmia	
Median (range), days	17 (3–61)
Time interval between SCL onset and psychophysical assessment	
Mean $\pm$ SD, days	37.0 ± 10.9

BMI body mass index (calculated as weight in kilograms divided by height in meters squared), *SCL* sudden chemosensory loss, *SD* standard deviation

Fig. 1 Flow diagram. Flow diagram illustrating cohort selection. *COVID-19* coronavirus disease 2019, *RT-PCR* reverse transcriptase-polymerase chain reaction, *IgG* immunoglobulin G
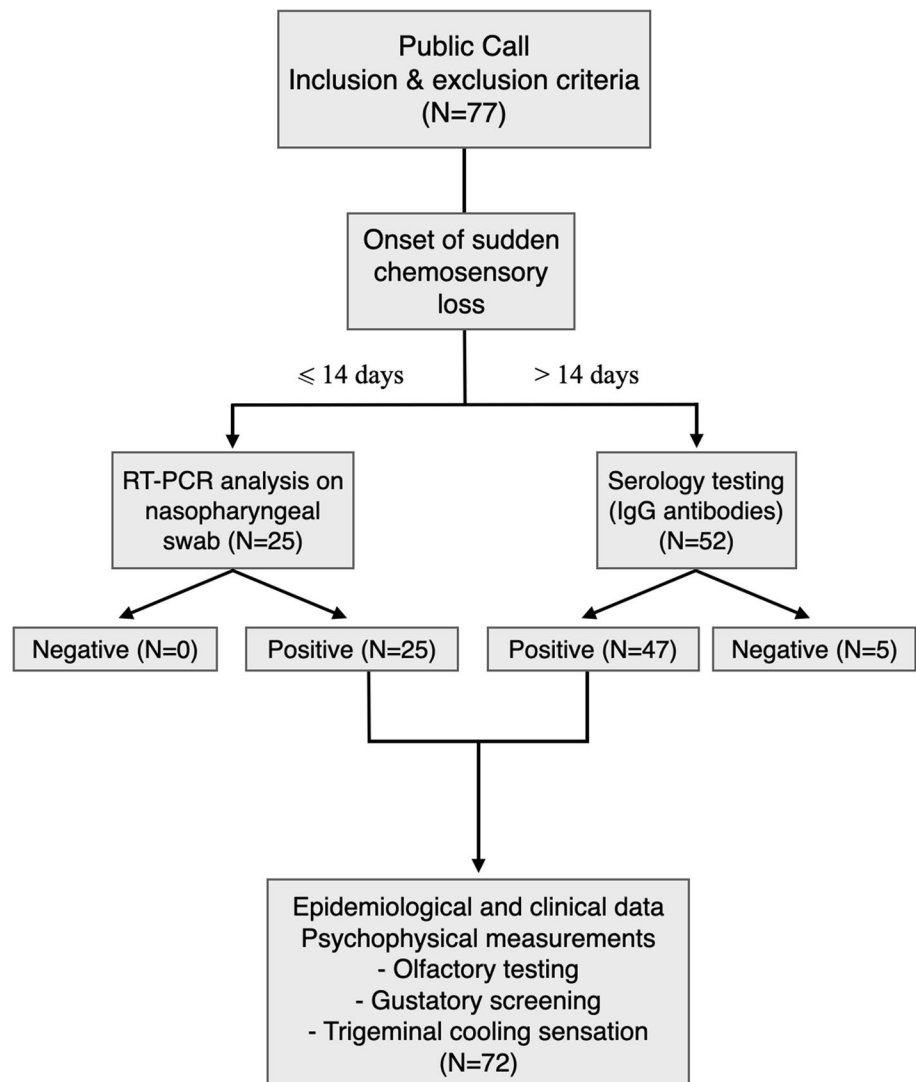
Fig. 2 Distribution of patients for each psychophysical test. Distribution of all 72 patients in different categories for each psychophysical test: olfactory (left), gustatory (middle), and trigeminal (right)
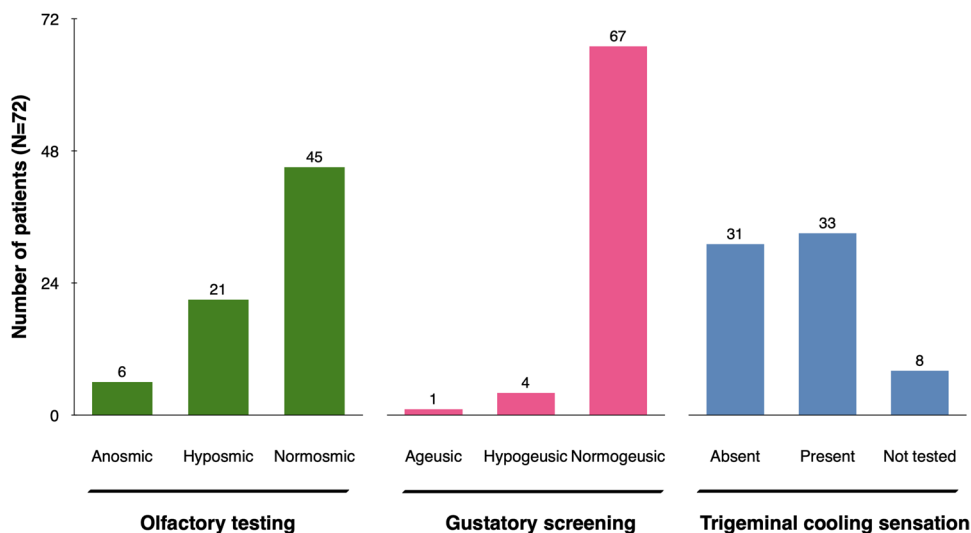

Table 2 Comparison of anosmic, hyposmic, and normosmic patients

	Anosmic (N=6)	Hyposmic (N=21)	Normosmic (N=45)	p value	Test
Sociodemographics and clinical data					
Age (mean ± SD), years old	42 ± 16.5	42.6 ± 15.0	37.0 ± 10.0	0.391	KW
Sex (F/M)	5/1	13/8	31/14	0.68	F
BMI (mean ± SD), kg/m^2	25.8 ± 5.6	25.1 ± 4.4	23.1 ± 3.9	0.134	KW
Allergic patients, N (%)	1 (17)	5 (24)	5 (11)	0.339	F
Time interval between SCL onset and psychophysical assessment					
Mean ± SD, days	41.1 ± 13.3	37.1 ± 8.5	35.3 ± 11.4	0.677	KW
Olfaction					
Threshold score, (median ± IQR), /16	1 ± 0.5	3 ± 1.5	13 ± 3.00		
Discrimination score, (median ± IQR), /16	4 ± 1.25	11 ± 1.25	13 ± 1.50		
Identification score, (median ± IQR), /16	5 ± 2.37	12 ± 2.00	14 ± 1.25		
TDI score, (mean ± SD), /48	9.8 ± 4.4	25.7 ± 3.7	37.8 ± 3.9		
Perceived complete recovery, N (%)	0 (0)	0 (0)	3 (7)	0.651	F
Duration of anosmia, median (range), days	31 (6–61)	28 (4–47)	12 (3–47)	<0.005	KW
Parosmia, N (%)	3 (50)	6 (29)	7 (13)	0.199	F
Phantosmia, N (%)	2 (33)	5 (24)	8 (15)	1	F
Gustatory screening, N (%)				0.821	F
Ageusia	0 (0)	0 (0)	1 (2)		
Hypogeusia	0 (0)	2 (9)	2 (4)		
Normogeusia	6 (100)	19 (91)	42 (94)		
Cooling sensation, N (%)				0.128	F
Incorrect/absent identification	4 (67)	13 (62)	14 (31)		
Correct identification	2 (33)	8 (38)	23 (51)		
Not tested	0 (0)	0 (0)	8 (18)		

BMI body mass index, *F* Fisher's exact test, *F/M* female/male, *KW* Kruskal–Wallis *H* test, *IQR* interquartile range, *SCL* sudden chemosensory loss, *SD* standard deviation, *TCS* trigeminal chemosensation, *TDI* threshold discrimination identification (olfactory score)

olfactory testing across all olfactory subtests (threshold, discrimination, identification, $\chi^2 = 30.83$ ($df = 2$, $N = 72$), $p < 0.001$). Post hoc pairwise comparisons showed that odor detection threshold score was significantly lower than both discrimination ($p = 0.001$) and identification scores ($p < 0.001$), whereas discrimination and identification

scores were not statistically different. Similarly, post hoc comparisons between each olfactory group confirmed that odor detection threshold was different for anosmic ($p = 0.031$) and hyposmic patients ($p < 0.005$), but not different for normosmic patients ($p = 0.185$) (Fig. 3). Taken together, these results indicate that odor detection was the olfactory task that mostly determined the final TDI score, and, therefore, was the most affected smell ability by COVID-19 in our cohort.

Moreover, parosmia and phantosmia were reported in 16 (22%) and 15 (21%) patients, respectively. Their presence was not correlated to lower olfactory score (Table 2). Of note, 6 out of 15 reports of phantosmia were described as a continuous smell of burning or tobacco. We found no correlation between TDI score and patient characteristics, in particular age, sex, and BMI. The relationship between TDI score and reported duration of anosmia was strong ($r = -0.53$; $p < 0.01$) but not with the time interval between onset of olfactory loss and olfactory testing.

Gustatory screening

Sixty-four patients (89%) reported having lost their taste concurrently with their loss of smell. After a mean of 37 days, screening revealed that 1 patient was ageusic (1%), 4 were hypogeusic (6%), and 67 were normogeusic (93%) (Fig. 2). In contrast to olfactory scores, there was no relationship between gustatory scores and duration of anosmia.
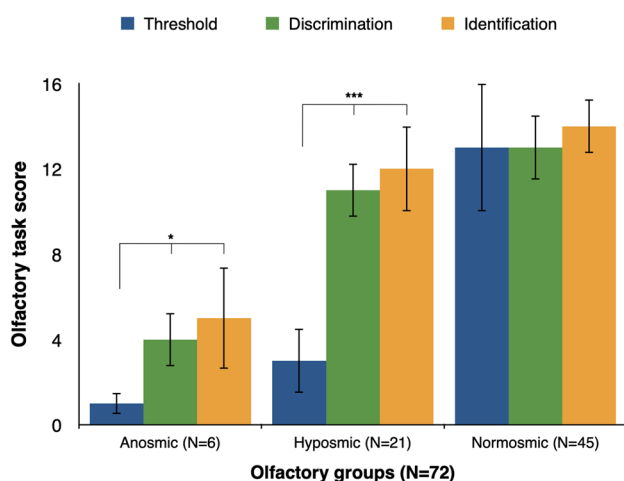

Fig. 3 Olfactory subtest scores in each olfactory group. Median olfactory subtest scores across each olfactory group (error bars represent interquartile range). *$p < 0.05$. ***$p < 0.005$

Cooling sensation

Eight patients (11%) were unable to answer any of the questions about TCS and were, therefore, not included in the analysis. Absence of at least one trigeminal chemosensory function during the period of SCL was reported by 37 patients (58%). Identification of menthol-induced cooling sensation was correct in 33 patients (52%). There was a higher prevalence of incorrect menthol identification among patients reporting at least one impaired trigeminal function compared with those reporting normal trigeminal function ($p < 0.001$; $N = 64$).

Discussion

Five weeks on average after the onset of olfactory loss, 37% of patients were still displaying olfactory dysfunction according to olfactory testing. These results suggest that complete recovery of smell may not always happen after a couple of weeks as it has been found in previous studies [4, 10]. This difference was not explained by the time interval between time of symptom onset and time of assessment. In contrast, reported duration of anosmia was inversely correlated with olfactory scores, suggesting that the longer the initial anosmia, the poorer the smell/taste recovery. The duration of initial anosmia may, therefore, be a useful prognostic factor for smell recovery. Interestingly, this correlation was not found in other studies [5]. Furthermore, neither age, sex, nor BMI predicted olfactory outcome, although they are known to be associated with more severe forms of COVID-19 [11].

Moreover, there was a clear mismatch between our proportion of normosmic patients (62%) and of those who reported full smell recovery (6%). An explanation may be that normosmia as defined by psychophysical measurement and population-based normative data, is not equivalent to the assumption that the patient's ability to smell returned to its normal level. It may be that some patients tested as normosmic are still recovering. On the other hand, it may also partially reflect the known disparity between olfactory self-rating and objective measuring, emphasizing the importance of studies based on psychophysical testing to investigate chemosensory function rather based on subjective rating alone [12]. Similarly, hyposmic and anosmic patients will have to be followed up to investigate the risk for permanent post-viral olfactory dysfunction, a known yet rare complication of upper respiratory viral infections [13]. Surprisingly, Boscolo-Rizzo et al. [14] found that almost half of their 202 patients reported full resolution after 4 weeks of olfactory loss. Unfortunately, their study focused on subjective assessment of olfactory function and not psychophysical testing which makes comparison to our study difficult.

This is the first study to fully explore olfactory loss due to COVID-19 via extended olfactory testing. We found that odor detection ability was the most affected olfactory task by COVID-19. In comparison to odor identification, this subtest is considered to more closely reflect functions of the olfactory neuroepithelium [6]. This appeals, therefore, to the concept that SARS-CoV-2 induces olfactory loss at the level of the peripheral rather than at a more central nervous level. This is consistent with recent studies showing that cells from the olfactory epithelium express two known proteins used by SARS-CoV-2 to infect human cells (ACE2 and TPMRSS2), to imaging studies showing olfactory cleft mucosal thickening during COVID-19 [15–17] and studies reporting olfactory neuritis during COVID-19 [18]. Regarding other human coronaviruses, experiments in animals showed also that viral spread to the central nervous system started at the olfactory neuroepithelium [19].

In our study, most COVID-19 patients quickly reached high identification scores, as soon as they started to recover smell detection ability. Yet, most studies on COVID-19-related olfactory loss have so far relied solely upon screening tests based on smell identification [5, 20]. This is likely the reason why one study found that 38% of their normosmic patients reported being anosmic [5]. We calculated that if we had used only the identification test, 20 patients (28%) would be in a different olfactory category and 12 hyposmic patients (17%) would have been misdiagnosed as normosmic. Our study suggests that the combined assessment of odor detection threshold and odor identification would be the most appropriate way to address olfactory function in COVID-19, rather than the commonly used odor identification task alone.

The mechanism by which SARS-CoV-2 leads to taste impairment is still unclear. It may be via direct damage of the gustatory organ, as ACE2 receptors have been identified in the mouth and in particular on the tongue. In our study, 93% of our cohort was normogeusic 5 weeks on average after SCL which confirms results by Hintschich et al. [21]. This contrast with olfactory recovery may suggest that patients tend to recover taste better than smell. On the other hand, patients may misinterpret loss of retronasal flavor perception as loss of taste. This may have produced an overestimation of the proportion of patients (89%) who considered themselves dysgeusic initially. Lastly, gustatory loss has also been reported as an accompanying symptom in patients with olfactory loss with the explanation that olfaction amplifies gustation (and vice versa) within the chemosensory system through central nervous interactions [22, 23]. A limitation of our study was the use of a basic taste strip test to screen for gustatory function. Future studies should include an extended taste strip test as proposed by Landis et al. [9] to improve precision in assessing gustatory function and help clarify the role of retro-nasal olfaction in the reported loss of taste.

To our knowledge, this study is among the first to psychophysically address trigeminal impairment due to COVID-19. We found that 58% of patients reported the absence of at least one trigeminal sensation and 48% did not identify menthol-induced cooling sensation. This association may suggest that SARS-CoV-2 affects TCS as well as olfaction and gustation, although proper psychophysical testing is required in future studies to support this idea. Parma et al. found a very similar rate of 46% of participants reporting decreased oral chemesthesis [24]. Intranasal trigeminal nerve endings may also be a potential target for respiratory neurotropic viruses, although this has not been shown yet for human coronaviruses [25]. This may agree with observations in patients with non-COVID-associated postviral olfactory loss where decreased TCS is typical [26]. However, our preliminary results on nasal cooling need to be considered carefully. They require rigorous trigeminal testing in future studies, using a lateralization test, or event-related potentials [27]. Future chemosensory studies should also include assessment of retronasal olfactory function and extended gustatory investigation to clarify the relative importance of retronasal olfaction and dysgeusia in reported loss of taste. Such testing is of particular importance when considering the discrepancies between results from subjective ratings and less biased psychophysical testing [12].

Conclusion

Five weeks after developing sudden olfactory loss due to COVID-19, more than a third of patients displayed olfactory dysfunction according to psychophysical testing. Odor detection was the olfactory ability most affected by SARS-CoV-2 compared to odor discrimination or odor identification. This may also indicate that COVID-19-related smell impairment is predominantly due to peripheral rather than central nervous system damage. Moreover, a longer duration of initial anosmia was correlated with a lower olfactory function, suggesting that it may be of clinical utility to predict smell recovery rate. In contrast to the evolution of smell function, the vast majority of patients scored in the normal range when screening their taste function at 5 weeks, casting doubt on the exact physiological mechanism underlying the reported loss of taste. Moreover, this study found that almost half of the patients appeared to exhibit signs of abnormal nasal cooling sensation prompting more systematic investigations of trigeminal sensitivity in COVID-19.

Compliance with ethical standards

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