

## Main Article

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# Six-month smell and taste recovery rates in coronavirus disease 2019 patients: a prospective psychophysical study

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## Abstract

**Background.** The long-term recovery rate for coronavirus disease 2019 related chemosensory disturbances has not yet been clarified.

**Methods.** Olfactory and gustatory functions were assessed with psychophysical tests in patients in the first seven days from coronavirus disease 2019 onset and one, two, three and six months after the first evaluation.

**Results.** A total of 300 patients completed the study. The improvement in olfactory function was significant at the two-month follow up. At the end of the observation period, 27 per cent of the patients still experienced a persistent olfactory disturbance, including anosmia in 5 per cent of cases. As for taste, the improvement in the psychophysical scores was significant only between the baseline and the 30-day control. At the 6-month evaluation, 10 per cent of the patients presented with a persistent gustatory disturbance with an incidence of complete ageusia of 1 per cent.

**Conclusion.** Six months after the onset of coronavirus disease 2019, about 6 per cent of patients still had a severe persistent olfactory or gustatory disturbance.

## Introduction

Olfactory dysfunctions represent one of the most frequent and specific symptoms of coronavirus disease 2019 (Covid-19), affecting approximately 50 to 85 per cent of patients.<sup>1–5</sup> Taste and smell dysfunctions, which are characteristic of the earliest stages of Covid-19, generally regress spontaneously within 15 days.<sup>6,7</sup> However, some authors have reported the persistence of severe chemosensitive dysfunctions in patients who were evaluated for more than 30 days after the clinical onset.<sup>8–10</sup> The long-term chemosensitive recovery rate has not yet been fully clarified because there have been only four studies in the literature with a follow up of six months from the first appearance of the disorder.<sup>11–14</sup> Such a long period of observation is necessary to understand the incidence of any permanent chemosensitive disorders because some authors have found that there are margins for recovery even two months after the clinical onset,<sup>15,16</sup> and in some forms of post-viral anosmia, recovery times of more than one year have been reported.<sup>17</sup>

In June 2020, we published the results of a chemosensitive psychophysical evaluation of a large series of 300 Covid-19 patients within the first seven days after the development of the disorder.<sup>18</sup> The purpose of this second report was to establish the functional recovery rate by objectively re-evaluating these patients one, two, three and six months later.

## Materials and methods

This prospective study represents the continuation of the report previously published by our research group which involved 300 Covid-19 out-patients who had undergone psychophysical evaluation of smell and taste within seven days of the clinical onset.<sup>18</sup> The study included adult patients diagnosed with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection confirmed by real-time polymerase chain reaction on a nasopharyngeal swab and who had not experienced any previous taste or smell disturbances, neurological disease, chronic rhinosinusitis, or a history of oral or nasal cancer, surgery, radiotherapy or trauma. All study participants were patients of the healthcare

staff of the Bellaria and Maggiore Hospital, Bologna, Italy, and were followed by the Surveillance and Prevention Department of the Bellaria and Maggiore Hospital.

After the first evaluation, the patients were re-evaluated at one, two, three and six months. The study protocol was approved by the AUSL Bologna Ethical Committee (approval number: 378-2020-OSS-AUSLBO). The smell and taste functions of all the patients were remotely assessed by means of the self-administered psychophysical test proposed and validated by Vaira *et al.*<sup>19–21</sup> The telephone interviews started with the request for an explicit consent to participate in the study. Next, the patient's demographics (i.e. age, gender and professional role), comorbidities or conditions that could be a reason for exclusion from the study were recorded. The presence of other Covid-19 symptoms and the date of onset were also noted for each patient.

All the patients were contacted by telephone by the same team of researchers who had explained the preparation of the odorants and flavoured solutions and guided the patients during the self-administration of the test. The test methodology and the scoring system have already been extensively described in previous studies.<sup>18–21</sup>

The olfactory test included the evaluation of the ethyl alcohol olfactory threshold and the discriminative function for six groups of common household odorants. The score thus obtained ranges from 0 (anosmia) to 100 (normal olfactory function), allowing a classification of the olfactory function of the patients into five clinical categories: anosmia (scores between 0 and 10), severe hyposmia (scores between 20 and 40), moderate hyposmia (scores between 50 and 60), mild hyposmia (scores between 70 and 80) and a normal sense of smell (scores between 90–100).

The gustatory function was assessed by means of four solutions, one for each primary taste. The taste score ranged from 0 (ageusia) to 4 (a normal perception), allowing a classification of the patients into five clinical categories: ageusia (score 0), severe hypogeusia (score 1), moderate hypogeusia (score 2), mild hypogeusia (score 3) and a normal sense of taste (score 4).

The statistical analysis was performed using SPSS® statistical software. Categorical variables were reported in numerals and percentages of the total. Descriptive statistics for quantitative variables are given as the mean and standard deviation or median (interquartile range). The Wilcoxon signed rank test for paired data was performed to evaluate the statistical significance of any changes in olfactory and gustatory scores during the observation period. Cross-tabulation analysis and the Fisher's exact tests were used to evaluate the significance of the correlations between the chemosensitive disorders and general and clinical variables. The level of statistical significance was set at  $p \leq 0.05$  with a 95 per cent confidence interval.

## Results

All of the 300 patients included in the first study completed the six-month follow up. The general and clinical features of the patients are reported in Table 1.

At baseline, 190 (63.3 per cent) and 184 (61.3 per cent) of patients experienced olfactory or gustatory dysfunction, respectively (Figures 1 and 2). The disorders presented were mostly severe, with psychophysical scores referable to anosmia in 47 per cent of cases and complete ageusia detected in 38 per cent of the patients. The improvement in olfactory function was significant at the two-month follow up. The

**Table 1.** General and clinical features of the study population

Parameter	Value
Gender ( <i>n</i> (%))	
– Male	75 (25)
– Female	225 (75)
Age (mean $\pm$ SD (IQR); years)	43.6 $\pm$ 12.2 (33–53)
Referred symptoms ( <i>n</i> (% (95% CI)))	
– Asymptomatic	28 (9.3 (6.3–13.2))
– Fever	204 (68 (62.4–73.2))
– Headache	133 (44.3 (38.6–50.1))
– Myalgia	128 (42.7 (37–48.5))
– Asthenia	109 (36.3 (30.9–42.1))
– Cough	95 (31.7 (26.4–37.3))
– Pneumonia	74 (24.7 (19.9–29.9))
– Diarrhoea	70 (23.3 (18.7–28.5))
– Nausea	35 (11.7 (8.3–15.8))
– Dyspnoea	31 (10.3 (7.1–14.3))
– Nasal obstruction	27 (9 (6–12.8))
– Sore throat	24 (8 (5.2–11.7))
– Conjunctivitis	11 (3.7 (1.8–6.5))

SD = standard deviation; IQR = interquartile range; CI = confidence interval

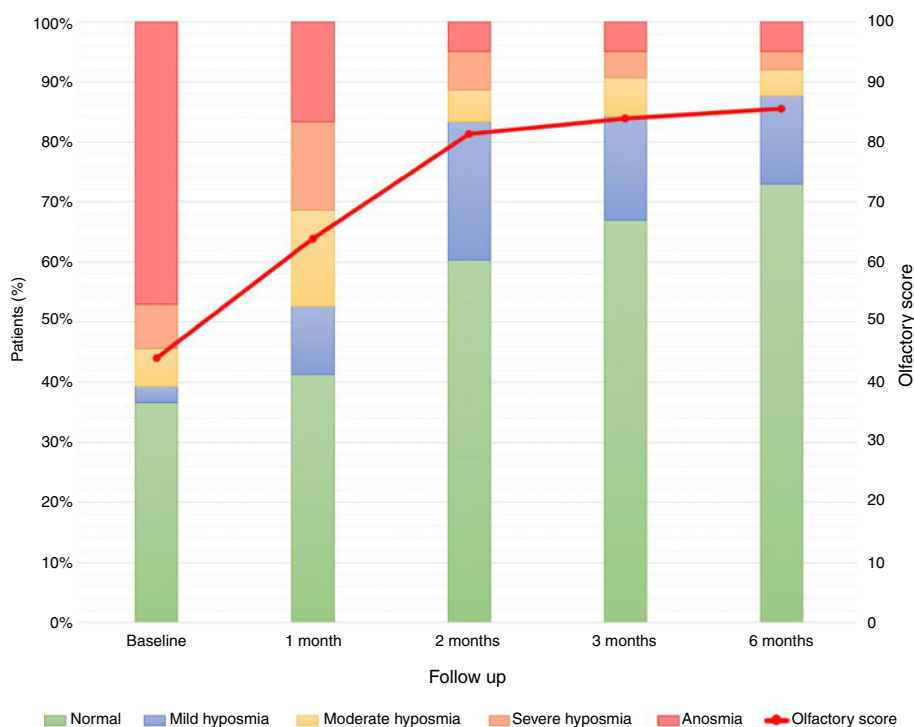
psychophysical scores did not change significantly at the subsequent control times (Table 2). At the end of the observation period, 81 patients (27 per cent) still experienced a persistent olfactory disturbance, including anosmia in 15 cases (5 per cent; Figure 1).

As for taste, the improvement in the psychophysical scores was significant only between the baseline and the 30-day control (Table 2). The mean score curve therefore reached a plateau with non-significant variations in subsequent control times. At the 6-month evaluation, 30 patients (10 per cent) presented with a persistent gustatory disturbance with an incidence of complete ageusia of 1 per cent (3 cases; Figure 2). The statistical association between the clinical and epidemiological characteristics of the patients and the presence of persistent disturbances of smell (Table 3) and taste (Table 4) was significant only between age and the persistence of the olfactory dysfunction (odds ratio, 41.5; 95 per cent confidence interval, 19.4–8.8;  $p < 0.001$ ).

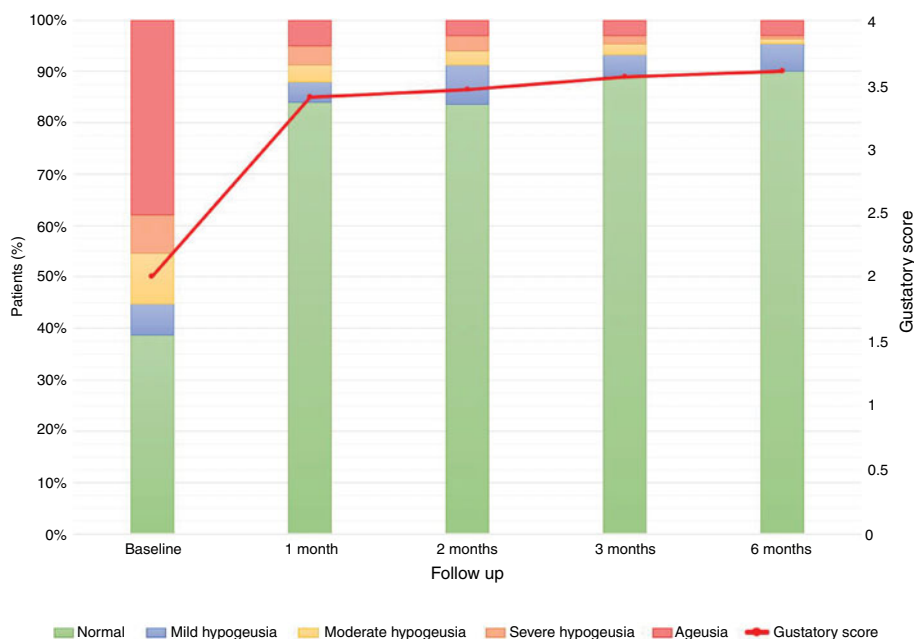
## Discussion

Persistent olfactory and gustatory disorders are emerging as one of the most frequent long-term morbidities of SARS-CoV-2 infection. The first long-term prospective studies report the persistence of severe disorders at 6-month follow up in around 10 per cent of patients who had previously been affected by Covid-19. Such a high prevalence in the population means that over the next few years a huge number of patients will seek assistance for the treatment of this disabling long-term morbidity. For this reason, it is essential to identify specific therapies that can prevent the chronicity of chemosensitive disorders in Covid-19 patients.<sup>22,23</sup>

However, to achieve this goal it is necessary to establish the exact frequency of long-term dysfunction to understand if there are any clinical or epidemiological risk factors and,



**Fig. 1.** Olfactory clinical diagnosis and score trend during the observation period.



**Fig. 2.** Gustatory clinical diagnosis and score trend during the observation period.

above all, to identify the temporal cut-off points beyond which there is no longer likelihood for significant improvements in olfactory and gustatory function. These cut-off points may therefore represent the time when specific therapy is certainly indicated. The very few studies published so far on this topic have the limitation of being based solely on patient interviews<sup>12</sup> or with regard to studies based on psychophysical tests, of not presenting intermediate evaluations.<sup>11,13</sup>

One of the strengths of this study was that the baseline was set within seven days of the onset of symptoms and before any recovery from chemosensory dysfunction had begun. In this way, it was possible to establish the exact prevalence of olfactory and gustatory disorders in the early stages of Covid-19 and to provide a reliable basis for the prospective evaluation. During the infection, 210 patients (70 per cent) had at least

one chemosensory dysfunction. These were mainly severe disorders with a prevalence of anosmia and ageusia of 47 per cent and 38 per cent, respectively. This frequency is in line with that reported in other previously published psychophysical studies.<sup>1,3,4,7,16,18,20,21,24-26</sup> Regarding any functional recovery over time, the average olfactory score showed statistically significant improvements within two months after clinical onset. The curve then flattened without any significant improvements in the subsequent controls. On the other hand, taste showed an earlier recovery with significantly better scores at the 30-day control and a plateau without any further improvement in the subsequent controls.

This is the first prospective study with a six-month follow up that presents intermediate evaluations. For this reason, to the best of our knowledge there are no data in the literature

**Table 2.** Chemosensitive trend score analysis

Parameter	Observation time	Olfactory score (median (IQR))	Wilcoxon signed rank test <i>p</i> -value
Olfactory function			
	Baseline	30 (0–100)	
	1 months	70 (40–100)	<0.001
	2 months	90 (70–100)	<0.001
	3 months	100 (80–100)	0.094
	6 months	100 (80–100)	0.139
Gustatory function			
	Baseline	2 (0–4)	<0.001
	1 months	4 (3–4)	0.092
	2 months	4 (3–4)	0.381
	3 months	4 (3.75–4)	0.745
	6 months	4 (4–4)	

Each *p*-value refers to the analysis of the differences in the median olfactory score between the observation time considered and the one immediately preceding. IQR = interquartile range

to provide the baseline to enable us to carry out a meta-analysis. Previous studies, with a two-month follow up,<sup>15,16</sup> had suggested the possibility of a later functional recovery. However, this possibility seems to be excluded on the basis of an analysis of our results. In our series, all patients presenting with anosmia or ageusia at two months continued

to experience this severe disorder until the end of the observation period.

At the 6-month evaluation, 27 per cent and 10 per cent of the patients had residual olfactory or gustatory disturbance, respectively. Any evaluation of this prevalence must certainly be performed while taking into account the fact that mild olfactory dysfunctions are present in about 15 per cent of the general population.<sup>27</sup> At the same time, the high frequency of persistent anosmia (5 per cent) and ageusia (3 per cent) found in our series of patients should be emphasised. This prevalence of severe olfactory disturbances is similar to that reported in the studies by Lechien *et al.*<sup>11</sup> and Boscolo-Rizzo *et al.*<sup>14</sup> but higher than the 1 per cent found by Niklassen *et al.*<sup>13</sup> Taste function at 6 months post-infection was previously identified only by Niklassen *et al.*<sup>13</sup> on a small series of 31 patients, with a residual dysfunction recorded in only 6.5 per cent of cases.

Given the high prevalence of the SARS-CoV-2 infection in the general population, these incidence rates mean that hundreds of thousands of patients worldwide will need care for permanent severe chemosensory disorders in the coming years. It is therefore essential to provide the colleagues who will face these problems in the future with reliable data in order to enable them to correctly inform their patients. On the basis of the present study, it is possible to state that the spontaneous recovery margins of a chemosensitive disorder, especially if severe, after two months from clinical onset are very poor. For this reason, we do not consider that there are any reasons to further delay any specific treatment<sup>22,23,27</sup> beyond this time limit.

To date, there are only a few therapeutic trials for olfactory dysfunctions in Covid-19 patients. Some authors reported that

**Table 3.** Olfactory logistic regression and cross-tabulation analysis results

Parameter	Persistent olfactory dysfunction ( <i>n</i> (%))	No persistent olfactory dysfunction ( <i>n</i> (%))	Odds ratio	95% CI for odds ratio		Fisher's exact test
				Lower limit	Upper limit	
DV: gender; IV: persistent olfactory dysfunction						
– Female	64 (28.4)	161 (71.6)	1.356	0.734	2.504	0.33
– Male	17 (22.6)	58 (77.4)				
DV: age; IV: persistent olfactory dysfunction						
– Age ≥50 years	71 (68.9)	32 (31.1)	41.5	19.4	88.8	<0.001
– Age <50 years	10 (5.1)	187 (94.9)				
DV: fever; IV: persistent olfactory dysfunction						
– Fever	56 (29.5)	134 (70.5)	1.421	0.824	2.448	0.206
– No fever	25 (22.7)	85 (77.3)				
DV: headache; IV: olfactory dysfunction						
– Headache	40 (30.1)	93 (69.9)	1.322	0.793	2.204	0.285
– No headache	41 (24.5)	126 (75.5)				
DV: pneumonia; IV: olfactory dysfunction						
– Pneumonia	24 (32.4)	50 (67.6)	1.423	0.803	2.521	0.226
– No pneumonia	57 (25.2)	169 (74.8)				

DV = dependent variable; IV = independent variable; CI = confidence interval

**Table 4.** Gustatory logistic regression and cross-tabulation analysis results

Parameter	Persistent gustatory dysfunction (n (%))	No persistent gustatory dysfunction (n (%))	Odds ratio	95% CI for odds ratio		Fisher's exact test
				Lower limit	Upper limit	
DV: gender; IV: persistent gustatory dysfunction						
- Female	203 (90.2)	22 (9.8)	0.622	0.268	1.474	0.286
- Male	67 (89.3)	8 (10.7)				
DV: age; IV: persistent gustatory dysfunction						
- Age ≥50 years	174 (62.4)	23 (37.6)	1.816	0.75	4.379	0.186
- Age <50 years	96 (59.2)	7 (40.8)				
DV: fever; IV: persistent gustatory dysfunction						
- Fever	186 (64.7)	18 (35.3)	0.677	0.312	1.469	0.324
- No fever	84 (49)	12 (51)				
DV: headache; IV: persistent gustatory dysfunction						
- Headache	118 (61.6)	15 (38.4)	1.288	0.605	2.74	0.511
- No headache	152 (61.1)	15 (38.9)				
DV: pneumonia; IV: persistent gustatory dysfunction						
- Pneumonia	69 (64.9)	5 (35.1)	0.583	0.215	1.581	0.289
- No pneumonia	201 (60.2)	25 (39.8)				

DV = dependent variable; IV = independent variable; CI = confidence interval

systemic steroids and steroid rinses may be effective in the management of Covid-19 related olfactory dysfunctions.<sup>22,23,27,28</sup> Furthermore, olfactory training is recommended to Covid-19 patients with loss of smell for more than two weeks.<sup>28</sup> The efficacy of alpha-lipoic acid, omega-3 supplements and retinoic acid derivatives has not yet found unequivocal indications that recommend their use in patients with Covid-19 related olfactory dysfunctions.<sup>27,28</sup>

Neither in this nor in any other studies already published has it been possible to detect any risk factors significantly related to the development of a long-term disorder. The significant correlation found between persistent olfactory disorder and age may be related to the normal higher frequency of these dysfunctions in the elderly population.<sup>29</sup> However, this correlation was not reported in the previous studies<sup>11-13</sup> and may therefore be related to a lower regenerative capacity of the olfactory epithelium in older patients.<sup>30</sup>

These findings reflect the great uncertainty that still surrounds the exact pathogenesis of chemosensitive disorders during SARS-CoV-2 infection, the severity and duration of which seem to be related to individual factors not yet identified.<sup>31-35</sup> However, we have detected that patients presenting with a partial disorder at baseline (i.e. hyposmia of varying degrees of severity) usually achieve a complete recovery whereas persistent disorders only affect patients with complete anosmia at clinical onset.

The main limitation of this study is the impossibility of establishing how many of the patients who presented with olfactory dysfunction at six months already had this problem even before infection. The evaluation of patients prior to infection was obviously impossible, but the inclusion of a control group could have been useful in establishing the extent of

this bias. Moreover, the six-month follow up is still too short to assess long-term recoveries. In fact, recoveries of some post-viral olfactory dysfunctions have been reported after more than a year after onset.<sup>17</sup>

- The long-term chemosensitive recovery rate after coronavirus disease 2019 (Covid-19) has not been clarified
- This study aimed to establish the functional recovery rate by objectively evaluating 300 Covid-19 patients for up to 6 months
- At 6 months, 27 and 10 per cent of the patients had residual olfactory or gustatory disturbance, respectively
- Functional recovery is significant in the first month in relation to taste and first two months in relation to smell
- After this period, the likelihood of improvement is significantly reduced
- This time limit indicates the period when specific therapies must be initiated for Covid-19 related chemosensitive disorder

Another limitation of the study was the inclusion of only mild-to-moderate Covid-19 patients in home isolation. In fact, the test is not applicable to hospitalised patients who do not have the possibility of accessing the odorants necessary for carrying out the self-administered test. These patients were evaluated with the Connecticut Chemosensory Clinical Research Center test and included in other studies.<sup>1,21</sup>

## Conclusion

Six months after the onset of Covid-19, about 6 per cent of patients still have a severe persistent olfactory or gustatory disturbance. The functional recovery is significant in the first month in relation to taste and in the first two months in relation to smell. After this period, the likelihood of improvement is significantly reduced. This time limit ideally represents the period

when specific therapies must be initiated in order to prevent the persistence of Covid-19 related chemosensitive disorders.

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**Competing interests.** None declared

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