

Acute smell and taste loss in outpatients: all infected with SARS-CoV-2?*

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To the Editor:

During SARS-CoV-2 pandemic, our region (Alsace, East of France) became a Covid-19 cluster quite early in Europe. Loss of smell and taste was quickly flagged by the Ears-Nose and Throat scientific community as a potential warning signs of SARS-CoV-2 infection⁽¹⁾. Many patients and medical/paramedical workers with mild to moderate form of SARS-CoV-2 infection complained about their loss of sense of smell and taste to our ENT department. The aim of our study was to compare the characteristics of loss of smell and taste between patients with a clinical diagnosis of SARS-CoV-2 infection to patients with a RT-PCR diagnosis.

This retrospective single-study included ambulatory adult pa-

tients with loss of smell and taste who had either a RT-PCR-proven SARS-CoV-2 diagnosis ("PCR +" group) or a clinical diagnosis of SARS-CoV-2 ("PCR -" group). Patients were referred to our center by their general practitioner and a 28-questions survey (Annex 1) was sent to them by e-mail. Duration of symptom was defined by the time between the onset of loss of smell and taste and the day of the participation to this study. Self-rating of the severity of symptoms was assessed by a 5-points scale⁽²⁾ ranging from 1, normal to 5, total loss (Annex 1). Patients were excluded for: history of olfactory loss (n=8), incomplete questionnaire (n=14) and hospitalization for the SARS-CoV-2 (n=2). Informed consent was obtained from all patients and the study was approved by the Ethics Committee of the University Hospital of Strasbourg on April 3, 2020 (CE-2020-31).

Table 1. Characteristics of the study population.

Characteristics	SARS-CoV-2 patients (n=347)	"PCR+" patients (n = 97)	"PCR-" patients (n = 250)	p-value "PCR+" vs. "PCR-"
Median age [range]	37 [18 -78]	35 [20 - 73]	38 [18 - 78]	0.053
Gender no (%)				
Female	234 (67.4)	67 (69.1)	167 (66.8)	0.69
Male	113 (32.6)	30 (30.9)	83 (33.2)	
Medical history no (%)				
Obesity	23 (6.6)	8 (8.3)	15 (6)	0.45
Hypertension	13 (3.8)	3 (3.1)	10 (4)	0.69
Cardiovascular diseases	4 (1.2)	1 (1)	3 (1.2)	0.89
Diabetes	5 (2)	0 (0)	5 (1.4)	0.16
Chronic Respiratory Diseases	21 (6.1)	6 (6.2)	15 (6)	0.95
Immunosuppression	1 (0.3)	0 (0)	1 (0.4)	0.53
Cancer/ Blood disease	6 (1.7)	0 (0)	6 (2.4)	0.12
Tobacco	32 (9.2)	7 (7.2)	25 (10)	0.42
No medical history	242 (69.7)	66 (68.0)	176 (70.4)	0.67
Occupation no (%)				
Medical / paramedical professional	129 (37.2)	77 (79.4)	52 (20.8)	<0.05*
Non-medical field or no occupation/retired	218 (62.8)	20 (20.6)	198 (79.2)	

* statistically significant (p<0.05)

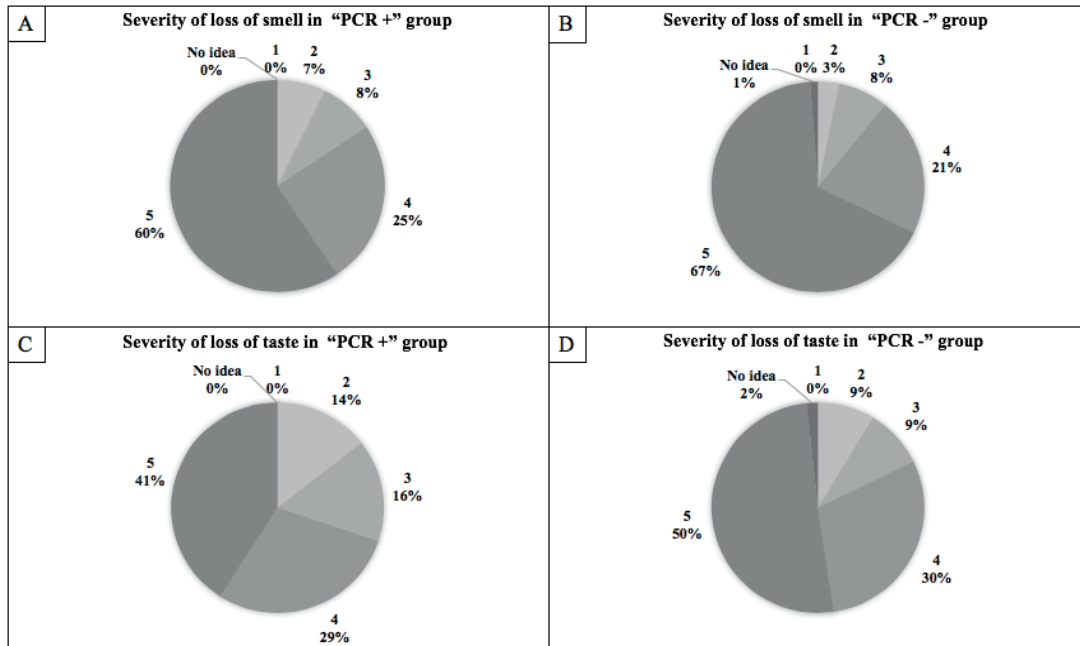


Figure 1. Comparison of self-rating of the severity of loss of smell (A and B) and taste (C and D) between the patients with a RT-PCR proven SARS-CoV-2 diagnosis ("PCR+" group) and patients with a clinical diagnosis ("PCR-" group). Severity of loss of smell and taste were assessed by the following scales: for smell: 1. normosmia, 2. mild hyposmia, 3. Moderate hyposmia, 4. Severe hyposmia and 5. Anosmia and for taste: 1. Normal taste, 2. Mild loss of taste, 3. Moderate loss of taste, 4. Severe loss of taste and 5. Unable to taste at all. No statistical difference was found between the "PCR+" and "PCR-" groups in terms of severity of loss of smell and taste ($p > 0.05$).

In a cohort of 347 outpatients, 97 patients (28%) median age 35 years [20 – 73] had a RT-PCR-proven SARS-CoV-2 infection and 250 patients (72%) median age 38 years [18 – 78]) had a clinical diagnosis (Table 1). Sex ratio was balanced ($p = 0.69$). In the "PCR+" group, 77 patients (79.4%) were working in the medical/paramedical field versus 52 (20%) in the "PCR-" group ($p < 0.05$). No previous medical history was found in 66 "PCR+" patients (68%) versus in 176 "PCR-" patients (70.4%) ($p = 0.67$). Olfactory loss was more frequently associated with flavor perception disorders ($n = 83$ "PCR+" (85.6%) vs $n = 228$ "PCR-" (91.2%) $p = 0.12$) than with taste loss ($n = 34$ "PCR+" (35.1%) vs $n = 89$ "PCR-" (35.6%), $p = 0.92$) (Table 2). No statistical difference was found for the self-rating of the severity of olfactory and taste loss (Figure 1). Olfactory loss was an isolated symptom in 6 "PCR+" patients (6.2%) vs. 14 "PCR-" patients (5.6%) ($p = 0.83$), while it appeared before the onset of other symptoms in $n = 6$ "PCR+" (6.2%) vs. $n = 22$ "PCR-" (8.8%) ($p = 0.42$), and at the same time as other symptoms in $n = 17$ "PCR+" (17.5%) vs. $n = 44$ "PCR-" (17.6%). Symptoms associated with loss of smell are reported in Table 2. Only 6 patients had medication (chloroquine ($n = 1$), oral ($n = 1$) or nasal ($n = 4$) corticosteroid therapy). Preliminary results of smell and taste recovery (Table 2) showed a higher rate of full recovery of smell in the "PCR+" group ($n = 12$ (12.5%) vs $n = 11$ (4.4%), $p = 0.01$) with a two-day difference in median duration symptom (12 days "PCR+" group vs. 10 days "PCR-", $p = 0.02$).

Post-infectious loss of smell is one of the main causes of olfac-

tory loss in adults. Many common viruses, including coronaviruses, are known to cause upper respiratory tract infections, as well as post-infectious loss of smell⁽³⁾. Usually, middle-age women are predominantly affected, but in SARS-CoV-2-related olfactory loss, recent studies showed that patients were usually younger than 40 years, with a balanced sex ratio^(4,5). Patients had fewer comorbidities in this study, due to their younger age but Lechien et al.⁽⁴⁾ confirmed that there was no significant association between co-morbidities and the occurrence of smell and taste loss.

A major limitation was the lack of tested patients $n = 250$ (72%), as testing capacities were and are still limited in our country. Healthcare authorities prioritized the testing of specific groups of patients (symptomatic healthcare workers, severe cases...), which explains the higher number of healthcare workers diagnosed by RT-PCR in this study. Another limitation was the inability to perform olfactory tests because patients were still contagious with a median duration of symptom of 10 days. Olfactory tests are recommended to confirm olfactory loss because of a low correlation to a self-rating olfactory loss. Few studies with olfactory tests are currently available^(6,7). Moreover, the severity of loss of smell in mild, moderate, severe hyposmia and anosmia is based in a questionnaire and not in a validated quantitative tool of smell and taste assessment.

Loss of smell and taste is a useful sign for the clinical diagno-

Table 2. Characteristics of loss of smell and taste associated with SARS-CoV-2 infection.

	SARS-Cov-2 patients (n=347)	"PCR+" patients (n = 97)	"PCR-" patients (n = 250)	p-value "PCR+" vs "PCR-"
Type of disorder no. (%)				
Olfactory disorder	345 (99.4)	96 (99)	249 (99.6)	0.49
Flavor perception disorder	311 (89.6)	83 (85.6)	228 (91.2)	0.12
Taste disorder	123 (35.5)	34 (35.1)	89 (35.6)	0.92
Median duration of symptoms in days [range]				
	10 [1 – 43]	12 [1 – 40]	10 [1 – 43]	0.02*
Symptoms presentation no. (%)				
Progressively	41 (11.8)	18 (18.6)	23 (9.2)	0.02*
Suddenly	251 (72.3)	63 (65)	188 (75.2)	0.06
No idea	55 (15.9)	16 (16.5)	39 (15.6)	0.84
Isolated loss of smell and taste	20 (5.8)	6 (6.2)	14 (5.6)	0.83
Loss of smell and taste before the onset of other symptoms	28 (8.1)	6 (6.2)	22 (8.8)	0.42
Same time as other symptoms	61 (17.6)	17 (17.5)	44 (17.6)	0.99
Second time after initial symptoms	223 (64.3)	65 (67)	158 (63.2)	0.51
No idea	15 (4.3)	3 (3.1)	12 (4.8)	0.48
Symptoms evolution no. (%)				
Constant	261 (75.2)	74 (76.3)	187 (74.8)	0.77
Fluctuation	79 (22.8)	22 (22.7)	57 (22.8)	0.98
No idea	7 (2)	1 (1)	6 (2.4)	0.43
Loss of smell and taste no. (%)				
As an isolated symptom	21 (6.1)	6 (6.2)	15 (6)	0.95
Associated with other symptoms	326 (94)	91 (93.8)	235 (94)	
Fever	170 (41.5)	50 (51.6)	120 (48)	0.55
Cough	151 (43.5)	47 (48.5)	104 (41.6)	0.25
Respiratory problems	46 (13.3)	16 (16.5)	30 (12)	0.27
Nasal obstruction	125 (36)	31 (32)	94 (37.6)	0.33
Rhinorrhea	132 (38)	40 (41.2)	92 (36.8)	0.44
Sinus pain	91 (26.2)	27 (27.8)	64 (25.6)	0.67
Headache	166 (47.8)	50 (51.6)	116 (46.4)	0.39
Sore throat	14 (4)	3 (3.1)	11 (4.4)	0.58
Digestive problems	103 (29.7)	29 (29.9)	74 (29.6)	0.96
Arthralgia - myalgia	53 (15.3)	15 (15.5)	38 (15.2)	0.95
Asthenia	44 (12.7)	13 (13.4)	31 (12.4)	0.80
Loss of smell as the strongest symptom				
	127 (39.3)	29 (33)	98 (41.7)	0.15
Recovery n (%)				
Full recovery of smell	23 (6.7)	12 (12.5)	11 (4.4)	0.01*
Full recovery of taste	26 (8.3)	9 (10.8)	17 (7.4)	0.33
Partial recovery of smell	131 (37.8)	42 (43.8)	89 (35.7)	0.12
Partial recovery of taste	126 (40.3)	37 (44.6)	89 (38.7)	0.35
No recovery of smell	186 (53.9)	41 (42.7)	145 (58.2)	0.01*
No recovery of taste	158 (50.2)	36 (43.4)	122 (52.6)	0.15
Worsening	4 (1.2)	1 (1)	3 (1.2)	0.89

* statistically significant (p<0.05)

sis of SARS-CoV-2 infection as it manifests early in the disease process in 109 patients (31.5%). Early reports referred to isolated loss of smell as a tell-tale sign of a SARS CoV-2. However, this was the least common situation, occurring in 48 patients (13.9%) either isolated or before other symptoms, which matches the results obtained by Hopkins et al. ⁽⁵⁾ (13%) and Lechien et al. ⁽⁴⁾ Nasosinus symptoms associated with loss of sense of smell have been frequently reported in this study and in the literature. Results are highly variable, ranging from "generally no sinonasal symptoms" ⁽⁸⁾ to "81.1% of nasal congestion with rhinorrhea"

⁽⁴⁾. At the acute phase of an upper respiratory tract infection, olfactory disorders may be caused by severe inflammation of the nasal mucosa with nasal obstruction blocking the passage of olfactory molecules to the olfactory clefts. However, the SARS-CoV-2 is known to be a neurotropic virus that can spread from the peripheral olfactory system to the central system. The hypothesis of direct damage of the olfactory pathways by the SARS-CoV-2 is highly probable, and could explain olfactory loss, in patients without sinonasal symptoms or with persistent olfactory loss after the acute phase of the infection ⁽⁹⁾.

In conclusion, during the SARS-CoV-2 pandemic, this study showed that outpatients with loss of smell and taste with a clinical diagnosis had strong similarities with the RT-PCR proven SARS-CoV-2 patients and should be considered positive. However, the presence of this symptom cannot replace a diagnosis by RT-PCR.

Conflict of interest

The authors state that they have no conflict of interest.

Acknowledgement

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SUPPLEMENTARY INFORMATION

Annex 1. 28-questions survey.

1. Agreement to participate in the study	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2. Are you living in East of France?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. Date of birth		
4. Age		
5. What is your gender ?	<input type="checkbox"/> Male	<input type="checkbox"/> Female
6. Are you working in the medical/paramedical field?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
7. What is your occupation?		
8. What type of problem do you have?	<input type="checkbox"/> Olfactory loss <input type="checkbox"/> Flavor perception disorder <input type="checkbox"/> Taste loss (inability to detect the four basic tastes: sweet, salty, sour and bitter)	
9. When did the problem start? (exact date if possible)		
10. How did it start ?	<input type="checkbox"/> Progressively	<input type="checkbox"/> Suddenly <input type="checkbox"/> I don't know
11. Do you have any associated symptoms?	<input type="checkbox"/> No <input type="checkbox"/> Fever <input type="checkbox"/> Asthenia <input type="checkbox"/> Sinus pain <input type="checkbox"/> Nasal obstruction <input type="checkbox"/> Rhinorrhea <input type="checkbox"/> Sore throat	<input type="checkbox"/> Headache <input type="checkbox"/> Cough <input type="checkbox"/> Respiratory problems <input type="checkbox"/> Digestive problems <input type="checkbox"/> Arthralgia-myalgia <input type="checkbox"/> Other:
12. What is or was the strongest symptom? (only one answer)	<input type="checkbox"/> Olfactory/taste loss <input type="checkbox"/> Fever <input type="checkbox"/> Asthenia <input type="checkbox"/> Sinus pain <input type="checkbox"/> Nasal obstruction <input type="checkbox"/> Rhinorrhea <input type="checkbox"/> Sore throat <input type="checkbox"/> Headache	<input type="checkbox"/> Cough <input type="checkbox"/> Respiratory problems <input type="checkbox"/> Digestive problems <input type="checkbox"/> Arthralgia-myalgia <input type="checkbox"/> I don't know <input type="checkbox"/> All symptoms had the same intensity <input type="checkbox"/> Other:
13. How did your loss of smell and taste come about?	<input type="checkbox"/> Isolated <input type="checkbox"/> Before the onset of the other symptoms <input type="checkbox"/> Same time as other symptoms <input type="checkbox"/> Second time after initial symptoms <input type="checkbox"/> I don't know	
14. Is your loss of smell and taste fluctuating or constant?	<input type="checkbox"/> Fluctuating	<input type="checkbox"/> Constant <input type="checkbox"/> I don't know
15. At the onset of your loss of smell, how severe was your loss on a scale of 1 to 5 (1 = normal and 5 = total loss)?	1 Able to smell normally (normosmia) 2 Mild hyposmia 3 Moderate hyposmia 4 Severe hyposmia 5 Unable to smell at all (very severe smell loss or anosmia)	
16. How is your loss of smell progressing?	<input type="checkbox"/> Full recovery of smell <input type="checkbox"/> Partial recovery of smell	<input type="checkbox"/> No recovery <input type="checkbox"/> Worsening
17. If you have a full recovery, how long did it take you to recover?	<input type="checkbox"/> < 3 days <input type="checkbox"/> 3-7 days <input type="checkbox"/> 7- 14 days	<input type="checkbox"/> 2 to 3 weeks <input type="checkbox"/> 3 to 4 weeks
18. At the onset of your loss of taste, how severe was your loss on a scale of 1 to 5 (1 = normal and 5 = total loss)?	1 Normal taste 2 Mild loss of taste 3 Moderate loss of taste 4 Severe loss of taste 5 Unable to taste at all (agueusia)	
19. How is your loss of taste progressing?	<input type="checkbox"/> Full recovery of smell <input type="checkbox"/> Partial recovery of smell	<input type="checkbox"/> No recovery <input type="checkbox"/> Worsening
20. If you have a full recovery, how long did it take you to recover?	<input type="checkbox"/> < 3 days <input type="checkbox"/> 3-7 days <input type="checkbox"/> 7- 14 days	<input type="checkbox"/> 2 to 3 weeks <input type="checkbox"/> 3 to 4 weeks
21. Do you have had a treatment for your loss of smell and taste?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

22. If yes, what was it?		
23. Do you have a history of loss of smell?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
24. If yes, which etiology?	<input type="checkbox"/> A head trauma <input type="checkbox"/> An upper respiratory tract infection <input type="checkbox"/> A chronic Rhinosinusitis <input type="checkbox"/> Other:	
25. Do you have a medical his-tory?	<input type="checkbox"/> Hypertension <input type="checkbox"/> Diabetes <input type="checkbox"/> Chronic respiratory disease <input type="checkbox"/> Cardiovascular disease <input type="checkbox"/> Immunosuppression	<input type="checkbox"/> Recent cancer or blood disease <input type="checkbox"/> Obesity <input type="checkbox"/> Active smoking <input type="checkbox"/> No medical history <input type="checkbox"/> Other:
26. Did you have a SARS-CoV-2 test (RT-PCR)?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
27. If yes, was is positive?	<input type="checkbox"/> Yes <input type="checkbox"/> No	
28. What type of care have you had?	<input type="checkbox"/> Ambulatory care <input type="checkbox"/> Hospitalization in a medical department or in reanimation *	