

1 **Olfactory and gustative disorders for the diagnosis of COVID-19**

2
3 **Sophia Boudjema^{1,2}*, Julie Finance^{2,3}*, Fatoumata Coulibaly², Line Meddeb¹, Hervé**
4 **Tissot-Dupont^{1,2}, Moïse Michel¹, Jean Christophe Lagier^{1,2}, Matthieu Million^{1,2},**
5 **Thomas Radulesco⁴, Justin Michel⁴, Philippe Brouqui^{1,2}, Didier Raoult^{1,2}, Florence**
6 **Fenollar^{1,5}, Philippe Parola^{1,5},**

7 * Equal contributors

8 ¹ IHU-Méditerranée Infection, Marseille, France

9 ² Aix Marseille Univ., IRD, AP-HM, MEPHI, Marseille, France

10 ³ Assistance Publique de Marseille, Explorations Fonctionnelles Respiratoires, Aix Marseille
11 Université, France

12 ⁴ Department of otorhinolaryngology, head and neck surgery, Assistance Publique-Hôpitaux
13 de Marseille, Aix Marseille Univ., Marseille, France.

14 ⁵ Aix Marseille Univ., IRD, AP-HM, SSA, VITROME, Marseille, France

15 * **Corresponding author:** Prof. Philippe Parola. VITROME, Institut Hospitalo-Universitaire
16 Méditerranée Infection, 19-21 Boulevard Jean Moulin 13385 Marseille Cedex 05,
17 France. Phone: + 33 (0) 4 13 73 24 01. Fax: + 33 (0) 4 13 73 24 02.

18 Email: philippe.parola@univ-amu.fr.

19
20
21
22
23 **Key words:** COVID-19, SARS-CoV-2, anosmia, ageusia, smell, taste.
24
25

26 Early in the course of the still on going COVID-19 pandemic, clinicians noticed the
27 significance of olfactory and gustative disorders¹. A recent systematic review and meta-
28 analysis of ten and nine available studies, reported a prevalence of 52.7% olfactory and 43.9%
29 gustatory dysfunction respectively².

30 As soon as the outbreak reached France, we established in Marseille massive early
31 PCR screening from a nasopharyngeal sample for patients suspected of having COVID-19,
32 and anybody seeking treatment or SARS-CoV-2 screening³. Here, we questioned for recent
33 loss of smell (LOS) and/or taste (LOT) in a cohort of patients and health care workers (HCW)
34 before they were tested for SARS-CoV-2 by asking “have you lost your sense of smell or
35 taste in the last 2 months?”

36 A total of 3,497 patients were questioned between 24 March and 25 April 2020
37 (Table). SARS-CoV-2 was detected by PCR on nasopharyngeal swabs in 673/3497 (19.24%)
38 of the patients tested. Of the 673 positive patients, 280 (41.6%) reported LOS and LOT, 41
39 (6.1%) reported LOS only, and 35 (5.2%) reported LOT only. Of the 2860 COVID-19
40 negative patients, 137 (4.85%) reported a LOS and LOT, 39 (1.38%) reported LOS only, and
41 81 (2.85%) reported LOT only. Among 2884 patients with no loss, 317 (10.99%) tested
42 positive for COVID-19 and 2567 (89.0%) tested negative. Overall, the prevalence of LOS
43 and/or LOT in COVID-19 patients was 356/673 (53%), which was higher than in non-
44 infected patients (257/2,824; 9.1%, $p < 0.001$; Chi-squared test). LOS and/or LOT were more
45 frequent in female COVID-19 patients (233/401, 58.10%) than in male COVID-19 patients
46 (123/272, 45.22%), particularly in patients under the age of 65 (women 221/361, 61.21%;
47 men 113/231, 48.91%) ($p < 0.05$). Regarding the diagnosis of COVID-19, the positive
48 predictive value (PPV) was 67.15 % for LOS and LOT, 51.25% for LOS only, 30.17% for
49 LOT only, and 58.08% (60% in women and 53% in men under the age of 65) for LOS and/or

50 LOT. Overall, the negative predictive value (NPV) of smell and/or taste disorders was
51 89.01% (92% in men and 88% in women under the age of 65) (**Table 1**).

52 A total of 432 HCWs, including 271 women, were tested for COVID-19 using RT-
53 PCR on nasopharyngeal swabs, in addition to an IgM / IgG antibody test (Sure Bio-Tech,
54 Hong Kong) which was performed according to the manufacturer's instructions, and using an
55 in-house indirect immunofluorescence assay (IFA), as described⁴, in the context of
56 occupational medicine consultation between 17 and 22 April 2020. Among of them, 23
57 reported having a fever or cough in the last two months. Of the HCWs who did not report
58 having a fever or cough (n=409), seven reported LOS and LOT, and two with LOT only. Of
59 the HCWs without a fever or cough, 10 (2.4%) reported LOS and/or LOT and all were
60 positive for COVID-19. In addition, three HCWs without a fever or cough did not report any
61 smell or taste loss, despite testing positive for SARS-Cov-2. In this population of HCWs, the
62 PPV of LOS and/or LOT was 73% and the NPV was 99%.

63 In this study, we did not use one of the numerous tests of olfactory/gustatory function,
64 nor did we use a score according to the number of smells recognised. We made the choice to
65 use a single question, in order to be able to use this question in the context of real-life triage,
66 family medicine, occupational medicine and self-evaluation, at an early stage of COVID.

67 To date, the exact pathogenesis responsible for olfactory or gustatory effects in
68 COVID-19 patients is not known². In acute phases of upper respiratory infection (URI), it is
69 common to experience transient olfactory symptoms, sometimes accompanied by taste
70 disorders, as a result of nasal inflammation, mucosal oedema, and obstruction of airflow.
71 SARS-CoV-2 may also cause an inflammatory response in the nasal cavity that temporarily
72 leads to the obstruction of airflow and then to anosmia/ageusia. Indeed, cells in the olfactory
73 epithelium present the highest expression of the SARS-CoV-2 receptor, angiotensin-
74 converting enzyme 2, making them a potential specific target.² Interestingly, the olfactory

75 bulb is known as an important pathway for neurotropic viruses such as influenza viruses and
76 previously known coronaviruses.⁵ However, these disorders have not been described in
77 previous URI epidemics, although this may be a bias of observation.

78 We found a higher prevalence of smell and taste complaints in women than in men. In
79 addition, we revealed that smell and taste complaints were more prevalent under the age of
80 65, whereas there were no difference in uninfected patients. This result is consistent with a
81 previous cross-sectional survey⁶. Moreover, our questionnaire appeared to be very suitable for
82 HCWs because this population in our institution is mainly composed of young women.

83 Questioning patients and HCWs will be useful for selecting patients or HCWs to be
84 tested in countries where access to testing is politically or technically limited, or when
85 identifying patients to be isolated or self-isolated while awaiting testing and treatment, and
86 with regard to taking public health measures.

87 **Ethics**

88 Data presented herein were collected in the context on regular care for patients, and
89 occupational medicine for HCWs; and analysed retrospectively using the electronic health
90 recording system of the hospital. This study is part of a non-interventional retrospective study
91 that was approved by our institutional review board committee (Mediterranean Infection N°:
92 2020-021). According to European General Data Protection Regulation No 2016/679, patients
93 were informed of the potential use of their medical data (N° MR 5010010520 in the AP-HM
94 register) and that they could refuse the use of their data.

95

96 **Transparency declaration**

97 The authors declare no competing interests.

98

99 **Acknowledgments**

100 This study was supported by the Institut Hospitalo-Universitaire (IHU) Méditerranée
101 Infection, and the French National Research Agency under the “Investissements d’avenir”
102 programme, reference ANR-10-IAHU-03.

103

104 **References**

105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136

1. Ollarves-Carrero MF, Rodriguez-Morales AG, Bonilla-Aldana K et al. Anosmia in a healthcare worker with COVID-19 in Madrid, Spain. *Travel Med Infect Dis* 2020: 101666. <https://doi.org/10.1016/j.tmaid.2020.101666>
2. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham C. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. *Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg* 2020. DOI: [10.1177/0194599820926473](https://doi.org/10.1177/0194599820926473)
3. Lagier JC, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A, Honoré S, Gaubert JY, Fournier PE, Tissot-Dupont H, Chabrière E, Stein A, Deharo JC, Fenollar F, Rolain JM, Obadia Y, Jacquier A, La Scola B, Brouqui JB, Drancourt M, Parola P, Raoult D, and IHU COVID-19 Task force. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. *Travel Med Infect Dis* 2020, in press; <https://doi.org/10.1016/j.tmaid.2020.101791>
4. Edouard S, Colson P, Melenotte M, De Pinto F, Thomas L, La Scola B, Million M, Tissot-Dupont H, Gautret P, Stein A, Brouqui P, Parola P, Lagier JC, Raoult D, Drancourt M. Evaluating the serological status of COVID-19 patients using an indirect immunofluorescent assay, France. *Eur J Clin Microbiol Infect* 2020, in press.
5. Gengler I, Wang JC, Speth M. Sinonasal pathophysiology of SARS-CoV-2 and COVID-19: A systematic review of the current evidence. *Laryngoscope Investig Otolaryngo* 2020;1–6. <https://doi.org/10.1002/lio2.384>
6. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini G, Antinori S, Galli M. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. 2020 Mar 26:ciaa330. doi: 10.1093/cid/ciaa330. Epub ahead of print.

137 Table 1: Olfactory and gustatory dysfunctions in patients seeking SARS-Cov-2 testing
 138 according to gender and threshold age 65 at the IHU Mediterranean-Infection, Marseille,
 139 France, between 24 March and 25 April 2020. CoV+ and CoV- : patients testing positive and
 140 negative for SARS-Cov-2 respectively. LOT: loss of taste; LOS: loss of smell. PPV Positive
 141 predictive value; NPV: negative predictive value.
 142

	Total n=3,497 ^s		Men n=1,801 ^{ss}		Women n= 1,696 ^{sss}		<65 n = 3,223		>65 n = 274	
	CoV+	CoV-	CoV+	CoV-	CoV+	CoV-	CoV+	CoV-	CoV+	CoV-
N	673	2,824	272	1,529	401	1,295	592	2,631	81	193
LOT only	35 ^a	81 ^a	10 [*]	36 [*]	25	45	31 ^k	78 ^k	4	3
PPV (%)	30.17		21.74		35.71		28.44		57.14	
LOS only	41 ^b	39 ^b	16 ^e	14 ^e	25 ^h	25 ^h	37 ^l	35 ^l	4	4
PPV (%)	51.25		53.33		50		51.39		50	
LOS and LOT	280 ^c	137 ^c	97 ^f	55 ^f	183 ⁱ	82 ⁱ	266 ^m	133 ^m	14 ^o	4 ^o
PPV (%)	67.15		63.82		69.06		67.17		77.78	
LOS and/or LOT	356 ^d	257 ^d	123 ^g	105 ^g	233 ^j	152 ^j	334 ⁿ	246 ⁿ	22 ^p	11 ^p
PPV (%)	58.08		53.95		60.52		57.59		66.67	
No loss	317	2,567	149	1,424	168	1,143	258	2,385	59	182
NPV (%)	89.01		90.53		87.19		90.24		75.52	

143 ^s mean age 42.5 years, SD=15.16 years); ^{ss} mean age 42.53 years, SD= 14.98 years; ^{sss} mean age 42.42 years,
 144 SD= 15.35 years; * p<0.05 ^{a - p}: p<0.001. All statistical analyses were performed using IBM SPSS Statistics
 145 (version 20 for windows). The Chi-squared test, mean comparison, and a logistical regression were used to
 146 explore the links between olfactory or gustative disorders and variables (age, gender). For statistical significance,
 147 the p<0.05 threshold was chosen. The performance of a binary classification of our method was measured by
 148 sensitivity and specificity percentages
 149