



**HAL**  
open science

## **Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study**

Jérome René Lechien, Carlos Miguel Chiesa-Estomba, Daniele R. de Siaty, Mihaela Horoi, Serge Daniel Le Bon, Alexandra Rodriguez, Didier Dequanter, Serge A. Blecic, Fahd El Afia, Léa Distinguin, et al.

### ► To cite this version:

Jérome René Lechien, Carlos Miguel Chiesa-Estomba, Daniele R. de Siaty, Mihaela Horoi, Serge Daniel Le Bon, et al.. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European Archives of Oto-Rhino-Laryngology*, 2020, 277 (8), pp.2251-2261. <10.1007/s00405-020-05965-1>. <hal-02938438>

**HAL Id: hal-02938438**

**<https://hal.science/hal-02938438v1>**

Submitted on 27 Oct 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

# Olfactory and gustatory dysfunctions as a clinical presentation of mild- to- moderate forms of the coronavirus disease (COVID- 19):a multicenter European study

Jerome R. Lechien<sup>1,2,3,4</sup> · Carlos M. Chiesa- Estomba<sup>1,5</sup> · Daniele R. De Siat<sup>1,6</sup> · Mihaela Horoi<sup>4</sup> · Serge D. Le Bon<sup>4</sup> · Alexandra Rodriguez<sup>4</sup> · Didier Dequanter<sup>4</sup> · Serge Blecic<sup>7</sup> · Fahd El Afia<sup>1,3</sup> · Lea Distinguin<sup>1,3</sup> · Younes Chekkoury- Idrissi<sup>1,3</sup> · Stéphane Hans<sup>3</sup> · Irene Lopez Delgado<sup>1,8</sup> · Christian Calvo- Henriquez<sup>1,9</sup> · Philippe Lavigne<sup>1,10</sup> · Chiara Falanga<sup>1,11</sup> · Maria Rosaria Barillari<sup>1,11</sup> · Giovanni Cammaroto<sup>1,12</sup> · Mohamad Khalife<sup>13</sup> · Pierre Leich<sup>14</sup> · Christel Souchay<sup>14</sup> · Camelia Rossi<sup>15</sup> · Fabrice Journe<sup>2</sup> · Julien Hsieh<sup>1,16</sup> · Myriam Edjlali<sup>17,18</sup> · Robert Carlier<sup>18</sup> · Laurence Ris<sup>19</sup> · Andrea Lovato<sup>20</sup> · Cosimo De Filippis<sup>20</sup> · Frederique Coppee<sup>21</sup> · Nicolas Fakhry<sup>1,22</sup> · Tareck Ayad<sup>1,10</sup> · Sven Saussez<sup>1,2,4,13</sup>

- <sup>1</sup> COVID-19 Task Force of the Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS), Paris, France
- <sup>2</sup> Department of Human Anatomy and Experimental Oncology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium
- <sup>3</sup> Department of Otorhinolaryngology and Head and Neck Surgery, Foch Hospital, School of Medicine, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France
- <sup>4</sup> Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Bruxelles, CHU Saint-Pierre, School of Medicine, Université Libre de Bruxelles, Brussels, Belgium
- <sup>5</sup> Department of Otorhinolaryngology-Head and Neck Surgery, Hospital Universitario Donostia, San Sebastian, Spain
- <sup>6</sup> Department of Otorhinolaryngology and Head and Neck Surgery, CHU Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
- <sup>7</sup> Department of Neurology, EpiCURA Hospital, Ath, Belgium
- <sup>8</sup> Department of Otorhinolaryngology-Head and Neck Surgery, Hospital Quironsalud Valencia, Valencia, Spain
- <sup>9</sup> Department of Otolaryngology-Hospital Complex of Santiago de Compostela, Santiago de Compostela, Spain
- <sup>10</sup> Division of Otolaryngology-Head and Neck Surgery, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada
- <sup>11</sup> Division of Phoniatrics and Audiology, Department of Mental and Physical Health and Preventive Medicine, University of L. Vanvitelli, Naples, Italy
- <sup>12</sup> Department of Otolaryngology-Head and Neck Surgery, Morgagni Pierantoni Hospital, Forli, Italy
- <sup>13</sup> Department of Otolaryngology-Head and Neck Surgery, EpiCURA Hospital, Baudour, Belgium
- <sup>14</sup> Department of Otolaryngology-Head and Neck Surgery, CHU Ambroise Paré, Mons, Belgium
- <sup>15</sup> Division of Infectious Disease, CHU Ambroise-Paré, Mons, Belgium
- <sup>16</sup> Rhinology-Olfactology Unit, Department of Otorhinolaryngology, Head and Neck Surgery, Geneva University Hospitals (HUG), Geneva, Switzerland
- <sup>17</sup> Department of Neuroradiology, Université Paris-Descartes-Sorbonne-Paris-Cité, IMABRAIN-INSERM-UMR1266, DHU-Neurovasc, Centre Hospitalier Sainte-Anne, Paris, France
- <sup>18</sup> Department of Radiology, APHP, Hôpitaux R. Poincaré-Ambroise Paré, DMU Smart Imaging, GH Université Paris-Saclay, U 1179 UVSQ/Paris-Saclay, Paris, France
- <sup>19</sup> Department of Neurosciences, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium
- <sup>20</sup> Department of Neuroscience, Audiology Unit, Padova University, Treviso, Italy
- <sup>21</sup> Department of Metabolic and Molecular Biochemistry, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium
- <sup>22</sup> Department of Otorhinolaryngology-Head and Neck Surgery, APHM, Aix Marseille University, La Conception University Hospital, Marseille, France

## **Abstract**

**Objective** To investigate the occurrence of olfactory and gustatory dysfunctions in patients with laboratory-confirmed COVID-19 infection.

**Methods** Patients with laboratory-confirmed COVID-19 infection were recruited from 12 European hospitals. The following epidemiological and clinical outcomes have been studied: age, sex, ethnicity, comorbidities, and general and otolaryngological symptoms. Patients completed olfactory and gustatory questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey, and the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS).

**Results** A total of 417 mild-to-moderate COVID-19 patients completed the study (263 females). The most prevalent general symptoms consisted of cough, myalgia, and loss of appetite. Face pain and nasal obstruction were the most disease-related otolaryngological symptoms. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively. There was a significant association between both disorders ( $p < 0.001$ ). Olfactory dysfunction (OD) appeared before the other symptoms in 11.8% of cases. The sQO-NS scores were significantly lower in patients with anosmia compared with normosmic or hyposmic individuals ( $p = 0.001$ ). Among the 18.2% of patients without nasal obstruction or rhinorrhea, 79.7% were hyposmic or anosmic. The early olfactory recovery rate was 44.0%. Females were significantly more affected by olfactory and gustatory dysfunctions than males ( $p = 0.001$ ).

**Conclusion** Olfactory and gustatory disorders are prevalent symptoms in European COVID-19 patients, who may not have nasal symptoms. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection.

---

## 1 Introduction

2 The coronavirus disease 2019 (COVID-19) is an ongo-ing viral pandemic that emerged from East Asia and quickly spread  
3 to the rest of the world [1]. This infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)  
4 and is so far responsible for more than 15,000 deaths worldwide [2]. Human-to-human transmis- sion is character- ized by a  
5 troubling exponential rate, which has led to steep curves of onset in many areas [3]. Accord- ing to the clinical studies from  
6 Asia, the most prevalent symptoms consist of fever, cough, dyspnea, sputum pro- duction, myalgia, arthralgia, headache,  
7 diarrhea, rhinor- rhea, and sore throat [4, 5]. The spread of the COVID-19 infection in Europe has highlighted a new atypical  
8 presen- tation of the disease: patients with olfactory and gustatory dysfunctions. The occurrence of smell dysfunction in viral  
9 infections is not new in otolaryngology. Many viruses may lead to olfactory dysfunction (OD) through an inflamma- tory  
10 reaction of the nasal mucosa and the developmentof rhinorrhea; the most familiar agents being rhinovirus, parainfluenza  
11 Epstein–Barr virus, and some coronavirus [6, 7]. However, olfactory dysfunction linked to COVID- 19 infection seems  
12 particular as it is not associated with rhinorrhea.

13 Over the past few weeks, some European otolaryngolo- gists observed that many patients infected by SARS-CoV-2presented  
14 with severe olfactory and gustatory dysfunctions without rhinorrhea or nasal obstruction. At baseline, no COVID-19 was  
15 suspected in some of these patients, because they had no fever, cough, or other systemic complaints. Faced with numerous  
16 reports from otolaryngologists allaround Europe, the Young–Otolaryngologists of the Inter- national Federation of Oto-rhino-  
17 laryngological Societies (YO-IFOS) decided to conduct an internatio- logical study to characterize olfactory and  
18 gustatory disor- ders in infected patients.

19 The aim of this study is to investigate and characterize the occurrence of olfactory and gustatory disorders in patients with  
20 laboratory-confirmed COVID-19 infection.

## 21 Materials and methods

22 Three ethics committees approved the current study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303).  
23 Patients were invited to participate and the informed consentwas obtained.

## 24 Subjects and setting

25 The clinical data of patients with laboratory-confirmed COVID-19 infection have been collected from four BelgianHospitals  
26 (CHU Saint-Pierre, Brussels; CHU Ambroise Paré, Mons; EpiCURA, Baudour; EpiCURA, Ath), and University of Mons  
27 (Belgium). In addition to these ones, many other patients, infected physicians and nurses have been voluntarily enrolled in the  
28 study from the following hospitals: Foch Hospital (Paris, France); Ambroise Paré

29 Hospital (AP-HP, Paris), CHU Ambroise Paré (Mons, Bel- gium), Hospital Universitario Donostia (Donostia, Spain);  
30 Hospital Universitario Santiago de Compostela (Santiago de Compostela, Spain); Morgagni Pierantoni Hospital (Forli,  
31 Italy), Department of Neuroscience, Audiology Unit (Padova University, Treviso, Italy), and Medical Depart- ments of the  
32 Università degli Studi della Campania ‘Luigi Vanvitelli’ (Naples, Italy).

33 The following inclusion criteria have been considered: adult (> 18 years old); laboratory-confirmed COVID-19 infection  
34 (reverse transcription polymerase chain reaction, RT-PCR); native speaker patients, and patients clinically able to fulfill the  
35 questionnaire. The following exclusion criteria have been considered: patients with olfactory or gustatory dysfunctions  
36 before the epidemic; patients with- out a laboratory-confirmed COVID-19 infection diagnosis; patients who were in the  
37 intensive-care unit at the timeof the study (due to their health status). Thus, we mainly included mild-to-moderate COVID-  
38 19 patients, defined as patients without need of intensive cares. Since we focused on the prevalence of olfactory and  
39 gustatory disorders, clinical presentation was not considered in as inclusioncriteria.

## 40 Clinical outcomes

41 Clinical data have been prospectively collected during the ear, nose, and throat (ENT) consultation; in the patient’s room; or  
42 over the phone for house-bound patients or infectedhealth professionals. The data were also collected through anonline form for  
43 house-bound patients. The online question-naire was created with Professional Survey Monkey (San Mateo, CA, USA), so  
44 that each participant could complete the survey only once.

45 The selection of the relevant epidemiological and clinical features composing the questionnaire was car- ried out by the

46 COVID-19 Task Force of YO-IFOS, which includes otolaryngologists from North America, Europe, and Asia [8]. Experts  
47 analyzed the epidemiological publications of the current and the previous coronavirus infections, including SRAS-  
48 CoV-1 (2002); Middle-East respiratory syndrome-related coronavirus infection (MERS-CoV, 2012), and the COVID-19  
49 infection. From the literature, ten experts (JRL, SS, MH, JHS, PL, TA, LD, FEA, CCH, and CMCE) developed the  
50 question-naire, which consisted of four general questions (age, sex, ethnicity, and date of diagnosis); three general clinical  
51 questions (comorbidities, general, and ENT symptoms associated with COVID-19 infection); seven questions about  
52 olfactory function; four questions investigating gustatory function; and one question about the treatment of the COVID-  
53 19 infection. All patients were asked to complete the short version of the Questionnaire of Olfac-tory Disorders-Negative  
54 Statements (sQOD-NS) [9]. The questionnaire has been translated into Spanish, Italian, and English by two native speaker  
55 otolaryngologists for each language.

## 56 **Olfactory and gustatory outcomes**

57 The occurrence of anosmia or hyposmia has been identified in the questionnaire. The impact of olfactory dysfunction on the  
58 quality of life (QoL) of patients has been assessed through the validated sQOD-NS (Appendix 1) [9]. This is a seven-item  
59 patient-reported outcome questionnaire including social, eating, annoyance, and anxiety questions. Each item is rated on a  
60 scale of 0–3, with higher scores reflecting better olfactory-specific QoL. The total score ranges from 0 (severe impact on QoL)  
61 to 21 (no impact on QoL) [9]. The rest of the olfactory and gustatory questions were based on the smell and taste component  
62 of the National Health and Nutrition Examination Survey [10]. This population survey was implemented by the Centers for  
63 Disease Control and Prevention to continuously monitor the health of adult citi-zens in the United States through a nationally  
64 representa-tive sample of 5000 persons yearly [10]. The questions have been chosen to characterize the variation, timing,  
65 and associated symptoms of both olfactory and gustatory dys-functions, and, therefore, they suggest a potential etiology.  
66 Note that we assessed the mean recovery time of olfaction through four defined propositions: 1–4 days; 5–8 days; 9–14 days;  
67 and > 15 days.

68 Referring to the studies that have demonstrated that the viral load was significantly decreased after 14 days [11], we  
69 assessed the short-term olfaction non-recovery rate on patients exhibiting double criteria: an onset of the infec-tion > 14 days  
70 before the assessment and the lack of general symptoms at the time of the evaluation.

## 71 **Statistical methods**

72 Statistical Package for the Social Sciences for Windows (SPSS version 22,0; IBM Corp, Armonk, NY, USA) was used to  
73 perform the statistical analyses. The potential associations between epidemiological, clinical and olfac-tory and gustatory  
74 outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi-  
75 square test. Incomplete responses were excluded from analysis. The differences in sQOD-NS scores between patients  
76 regarding the olfac-tory dysfunction were made through the Kruskal–Wallis test. A level of  $p < 0.05$  was used to determine  
77 statistical significance.

## 78 **Results**

79 A total of 417 patients completed the study. The mean age of patients was  $36.9 \pm 11.4$  years (range 19–77). There were 263  
80 females and 154 males. The following ethnicities composed the cohort: European (93.3%), South American (2.7%), Sub-  
81 Saharan African (2.2%), Black African (1.4%), Asian (0.2%), and North American (0.2%) (Table 1). The most prevalent  
82 comorbidities of patients were allergic rhi-nitis, asthma, high blood pressure, and hypothyroidism (Fig. 1). The mean time  
83 between the onset of the infection and the evaluation was  $9.2 \pm 6.2$  days. At the time of the study, 34.5% of patients were in  
84 the acute phase of the infec-tion, whereas the rest of the patients did not yet have general symptoms.

## 85 **Clinical outcomes**

86 The general symptoms of patients during the infection are described in Fig. 2. Cough, myalgia, loss of appetite, diar-rhea,  
87 fever, headache, and asthenia were the most prevalent symptoms, accounting for more than 45% of patients. The  
88 otolaryngological symptoms most related to the infection are reported in Table 2.

## 89 **Olfactory outcomes**

90 A total of 357 patients (85.6%) had olfactory dysfunction related to the infection. Among them, 284 (79.6%) patients were  
91 anosmic and 73 (20.4%) were hyposmic. Phantosmia and parosmia concerned 12.6% and 32.4% of patients during the disease

92 course, respectively. The olfactory dysfunction appeared before (11.8%), after (65.4%) or at the same time as the appearance  
93 of general or ENT symptoms (22.8%). Note that 9.4% of patients did not remember the time of onset of olfactory  
94 dysfunction and, therefore, were not considered for the percentage evaluation.

95 Considering the 247 patients with a clinically resolved infection (absence of general and ENT symptoms), the olfactory  
96 dysfunction persisted after the resolution of other symptoms in 63.0% of cases. The mean time between the onset of the  
97 disease and the assessment of this group of patients was  $9.77 \pm 5.68$  days.

98 The short-term olfaction recovery rate, which was assessed in 59 clinically cured patients, was 44.0%. The different recovery  
99 times of the olfactory function of patients who reported a recovery of the olfactory function are available in Fig. 3. In total,  
100 72.6% of these patients recovered olfactory function within the first 8 days following the resolution of the disease. Among  
101 the patients who reported anosmia, then, excluding hyposmic patients, the olfactory function recovered throughout the 8 first  
102 days following the resolution of the disease in 67.8% of cases (Fig. 3).

103 In the present study, 76 patients did not suffer from nasal obstruction or rhinorrhea (18.2%). Among them, 20.3% did not report  
104 olfactory dysfunction, whereas 66.2% and 13.5% suffered from anosmia and hyposmia, respectively.

105 **The impact of olfactory dysfunction on patient QoL is reported in Table 3. Anosmic patients at the time**  
106 **of the evaluation had a significant lower sQOD-NS score compared with hyposmic and normosmic**  
107 **individuals ( $p = 0.001$ ; Kruskal–Wallis).**

### 108 Gustatory outcomes

109 A total of 342 patients (88.8%) reported gustatory disorders, which was characterized by impairment of the following four taste  
110 modalities: salty, sweet, bitter, and sour. Note that 32 patients did not remember if they had gustatory dysfunction and,  
111 therefore, they were not considered for the assessment of the gustatory disorder prevalence. The gustatory dysfunction  
112 consisted of reduced/discontinued or distorted ability to taste flavors in 78.9% and 21.1% of patients, respectively.

113 Among the 43 patients without gustatory dysfunction, 19 (44.2%) have no olfactory dysfunction, whereas 16 (37.2%) and 4  
114 (9.3%) patients had anosmia or hyposmia.

115 The olfactory and gustatory disorders were constant and unchanged over the days in 72.8% of patients, whereas they fluctuated  
116 in 23.4% of patients. Among the patients who reported gustatory and olfactory disorders, 3.8% revealed that these disorders  
117 occurred during their rhinorrhea or nasal obstruction episodes.

118 Among the cured patients who had residual olfactory and/or gustatory dysfunction, 53.9% had isolated olfactory  
119 dysfunction, 22.5% had isolated gustatory dysfunction, and 23.6% had both olfactory and gustatory dysfunctions.

### 120 Olfactory and gustatory outcome associations

121 There was no significant association between comorbidities and the development of olfactory or gustatory dysfunctions.  
122 Olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction. There was a significant positive  
123 association between olfactory and gustatory dysfunctions ( $p < 0.001$ ). The statistical analysis identified a significant  
124 association between the fever and the anosmia ( $p = 0.014$ ). The females would be proportionally more affected by  
125 hyposmia or anosmia compared with males ( $p < 0.001$ ). Similar results were found for gustatory dysfunction ( $p = 0.001$ ,  
126 Mann–Whitney  $U$  test).

### 127 Treatments of COVID-19 patients

128 The following general treatments have been considered for patients with the COVID-19 infection: paracetamol (62.4%); non-  
129 steroidal anti-inflammatory drugs (9.8%); nasal saline irrigations (9.6%); Chloroquine (7.9%); mucolytics (5.0%); and oral  
130 corticosteroids (1.4%, with concomitant antibiotics) (Fig. 4). The treatments that have been most used for olfactory  
131 dysfunction were nasal saline irrigations (16.7%); nasal corticosteroids (8.1%), oral corticosteroids (2.5%), and others (2.5%,  
132 e.g., vitamins, non-corticoid decongestants, and trace elements) (Fig. 4). Gustatory dysfunction was treated in 1.4% of  
133 patients: four patients received treatment, consisting of L-carnitine or trace elements and vitamins. Telemedicine has been used  
134 in 42.6% of patients for prescribing the treatment.

## Discussion

Over the past few weeks, an increasing number of otolaryngologists reported sudden anosmia or hyposmia as concurrent symptoms of COVID-19 infection. In these patients, the diagnosis of COVID-19 could be missed, because these symptoms were not known to be specific. As a result, the patients were not isolated and the spread of the virus continued. In this context, the COVID-19 Task Force of the YO-IFOS has conducted this study to investigate the prevalence and the short-term evolution of both olfactory and gustatory disorders.

Based on the National Health and Nutrition Examination Survey questions, our results support that olfactory and gustatory dysfunctions are both prevalent in patients with mild-to-moderate COVID-19 infection. Thus, 85.6% of patients reported olfactory dysfunction; 79.6% of them having anosmia. Interestingly, many profiles of patients have been identified. First, our data showed that 79.7% of patients without nasal obstruction or rhinorrhea reported hyposmia or anosmia, supporting the role of otolaryngologists as the first-line physicians for some COVID-19 patients. Second, the olfactory dysfunction may appear before, during, or after the general symptoms, with the occurrence of fever being associated with the olfactory dysfunction. There have been few studies on the occurrence of olfactory and gustatory dysfunctions in Asia, since only one study reported hyposmia as a symptom of the COVID-19 infection [12]. In the study of Mao et al., patients with peripheral nervous system symptoms attributed to COVID-19 infection, the most common complaints were hypogeusia (5.6%) and hyposmia (5.1%) [12]. According to the data of the present study, the prevalence of olfactory and gustatory dysfunction is substantially higher in European COVID-19 patients. In addition to the high prevalence, physicians must keep in mind that olfactory disorder may appear before the rest of the complaints in 11.8% of cases, yielding the symptoms important for the early detection of the disease.

One of the most important questions from the otolaryngologists concerned the recovery of olfactory and gustatory functions. Although our results are still preliminary, it seems that, at least, 25.5% of patients recovered both olfactory and gustatory functions throughout the 2 weeks after the resolution of general symptoms. Considering the time to get a significant reduction of the viral load [10], we have estimated that 56% of patients have persistent olfactory dysfunction over the days following the resolution of the COVID-19 general clinical manifestations. In the same vein, some patients seemed to recover olfaction, but not taste, and vice versa. Naturally, there are short-term observations and it is reasonable to think that a large number of these patients will recover the olfactory or gustatory functions over the weeks following the disease resolution. To summarize, the present study clearly supports the recent declarations of many physicians from South Korea, Iran, Germany, Italy, Spain, France, Belgium, UK, and US that olfactory and gustatory functions may be impaired in COVID-19 patients.

The pathophysiological mechanisms leading to the olfactory and gustatory dysfunctions in the COVID-19 infection are still unknown. Coronavirus has already been identified as a family of viruses that may be associated with anosmia [6]. In 2007, Suzuki et al. demonstrated that coronavirus may be detected in the nasal discharge of patients with olfactory dysfunction. Moreover, they observed that some patients with normal acoustic rhinometry did not recover their olfaction, suggesting that nasal inflammation and related obstruction were not the only etiological factors underlying the olfactory dysfunction in viral infection.

The ability of human coronavirus to invade the olfactory bulb and, therefore, the central nervous system, is most likely a future research path for improving the knowledge about the clinical presentation of patients. From a biomolecular standpoint, viruses could infect peripheral neurons, using the cell machinery of active transport to access the central nervous system [13]. Thus, for the SARS-CoV receptor (human angiotensin-converting enzyme 2), it has been demonstrated on transgenic mice that SARS-CoV may enter the brain through the olfactory bulb, leading to rapid transneuronal spread [14]. Interestingly, authors demonstrated that the virus antigen was first detected 60–66 h post-infection and was most abundant in the olfactory bulb. Regions of the cortex (*piriform* and *infralimbic cortices*), basal ganglia (*ventral pallidum* and *lateral preoptic* regions), and midbrain (*dorsal raphe*) were also strongly infected after the virus had spread [14]; these regions are connected with the olfactory bulb. The rapid spread of SARS-CoV in the brain was also associated with significant neuronal death. In humans, autopsy samples from eight patients with SARS revealed the presence of SARS-CoV in brain samples by immunohistochemistry, electron microscopy, and real-time RT-PCR [15]. It is currently suspected that the neuroinvasive potential of SARS-CoV2 plays a key role in the respiratory failure of COVID-19 patients [16]. Medical imaging and neuropathology will certainly play an important role to detect abnormalities in olfactory bulb, cranial nerves, and brain of COVID-19 patients.

The otolaryngological symptoms in our European cohort were particularly prevalent compared with the Asian cohorts. In

185 their clinical series of 99 patients, Chen et al. reported four patients with rhinorrhea (4%) [17]. Then, Guan et al. reported a  
186 prevalence of nasal obstruction in 5% of patients in a cohort of 1099 patients [18]. The lack of otolaryngological  
187 complaints in Asian papers, e.g., nasal obstruction, rhinorrhea, and olfactory and gustatory dys- functions, raises many  
188 questions. Either they did not assess the ENT complaints, or the Chinese patients had a few ENT complaints. The second  
189 hypothesis may be likely regard- ing previous studies. Benvenuto et al. have recently com- pared the complete genomes of  
190 15 virus sequences from patients treated in different regions of China with other coronaviruses [19]. Interestingly, they  
191 observed mutations of surface proteins (spike-S-protein and nucleocapsid-N- protein), conferring stability to the viral particle.  
192 Such muta- tions could be clinically relevant, because the viral spike protein is responsible for virus entry into the cell,  
193 whereas the N-protein plays a pivotal role in the virus transcription and assembly efficiency. Previously, Chan et al.  
194 determined five virus sequences from patients traveling in Wuhan at the end of December 2019. This study reported identities,  
195 but less than 68%, with the SARS-related coronaviruses in spe- cific domains. Particularly, the external subdomain region of  
196 receptor-binding domain of the S-protein only presents 39% identity, and Chan et al. propose that it might affect the  
197 choice of human receptor and, therefore, the biological behaviour of this virus [20]. The affinity of some viruses for some  
198 tissues and individuals constitutes another area to investigate and explain the potential clinical differences between patients  
199 from different world regions. Recent stud- ies suggested that the angiotensin converting enzyme 2 (ACE2), which is the  
200 receptor of SARS-CoV-2, could be specific to certain populations. Li et al. demonstrated that some ACE2 variants could  
201 reduce the association between human ACE2 and SARS-CoV S-protein [21]. In other words, the expression level of ACE2 in  
202 different tissues might be critical for the susceptibility, symptoms, and outcomes of COVID-19 infection [21]. Moreover, the  
203 comparison of the 15 expression quantitative trait loci (eQTLs) variants of the ACE2 gene suggested that there will be a lot of  
204 ACE2 poly- morphisms and ACE2 expression levels between Asian and European populations [22]. According to these  
205 studies, it is conceivable that the diversity of ACE2 expression pattern in Asian and European populations could be an  
206 important track that needs further investigation.

207 Moreover, regarding our results, future studies have to explore the potential gender differences in the development of  
208 anosmia. The highest susceptibility of females to develop olfactory and gustatory dysfunctions would be related to the gender-  
209 related differences in the inflammatory reaction pro- cess [23]. The present study has several limitations. First, our patients did  
210 not benefit from specific examinations for olfactory and gustatory functions, including psychophysi- cal tests or  
211 electrophysiological methods [24, 25]. The use of objective approaches makes sense for investigating both gustatory and  
212 olfactory functions in COVID-19 patients, and to avoid the confusion related to the retro-olfaction. These approaches would  
213 provide many responses for patients who may recover olfaction, but not taste, and vice versa. Second, our patient sample  
214 consisted of young and mild- to-moderate COVID-19 patients with little comorbidities. They may be not representative of the  
215 infected population. However, it seems ethically difficult to investigate olfaction and gustatory function in patients in life-  
216 threatening condi- tion, such as patients in intensive-care units. Note that in this study, the majority of included patients were  
217 identified from hospital laboratory results. However, many infected physicians completed the study, and, therefore, it remains  
218 possible that many infected physicians participated to the study, because they suffered from olfactory dysfunction, although  
219 the authors have been particularly vigilant to this potential bias. Third, the lack of consistent follow-up of our patients limits us  
220 from inquiring into the recovery time of olfactory and gustatory functions, and, therefore, the rate of permanent anosmia or  
221 ageusia. Fourth, it seems difficult to identify the potential negative impact of nasal and oral corticosteroids on the clinical  
222 course of the disease; these treatments are usually used for anosmia or in common nasal complaints. In the absence of such  
223 data, the precautionary principle may prevail and, according to the guidelines of the French Society of Otolaryngology, patients  
224 must avoid corti- costeroids for the treatment of the COVID-19 infection. All of these weaknesses should be considered in  
225 future studies to investigate and characterize the olfactory and gustatory functions in COVID-19 patients.

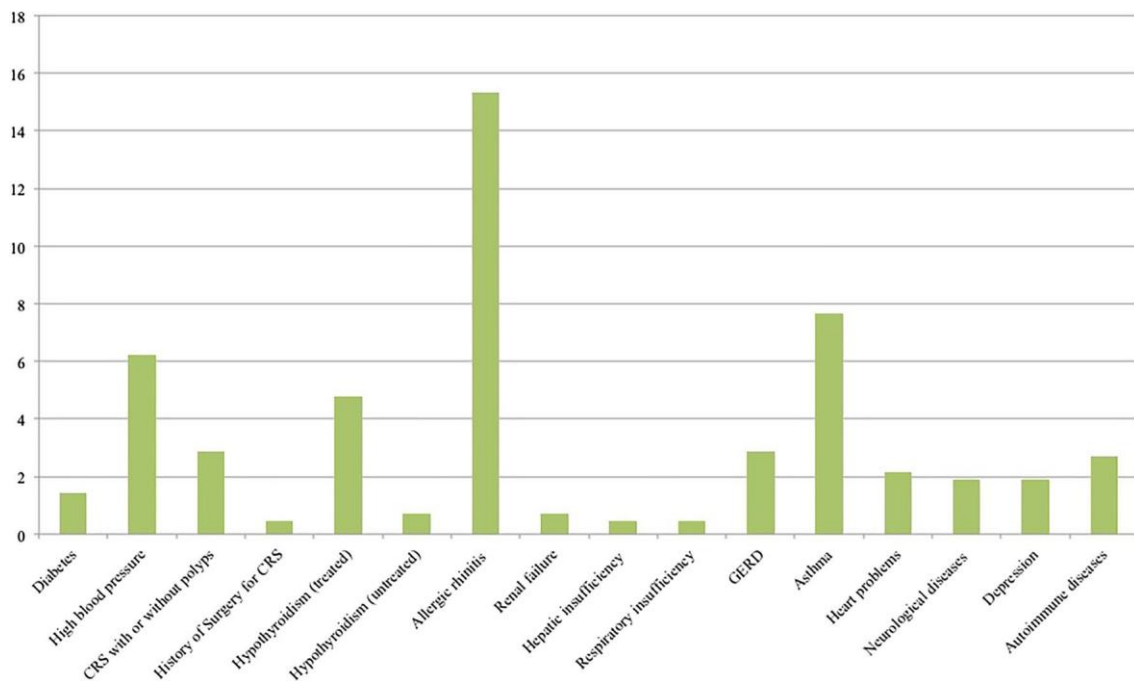
## 226 **Conclusion**

227 Since the disease is new and the virus is most likely asso- ciated with different mutations and clinical patterns, as of yet,  
228 there remain more questions than answers. This study is the first to identify both olfactory and gustatory dysfunc- tions as  
229 significant symptoms in the clinical presentation of the European COVID-19 infection. Based on our results, it seems that  
230 infected patients may just present olfactory and gustatory dysfunctions without other significant complaints. The sudden  
231 anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19  
232 infection. Future epidemiological, clinical, and basic science studies must elucidate the mechanisms underlying the  
233 development of these symptoms in such a specific world population.

**Table 1** Demographic and epidemiological characteristics of patients

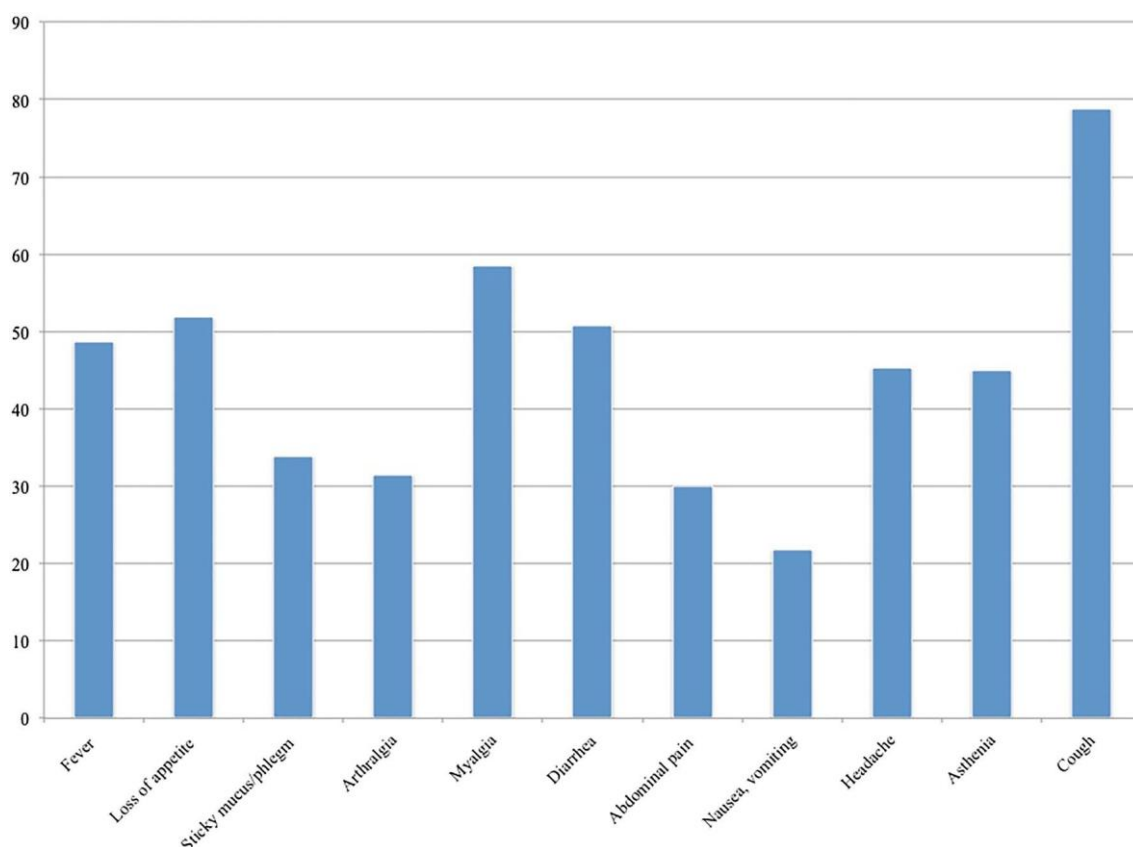
Characteristics	Mean $\pm$ SD	Range
Age (years old)	36.9 $\pm$ 11.4	19–77
Characteristics	Number	Percentages
<b>Gender</b>		
Male	154	36.9
Female	263	63.1
<b>Ethnicity</b>		
European	389	93.3
Asian	1	0.2
Black African	6	1.4
Sub-Saharan African	9	2.2
North American	1	0.2
South American	11	2.6
Oceanian	0	0.0
<b>Addictions</b>		
Non-smoker	361	86.6
Mild smoker (1–10 cigarettes daily)	40	9.6
Moderate smoker (11–20 cigarettes daily)	16	3.8
Heavy smoker (>20 cigarettes daily)	0	0.0
Allergic patients	85	20.4

SD standard deviation



**Fig. 1** Comorbidities of COVID-19 patients. The ordinate axis consists of percentages of patients with comorbidities in the cohort. Respiratory insufficiency consists of COPD, emphysema, fibrosis, or other chronic disease associated with a respiratory insufficiency. Neu-

rological diseases include Parkinson disease, myasthenia, multiple sclerosis, and all degenerative diseases. COPD chronic obstructive pulmonary disease, CRS chronic rhinosinusitis, GERD gastroesophageal reflux disease



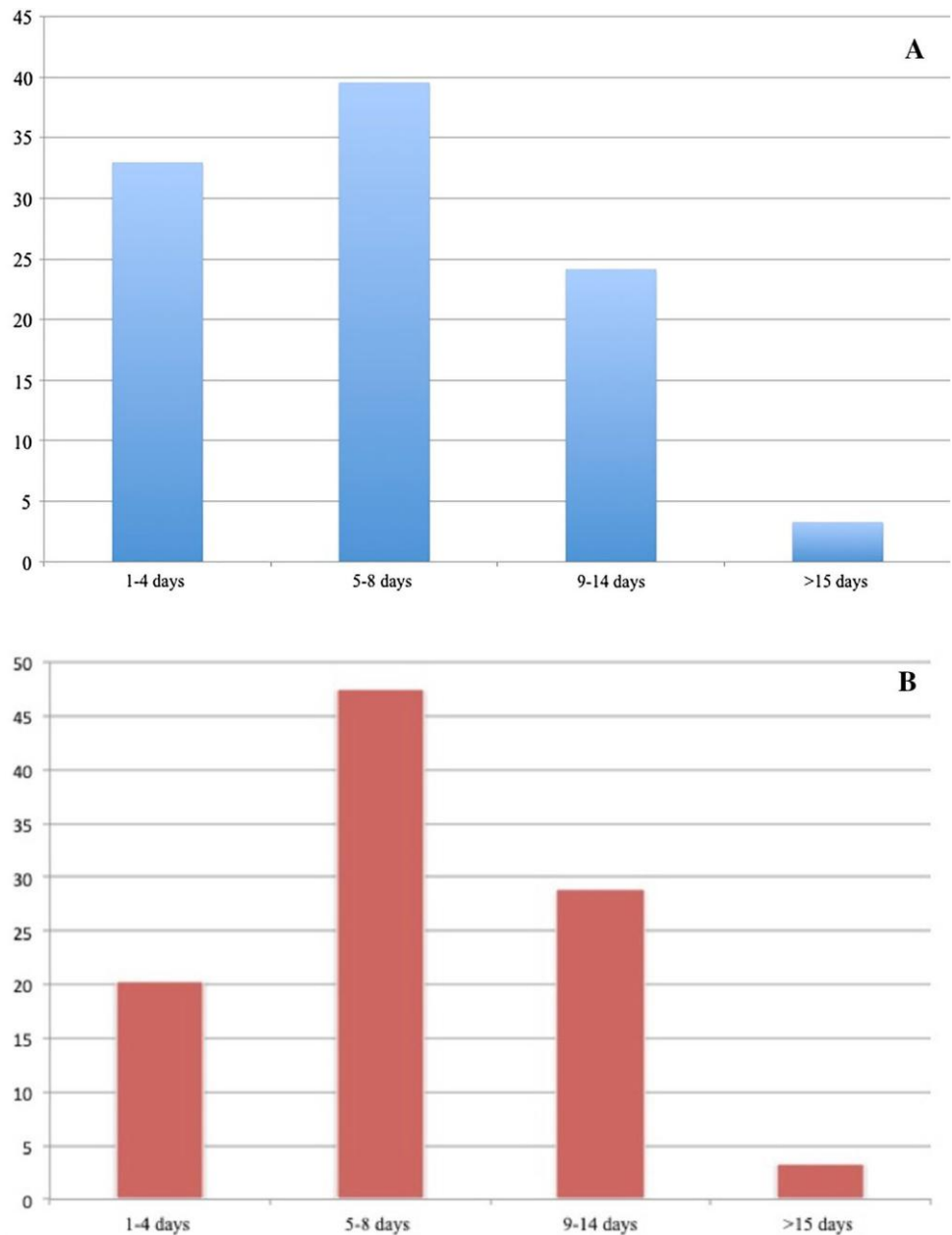
**Fig. 2** General symptoms associated with COVID-19 infection. The ordinate axis consists of percentages of patients with such symptoms associated with the infection

**Table 2** Otolaryngological complaints associated with COVID-19 Infection

	Not related		Somewhat related		Highly related
	(0)	(1)	(2)	(3)	(4)
Nasal obstruction	131 (31.49)	91 (21.88)	77 (18.51)	67 (16.11)	50 (12.02)
Rhinorrhea	154 (37.11)	122 (29.40)	81 (19.52)	40 (9.64)	18 (4.34)
Postnasal drip	203 (48.80)	97 (23.32)	61 (14.66)	26 (6.25)	29 (6.97)
Sore throat	192 (46.15)	96 (23.08)	57 (13.70)	38 (9.13)	33 (7.93)
Face pain/heaviness	198 (47.60)	66 (15.87)	59 (14.18)	39 (9.38)	54 (12.98)
Ear pain	310 (74.52)	45 (10.82)	32 (7.69)	16 (3.85)	13 (3.13)
Dysphagia	24 (22.64)	40 (37.74)	24 (22.64)	11 (10.38)	7 (6.60)
Dyspnea	218 (52.40)	83 (19.95)	61 (14.66)	35 (8.41)	19 (4.57)

Percentages are in brackets. Patients had to rate each of the following symptoms in terms of their relationship with your COVID-19 infection (scale: 0–4, where 0=not related, 4=highly related)

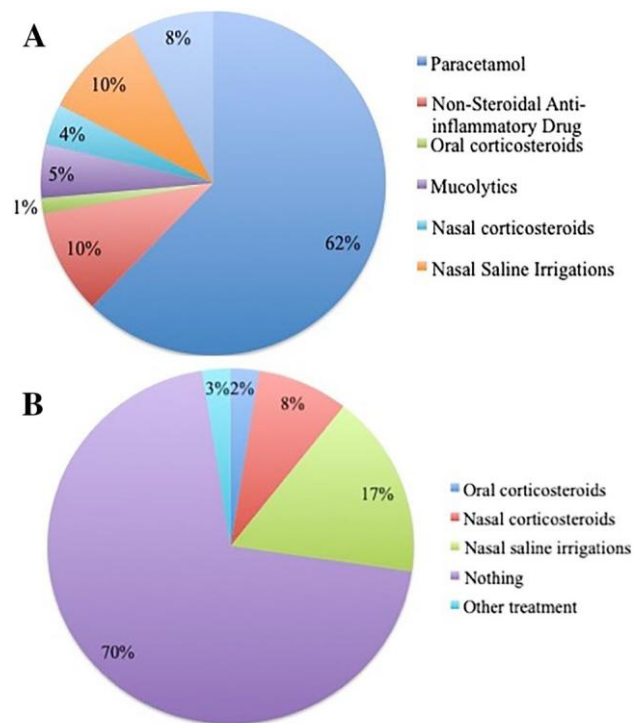
**Fig. 3** Pattern of recovery time for patients with olfactory dysfunction. The ordinate axis consists of percentages of patients. The patients with hyposmia or anosmia had the following recovery times **a** 1–4 days (33.0%), 5–8 days (39.6%), 9–14 days (24.2%), and more than 15 days (3.3%). The patients with anosmia had the following recovery times **b** 1–4 days (20.3%), 5–8 days (47.5%), 9–14 days (28.8%), and more than 15 days (3.4%)



Short version QOD-NOS total score

Short version QOD-NS items	Hyposmia	Anosmia	Hyposmia + Anosmia
Changes in my sense of smell isolate me socially	1.68 ± 0.91*	2.34 ± 0.75	2.53 ± 0.65
The problems with my sense of smell have a negative impact on my daily social activities (no impact on QoL) [9]. The item is rated on a scale of 0–3, with higher scores reflecting better olfactory-specific QoL. The total score ranges from 0 (severe impact) to 3 (no impact on QoL) [9].	1.37 ± 0.93	2.18 ± 0.84	2.56 ± 0.69
The problems with my sense of smell make me more irritable	1.46 ± 0.92	2.21 ± 0.82	2.64 ± 0.59
Because of the problems with my sense of smell, I eat out less	1.30 ± 1.09*	2.12 ± 0.99	2.51 ± 1.04
Because of the problems with my sense of smell, I eat less than before (loss of appetite)	1.00 ± 0.88*	1.59 ± 0.97	2.36 ± 0.90
Because of the problems with my sense of smell, I have to make more effort to relax	1.67 ± 0.88*	2.91 ± 0.79	2.61 ± 0.60
I'm afraid I'll never be able to get used to the problems with my sense of smell.	0.73 ± 0.86*	1.90 ± 1.06	2.06 ± 1.19

LS loss of smell, sQOD-NS Short version of Questionnaire of Olfactory Disorders-Negative Statements



**Fig. 4** Therapeutic strategies for COVID-19 infection (a) and olfactory dysfunction (b)

## References

1. Guan WJ, Ni ZY, Hu Y et al (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2002032>
2. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K (2020) Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med*. [https://doi.org/10.1016/s2213-2600\(20\)30121-1](https://doi.org/10.1016/s2213-2600(20)30121-1)
3. Wu YC, Chen CS, Chan YJ (2020) Overview of the novel coronavirus (2019-nCoV): the pathogen of severe specific contagious pneumonia (SSCP). *J Chin Med Assoc*. <https://doi.org/10.1097/JCMA.0000000000000270>
4. Young BE, Ong SWX, Kalimuddin S et al (2020) Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. <https://doi.org/10.1001/jama.2020.3204>
5. Wan S, Xiang Y, Fang W, Zheng Y et al (2020) Clinical features and treatment of COVID-19 patients in Northeast Chongqing. *J Med Virol*. <https://doi.org/10.1002/jmv.25783>
6. Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S (2007) Identification of viruses in patients with post-viral olfactory dysfunction. *Laryngoscope* 117(2):272–277
7. van Riel D, Verdijk R, Kuiken T (2015) The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol* 235(2):277–287. <https://doi.org/10.1002/path.4461>
8. Ayad T, Stephenson K, Smit D et al (2018) Young Otolaryngologists of International Federation of Oto-rhino-laryngological Societies (YO-IFOS) committees. *Eur Ann Otorhinolaryngol Head Neck Dis* 135(5S):S61–S65. <https://doi.org/10.1016/j.anorl.2018.08.004>
9. Mattos JL, Edwards C, Schlosser RJ, Hyer M, Mace JC, Smith TL, Soler ZM (2019) A brief version of the questionnaire of olfactory disorders in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol* 9(10):1144–1150. <https://doi.org/10.1002/alr.22392>
10. Bhattacharyya N, Kepnes LJ (2015) Contemporary assessment of the prevalence of smell and taste problems in adults. *Laryngoscope* 125(5):1102–1106. <https://doi.org/10.1002/lary.24999>
11. Zou L, Ruan F, Huang M et al (2020) SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 382(12):1177–1179. <https://doi.org/10.1056/NEJMc2001737>
12. Mao L, Wang M, Chen S et al (2020) Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. *MedRxiv*. <https://doi.org/10.1101/2020.02.22.20026500>
13. Koyuncu OO, Hogue IB, Enquist LW (2013) Virus infections in the nervous system. *Cell Host Microbe* 13(4):379–393. <https://doi.org/10.1016/j.chom.2013.03.010>
14. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S (2008) Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 82(15):7264–7275. <https://doi.org/10.1128/JVI.00737-08>
15. Gu J, Gong E, Zhang B et al (2005) Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 202(3):415–424
16. Li YC, Bai WZ, Hashikawa T (2020) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. <https://doi.org/10.1002/jmv.25728>
17. Chen N, Zhou M, Dong X et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395(10223):507–513. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7)
18. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al (2020) Clinical characteristics of 2019 novel coronavirus infection in China. *Medrxiv*
19. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M (2020) The 2019-new coronavirus epidemic: evidence for virus evolution. *J Med Virol* 92(4):455–459
20. Chan JF, Yuan S, Kok KH et al (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 395(10223):514–523. [https://doi.org/10.1016/S0140-6736\(20\)30154-9](https://doi.org/10.1016/S0140-6736(20)30154-9)
21. Li W, Zhang C, Sui J, Kuhn JH et al (2005) Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. *EMBO J* 24(8):1634–1643
22. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W (2020) Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* 6:11. <https://doi.org/10.1038/s41421-020->

23. Lefèvre N, Corazza F, Valsamis J, Delbaere A, De Maertelaer V, Duchateau J, Casimir G (2019) The number of X chromosomes influences inflammatory cytokine production following toll-like receptor stimulation. *Front Immunol* 10:1052. <https://doi.org/10.3389/fimmu.2019.01052>
24. Hummel T, Whitcroft KL, Andrews P et al (2017) Position paper on olfactory dysfunction. *Rhinol Suppl* 54(26):1–30
25. Gudziol H, Guntinas-Lichius O (2019) Electrophysiologic assessment of olfactory and gustatory function. *Handb Clin Neurol* 164:247–262. <https://doi.org/10.1016/B978-0-444-63855-7.00016>