JIM Brief Report

doi: 10.1111/joim.13259

Clinical features of patients who had two COVID-19 episodes: a European multicentre case series

J. R. Lechien[1,2,3,4,†], C. M. Chiesa-Estomba[1,5,†], T. Radulesco[1,6], J. Michel[1,6], L. A. Vaira[1,7], S. D. Le Bon[1,4], M. Horoi[4], C. Falanga[1,8], M. R. Barillari[1,8], S. Hans[1,3], M. Tucciarone[1,9,‡] & S. Saussez[1,2,3,4,‡]

From the [1]COVID-19 Task Force of the Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS), Paris, France; [2]Department of Human Anatomy and Experimental Oncology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium; [3]Department of Otolaryngology-Head & Neck Surgery, Foch Hospital, School of Medicine, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France; [4]Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Bruxelles, CHU Saint-Pierre, School of Medicine, Université Libre de Bruxelles, Brussels, Belgium; [5]Department of Otorhinolaryngology— Head & Neck Surgery, Hospital Universitario Donostia, San Sebastian, Spain; [6]Department of Otorhinolaryngology-Head & Neck Surgery, AP-HM, Hopital La Conception, Marseille, France; [7]Maxillofacial Surgery Unit, University Hospital of Sassari, Sassari, Italy; [8]Division of Phoniatrics and Audiology, Department of Mental and Physical Health and Preventive Medicine, University of L. Vanvitelli, Naples, Italy; and [9]ENT Department Hospital Universitario de Jerez, Jerez de la Frontera, Spain

Abstract. Lechien JR, Chiesa-Estomba CM, Radulesco T, Michel J, Varia LA, Le Bon SD, Horoi M, Falanga C, Barillari MR, Hans S, Tucciarone M, Saussez S (COVID-19 Task Force of the Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS), Paris Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, Belgium; Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France; School of Medicine, Université Libre de Bruxelles, Brussels, Belgium; Hospital Universitario Donostia, San Sebastian, Spain; AP-HM, Hopital La Conception, Marseille, France; University Hospital of Sassari, Sassari, Italy; University of L. Vanvitelli, Naples, Italy Jerez de la Frontera, Spain). Clinical features of patients who had two COVID-19 episodes: a European multicentre case series (Brief Report). *J Intern Med* 2021; **290**: 421–429. https://doi.org/10.1111/joim.13259

Objective. To investigate the clinical features of patients who had two demonstrated coronavirus disease 2019 (COVID-19) episodes.

Methods. Data of patients with both COVID-19 episodes were recruited from 22 March to 27 December 2020. The following outcomes were studied: epidemiological, comorbidities, prevalence and severity of general and otolaryngological symptom, olfactory, aroma, and gustatory dysfunctions. A comparison between first and second episodes was performed.

Results. Forty-five patients reported having two confirmed COVID-19 episodes. The majority of patients had mild infections in both episodes. The second clinical episode was significantly similar to the first. The symptom duration of the second episode was shorter than the first. The occurrence of loss of smell was unpredictable from the first to the second episode.

Conclusion. The recurrence of COVID-19 symptoms is associated with a similar clinical picture than the first episode in patients with initial mild-to-moderate COVID episode. The pathophysiological mechanisms underlying the development of second episode remain uncertain and may involve either true reinfection or virus reactivation from sanctuaries.

Keywords: clinical, COVID-19, reinfection, SARS-CoV-2, severity, symptoms.

Introduction

Globally, at the end of 2020, coronavirus disease 2019 (COVID-19) has affected more than seventy-eight million people worldwide resulting in over one and a half million deaths [1]. The European pandemic was characterized by two infection 'waves' between February and December 2020 [2]. Indeed, there was a relapse of COVID-19 cases in the second semester that was potentially attributed to the relaxation of the quarantine measures, the patient travel and other epidemiological factors [3].

[†]Dr Lechien & Dr Chiesa-Estomba have equally contributed to this work and should be regarded as joint first authors.
[‡]Dr Saussez & Dr Tucciarone have equally contributed to the work supervision and are co-senior authors.

From the relapse of the infections, a significant number of papers reported the cases of presumed reinfected persons a few months after a first COVID-19 episodes [4–6]. The aetiology of the relapse of COVID-19 symptoms in these patients is however poorly understood, and physicians did not know if the clinical relapse of COVID-19 is a true reinfection or a virus reactivation from sanctuaries [6]. To date, the majority of publications are case reports or very little case series [4–6] and there are few data about the pattern and the features of the second infection. Since the start of the pandemic in Europe, our group has collected clinical data of many thousands of patients who were followed over the months following the infection [7–9]. The aim of this case series is to present the clinical features of patients who had two clinical episodes of COVID-19 infections.

Methods

From 22 March to 27 December 2020, 2626 patients with a confirmed diagnosis of COVID-19 were prospectively included and followed in the studies of the COVID-19 Task Force of Young Otolaryngologists of the International Federation of Otorhinolaryngological Societies (YO-IOFS). At this time, patients were recruited from 18 European hospitals located in Belgium, France, Italy and Spain [7]. The study was approved by 5 European Institutional Review Boards (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303, CHUC, P20/30-24/03-B325-2020; IJB: CE3137). Patients agreed to participate and fulfilled electronic or paper informed consent. Amongst the 2626 patients, 51 were identified as subjects who had two presumed COVID-19 infections over the follow-up.

The diagnosis of COVID-19 infection was based on the WHO interim guidance [10]. To be included, patient had to have confirmed COVID-19 diagnosis through nasal swabs and positive reverse transcriptase polymerase chain reaction (RT-PCR) or positive serology (IgM or IgG). The two clinical episodes of the infection should be at least 1 month apart with total symptom (excluding smell and taste dysfunction) recovery between both episodes. The threshold to consider a serology as positive may differ from one to another laboratory. For this reason, we considered serology as positive or negative in the present study according to the laboratory thresholds. In practice, the diagnosis was performed in hospital or private laboratories. The RT-PCR or serology results from private (external) laboratories were controlled before inclusion. The definition of the COVID-19 severity, including mild, moderate, severe and critical forms, was based on the COVID-19 Disease Severity Scoring of WHO [10]. Mild patients were defined as patients without evidence of viral pneumonia or hypoxia and were commonly home-managed and followed. Moderate COVID-19 patients had clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no sign of severe pneumonia (including $SpO_2 \geq 90\%$ on room air). Severe COVID-19 patients were defined as individuals with clinical signs of pneumonia plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or $SpO_2 < 90\%$ on room air.

Patients with a clinical diagnosis of COVID-19 without RT-PCR or positive serology were excluded as well as those who did not complete clinical data for one of both infections.

Epidemiological and clinical outcomes

The following epidemiological outcomes were collected through a standardized online questionnaire or medical records: gender, age, allergy, smoking and comorbidities, that is hypercholesterolaemia, hypertension, diabetes, reflux, heart, respiratory, kidney, liver, autoimmune diseases, neurological, chronic rhinitis, depression and hypothyroidism. The daily medications of patients were collected.

General and otolaryngological symptoms of patients during both infections were collected through a standardized 5-point scale ranging from 0 (absent) to 4 (very severe symptoms) [8]. Patients were invited to assess the evaluation of the general and otolaryngological symptoms at both infections (excluding the loss of smell that was evaluated separately). The duration of the disease, the need to hospitalization and oxygen therapy were recorded. The occurrence of self-reported smell, taste and aroma dysfunctions was evaluated with the smell and taste component of the National Health and Nutrition Examination Survey [11]. Taste dysfunction was defined as the impairment of salty, sweet, bitter and sour, whilst aroma dysfunction included all aroma that are not salty, sweet, bitter and sour [11].

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for

Windows version 22.0 (IBM Corp, Armonk, NY, USA). A comparison between clinical presentation of first and second episodes was performed with chi-square or Mann–Whitney test regarding the type of variable. According to the type of outcomes, chi-square and multivariate analysis were used to study the relationship between epidemiological and clinical outcomes. A *P*-value < 0.05 was considered as significant.

Results

Fifty-one patients were identified as potential patients who had two COVID-19 clinical episodes. The laboratory data confirming the COVID-19 diagnosis twice were available and consistent for 45 patients (8 healthcare workers). The patients without laboratory information ($N = 8$) were excluded (Appendix 1). There were 31 females (68.9%). The mean age of patients was 38.5 ± 13.3 years old. During the first infection wave, the diagnosis of patients was performed with RT-PCR in 23 patients, whilst 22 benefited from serology. During the second wave, 40 patients had positive RT-PCR diagnosis and the diagnosis was confirmed with serology in the 5 remaining patients. The main comorbidities consisted of hypothyroidism (15.6%) and gastroesophageal or laryngopharyngeal reflux disease (15.6%, Table 1). The daily patient medications included L-Thyroxin, proton pump inhibitors, statin, metformin, inhaled corticosteroids and anti-coagulant.

Table 1 *Epidemiological and clinical features*

Characteristics	Patients $N = 45$
Age (y - Mean; SD)	38.5 ± 13.3
Gender (F/M)	31 (68.9)/14 (31.1)
Tobacco	3 (6.7)
Allergy	3 (6.7)
Comorbidities	
Hypothyroidism	7 (15.6)
Reflux	7 (15.6)
Asthma	4 (8.9)
Diabetes	3 (6.7)
Heart problems	3 (6.7)
Chronic Rhinitis	2 (4.4)
Hypercholesterolaemia	2 (4.4)
Hypertension	1 (2.2)
Neurological disease	1 (2.2)
Respiratory insufficiency	1 (2.2)
Depression	1 (2.2)
Auto-immune disease	1 (2.2)
Kidney insufficiency	0 (0)
Liver insufficiency	0 (0)
Medications	
L-Thyroxin	7 (15.6)
Proton pump inhibitors	4 (8.9)
Statin	2 (4.4)
Metformin	2 (4.4)
Inhaled corticosteroids	1 (2.2)
Anti-coagulant	1 (2.2)

Abbreviations: F/M, female/male; N, number; SD, standard deviation.

Clinical forms and serology

The first COVID-19 clinical episode consisted of home-managed mild forms of COVID-19 with ($N = 12$, 26.7%) or without ($N = 30$, 66.7%) dyspnoea, whilst three patients (6.7%) required oxygen therapy and hospitalization for a moderate form (Table 2). Amongst the 12 patients who had mild COVID-19 with home-managed dyspnoea, the second infection consisted of mild form with dyspnoea in 8 patients (66.7%), whilst the 4 remaining patients had mild form without dyspnoea (Appendix 1). Amongst the 3 hospitalized patients who initially had moderate COVID-19 form, one patient developed a second infection with home-managed dyspnoea. At the time of the second COVID-19 clinical episode, this patient had positive serology (IgG). The two others had mild form without dyspnoea. The two other patients had mild second infection without dyspnoea and negative serology at the time of the second infection. There were 32 (71.1%) and 13 (28.9%) second mild infections without or with dyspnoea, respectively (Table 2). The mean time between both COVID-19 clinical episodes was 5.6 ± 2.3 months.

Thirty-five patients had serology after the first infection. The serology was realized 2.3 months after the infection. Amongst them, 10 (28.6%) patients did not have detectable IgG. The delay between the end of the infection and the serology in patients without detectable IgG was 1 month. After the second COVID-19 clinical episode, 10 patients benefited from IgG detection within the 2 weeks and the serology was positive in 9 cases (90%). The serology of the patient with negative

IgG detection was performed 2 months post-infection.

Symptoms

The most prevalent symptoms during the first COVID-19 clinical episode were asthenia (86.7%), headache (80.0%), fever (73.3%) and anorexia (73.3%). The most prevalent symptoms of the second episode were headache (93.3%), asthenia (91.1%), fever (71.1%) and myalgia (71.1%, Table 2). The symptoms that reported the higher severity in both episodes were asthenia and headache according to 5-point scale severity evaluations (Table 2). Furthermore, the occurrence and the severity of dyspnoea significantly increased with the age of patient (r_s = 0.308; P = 0.040). The clinical presentations of the disease were significantly similar from the first episode to the second episode regarding symptoms prevalence and severity (Table 3). The following symptoms did not reach significant association between first and second infection: headache, anorexia, diarrhoea and abdominal pain. Note that the otolaryngological symptoms were those that reached the higher correlation coefficients between both episodes. The duration of the second episode (15.7 days) was evaluated as shorter than the first one (17.0 days, Table 2).

Olfactory, gustatory and aroma dysfunctions

Self-reported olfactory dysfunction occurred in 53.3% and 62.2% of cases in first and second episodes, respectively (Table 2). Amongst the patients who reported partial (N = 8; 33.3%) loss of smell in the first episode, 3 and 4 patients had partial or total loss of smell in the second episode, respectively. One patient who had initially partial loss of smell did not smell disorder in the second episode.

Sixteen patients reported total loss of smell during the first episode. Amongst them, 5 (31.3%) and 2 (12.5%) had partial or total loss of smell in the second episode, respectively. The occurrence of a self-reported partial or total loss of smell during the first episode was not significantly predictive of the development of partial or total loss of smell during the second COVID-19 episode. Note that there was a significant positive association between the nasal burning symptom and the development of total loss of smell (r_s = 0.392; P = 0.026). The duration of smell disorder was significantly associated with the duration of taste dysfunction in the first (r_s = 0.862, P = 0.001) and the second episodes (r_s = 0.514, P = 0.029).

Taste dysfunction concerned 40.0% and 55.6% of patients in the first and the second episodes. The durations of taste dysfunction were 11.3 ± 13.1 and 9.4 ± 7.7 in first and second episodes, respectively. Aroma dysfunction was identified in 44.4% and 60.0% of patients regarding the first and the second episodes (Table 2). In patients who had loss of smell during both episodes, the duration of olfactory dysfunction was significantly shorter in the second episode (P = 0.001).

Discussion

In the recent weeks, there was an increasing number of second COVID-19 episodes, which may be attributed to reinfection or viral reactivation from human body sanctuaries [6].

The primary findings of the present study are the observation of patients who developed two distinct COVID-19 episodes and the high similarity between both clinical presentations. Goussef *et al.* published a case series of 11 patients who had symptom recurrence a few weeks/months after the first infection [6]. In their study, these authors also observed that the clinical presentation of the disease was quite similar between both episodes. Precisely, they reported that patients with dyspnoea in the first episode developed dyspnoea in their second episode, which required oxygen therapy [6]. Moreover, they found that the duration of symptoms was shorter in the second episode compared with the first one, which may corroborate our observations. To the best of our knowledge, the study of Goussel *et al.* and our study are the only two case series of patients who developed both COVID-19 episodes, which limits the comparison of our data with the literature. The match between first and second clinical pictures of the disease should not concern the self-reported smell and taste dysfunctions, the development of this symptom remaining unpredictable. A likely hypothesis could be that the patients who developed loss of smell had a nasal virus entrance and a related nasal and olfactory cleft mucosa injuries, whilst those who are infected through oral cavity had no virus in the nose mucosa and no smell-related mucosa injury and disorder. Interestingly, the significant positive association between patient-reported nasal burning and the

Table 2 *Clinical features*

Clinical features	First infection	Second infection
Initial infection features		
Mild form home-managed without dyspnoea	30 (66.7)	32 (71.1)
Mild form home-managed with dyspnoea	12 (26.7)	13 (28.9)
Moderate form requiring hospitalization	3 (6.7)	0 (0)

	Prevalence	Score (m, SD)	Prevalence	Score (m, SD)
General symptoms (N - %)				
Fever (>38C)	33 (73.3)	1.4 ± 1.2	32 (71.1)	1.6 ± 1.4
Asthenia	39 (86.7)	2.3 ± 1.4	41 (91.1)	2.4 ± 1.2
Cough	30 (66.7)	1.5 ± 1.4	29 (64.4)	1.3 ± 1.3
Chest pain	26 (57.8)	1.1 ± 1.3	26 (57.8)	1.1 ± 1.2
Anorexia	33 (73.3)	1.4 ± 1.1	30 (66.7)	1.3 ± 1.2
Arthralgia	27 (60.0)	1.3 ± 1.3	24 (53.3)	1.2 ± 1.4
Myalgia	32 (71.1)	1.6 ± 1.3	32 (71.1)	1.7 ± 1.3
Headache	36 (80.0)	1.7 ± 1.3	42 (93.3)	2.2 ± 1.2
Diarrhoea	29 (64.4)	1.1 ± 1.1	26 (57.8)	0.8 ± 0.9
Abdominal pain	25 (55.6)	0.8 ± 0.9	26 (57.8)	0.8 ± 0.7
Nausea, vomiting	17 (37.8)	0.5 ± 0.8	22 (48.9)	0.7 ± 0.8
Conjunctivitis	16 (35.6)	0.4 ± 0.7	14 (31.1)	0.4 ± 0.8
Urticaria	14 (31.1)	0.4 ± 0.6	11 (24.4)	0.2 ± 0.4
Sticky mucus/postnasal drip	16 (35.6)	0.4 ± 0.7	16 (35.6)	0.4 ± 0.7
Dyspnoea	26 (57.8)	1.3 ± 1.3	25 (55.6)	1.0 ± 1.2
Ear, nose and throat symptoms (N - %)				
Nasal obstruction	23 (51.1)	0.9 ± 1.1	27 (60.0)	1.1 ± 1.1
Rhinorrhea	25 (55.6)	0.9 ± 1.0	28 (62.2)	1.0 ± 1.0
Nasal burning	15 (33.3)	0.4 ± 0.7	21 (46.7)	0.7 ± 1.0
Throat pain	31 (68.9)	1.2 ± 1.2	28 (62.2)	1.0 ± 1.0
Otalgia	18 (40.0)	0.5 ± 0.7	19 (42.2)	0.5 ± 0.7
Face pain/heaviness	16 (35.6)	0.4 ± 0.7	16 (35.6)	0.5 ± 0.8
Dysphagia	19 (42.2)	0.8 ± 1.1	15 (33.3)	0.4 ± 0.7
Dysphonia	17 (37.8)	0.5 ± 0.7	19 (42.2)	0.7 ± 1.0
Tongue burning	10 (22.2)	0.3 ± 0.6	12 (26.7)	0.3 ± 0.4
Duration of symptoms (days)	17.0 ± 18.0		15.7 ± 18.5	
Smell & taste disorders				
Self-reported olfactory disorder	24 (53.3)		28 (62.2)	
Partial loss of smell	8 (33.3)		9 (32.1)	
Complete loss of smell	16 (66.6)		19 (67.9)	
Duration of smell loss	16.2 ± 20.1		11.2 ± 14.0*	
Aroma sense dysfunction (retro-olfaction)	20 (44.4)		27 (60.0)	
Total loss of aroma perception sense	8 (40.0)		14 (51.9)	
Partial loss of aroma	4 (20.0)		6 (22.2)	
Distortion	8 (40.0)		7 (25.9)	

Table 2 (*Continued*)

	Prevalence	Score (m, SD)	Prevalence	Score (m, SD)
No problem	25 (55.6)		18 (40.0)	
Taste disorders	18 (40.0)		25 (55.6)	
Duration of taste loss	11.4 ± 14.1		9.4 ± 7.7	

Abbreviation: *N*, number.
*Significant ($P < 0.05$).

development of loss of smell, which often occurred after the other symptoms, may support this hypothesis.

Another point that may explain the development (or not) of smell disorder concerns the nasal expression of the angiotensin-converting enzyme 2 (ACE2) receptor, which may be particularly important in some individuals [12]. Patients with a high ACE2 nasal/olfactory expression could easily develop smell dysfunction compared with others that exhibited poor expression of ACE2.

The debate is still on about the aetiology of the second episode of COVID-19 [13]. The first aetiological hypothesis is the reinfection theory, whilst the second involves the virus reactivation from sanctuaries [13]. Many points support the reinfection hypothesis. First, as for many other viral infections, the patients may have a high risk of reinfection when the individual is continuously exposed to the virus. The high proportion of healthcare workers in our study (18%) and the study of Goussel *et al.* trends to support the reinfection hypothesis because they are continuously exposed. Secondly, it seems that antibody against SARS-CoV-2 can be found in most COVID-19 patients within 2 weeks of infection [14], with a more rapid and robust neutralizing antibody response in severe-to-critical patients compared with mild cases [15]. Regarding the waning of antibody level in patients with mild COVID-19, they are more easily predisposed to potential reinfections [16]. In that way, we did not detect IgG in one-third of patients 2–6 months after the first episode, which confirms the lack of protective neutralizing antibodies. Secondly, the virus is known to rapidly mute, leading to the escape of neutralizing antibody due to variations on the spike protein that were recently found in a recent study [17]. The delay between both episodes (waves) in our study (5.6 months) may be sufficient to have substantial changes in the RNA of the virus and related mutant as virus of the second episode.

In the second hypothesis, patient had suboptimal control of the infection by the local and systemic immunological system, which led to a second episode of viral replication occurring in an immunosuppressive period related to medication or other pathological conditions. According to this hypothesis, healthcare workers would not be more at risk than the other patients. However, the 'reinfected' patients are healthcare workers in the majority of case reports [4,5,18] or in the case series of Goussef *et al.* [13]. Naturally, future studies have to investigate the clinical, biological and immunological profile of patient who developed second COVID-19 episode to better understand the mechanisms underlying the reinfection of the virus reactivation.

This preliminary observational study has many limitations, the primary being the low number of patients. Secondly, regarding our methodological approach, we only detected patients with second symptomatic episode. In that way and because we did not follow all patients with serology or nasal swabs, we cannot detect asymptomatic or paucisymptomatic presumed reinfection. Thirdly, the present cohort only included patients with mild or moderate COVID-19, limiting the result inference to other stages of the disease. However, it is not excluded that the high proportion of mild-to-moderate COVID-19 patients in this study may reflect the higher risk of these patient categories to have a second episode regarding their lower rate of neutralizing IgG. In that way, it seems probable that severe-to-critical patients have better immunogenic protection against the virus than mild or moderate forms and therefore may develop less frequently a clinically similar second episode. Fourthly, we did not control the negativity of nasal swab after the first infection to be sure that there was no detectable virus RNA. Although these cases are still rare, it is possible that some patients were healthy carrier of the virus from the end of the first to the second infection episode.

Table 3 *Symptom association between first and second episodes*

Symptoms	Rs	*P*-value
General symptoms		
Fever (>38C)	0.399	0.007
Asthenia	0.457	0.002
Cough	0.488	0.001
Chest pain	0.344	0.021
Anorexia	0.257	0.088
Arthralgia	0.371	0.012
Myalgia	0.304	0.042
Headache	0.057	0.712
Diarrhoea	0.031	0.841
Abdominal pain	0.068	0.655
Nausea, vomiting	0.558	0.001
Conjunctivitis	0.558	0.001
Urticaria	0.790	0.001
Sticky mucus/postnasal drip	0.901	0.001
Dyspnoea	0.358	0.016
Ear, nose and throat symptoms		
Nasal obstruction	0.547	0.001
Rhinorrhea	0.354	0.017
Nasal burning	0.532	0.001
Throat pain	0.392	0.008
Otalgia	0.536	0.001
Face pain/heaviness	0.739	0.001
Dysphagia	0.763	0.001
Dysphonia	0.683	0.001
Tongue burning	0.884	0.001

The symptoms of patients during the clinical course of the disease were evaluated with a 5-point scale ranging from 0 (absent) to 4 (very severe symptoms).
Abbreviation: rs, Spearman coefficient.

Conclusion

The recurrence of COVID-19 symptoms is associated with a similar clinical picture than the first episode in patients with initial mild-to-moderate COVID episode. The similar clinical pattern does not concern loss of smell that is still unpredictable. Future studies are needed to better understand the pathophysiological mechanisms underlying the development of second episode or virus reactivation from sanctuaries, especially in the context of persisting issues about the interest to vaccine patients who already had COVID-19.

Acknowledgements

None.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Electronic informed consent was obtained from all individual participants.

References

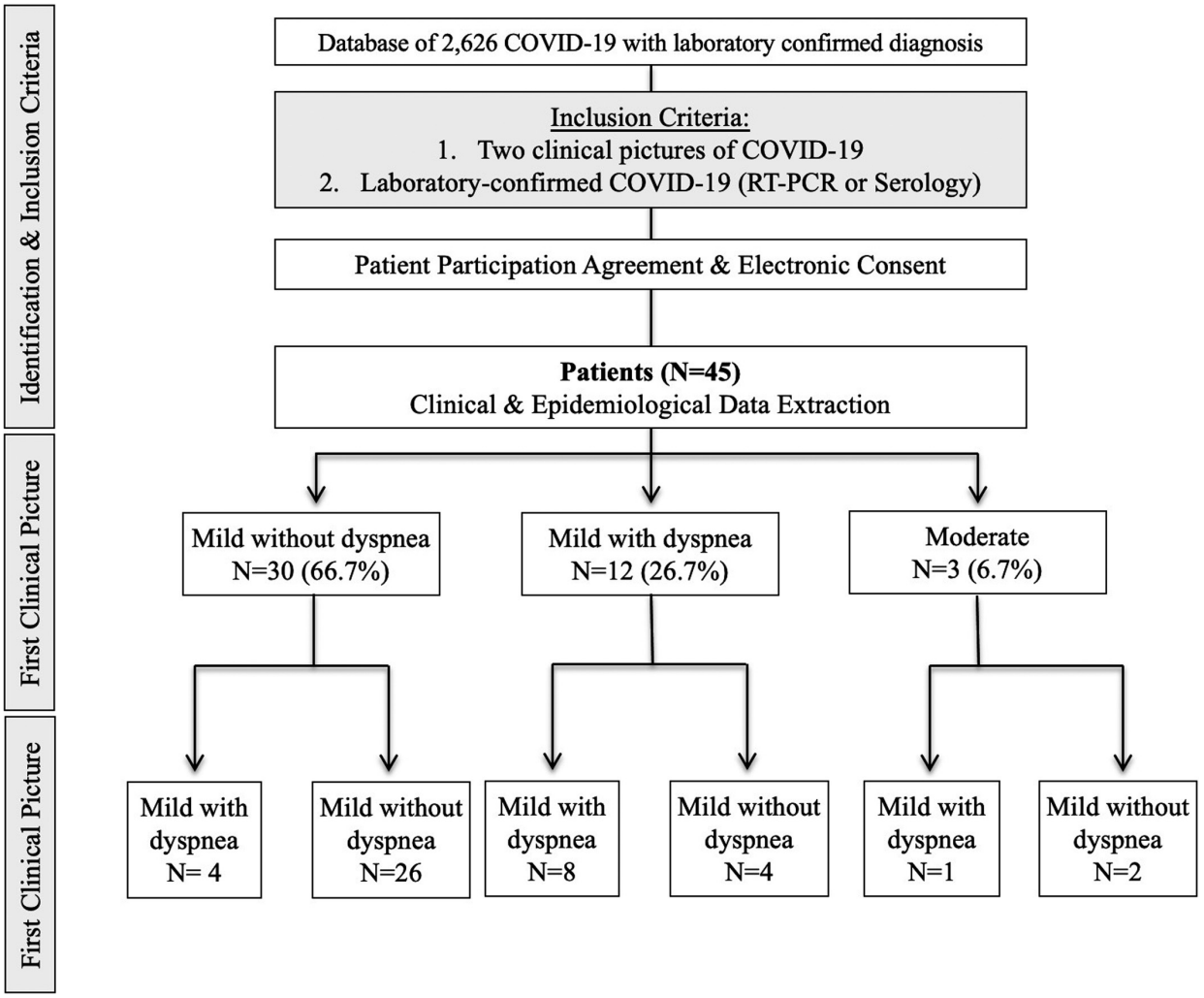
1 WHO website. www.who.int/docs Consulted December 30, 2020.
2 https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases.
3 Grech V, Cuschieri S. COVID-19: a global and continental overview of the second wave and its (relatively) attenuated case fatality ratio. *Early Hum Dev* 2020; **3:** 105211.
4 Fernandes Valente Takeda C, Moura de Almeida M, Gonçalves de Aguiar Gomes R, Cisne Souza T, Alves de Lima Mota M, Pamplona de Góes Cavalcanti L, *et al.* Case report: recurrent clinical symptoms of COVID-19 in healthcareprofessionals: a series of cases from Brazil. *Am J Trop Med Hyg* 2020; **103(5):** 1993–6.
5 Gupta V, Bhoyar RC, Jain A, Srivastava S, Upadhayay R, Imran M, *et al.* Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2. *Clin Infect Dis* 2020:ciaa1451. https://doi.org/10.1093/cid/ciaa1451. Online ahead of print.
6 Gousseff M, Penot P, Gallay L, Batisse D, Benech N, Bouiller K, *et al.* Clinical recurrences of COVID-19 symptoms after recovery: viral relapse, reinfection or inflammatory rebound? *J Infect* 2020; **81(5):** 816–46.
7 Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, *et al.* COVID-19 task force of YO-IFOS. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020; **288(3):** 335–44.

8 Lechien JR, Chiesa-Estomba CM, Hans S, Barillari MR, Jouffe L, Saussez S. Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. *Ann Intern Med* 2020; **173(8):** 672–5.
9 Lechien JR, Chiesa-Estomba CM, Beckers E, *et al.* Prevalence and recovery of olfactory dysfunction: a multicenter study of 1,363 COVID-19 patients. *J Int Med* 2021. https://doi.org/10.1111/joim.13209. Online ahead of print.
10 World Health Organization, 2020. Clinical Management of COVID-19: interim guidance, 27 may 2020 (No. WHO/2019-nCoV/clinical/2020.5). World Health Organization.
11 Bhattacharyya N, Kepnes LJ. Contemporary assessment of the prevalence of smell and taste problems in adults. *Laryngoscope* 2015; **125:** 1102–6.
12 Descamps G, Verset L, Trelcat A, Hopkins C, Lechien JR, Journe F, *et al.* ACE2 protein landscape in the head and neck region: the conundrum of SARS-CoV-2 infection. *Biology (Basel)* 2020; **9(8):** 235.
13 Roy S. COVID-19 reinfection: myth or truth? *SN Compr Clin Med* 2020; **29:** 1–4.
14 To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, *et al.* Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis* 2020; **20:** 565–74.
15 Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, *et al.* Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. *Clin Infect Dis* 2020; **71(16):** 2027–34.
16 Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, *et al.* Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020; **26:** 1200–4.
17 Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JC, *et al.* Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. *Elife.* 2020; **28(9):** e61312.
18 Lechien JR, Chiesa-Estomba CM, Vaira LA, Saussez S, Hans S. COVID-19 reinfection and second episodes of olfactory and gustatory dysfunctions: report of first cases. *Ear Nose Throat J* 2020; **10:** 145561320970105.

Correspondence: Jerome R. Lechien, 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.
(e-mail: Jerome.Lechien@umons.ac.be)

APPENDIX

Chart flow of the study



Abbreviations: COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription polymerase chain reaction.

