DR. JEROME R LECHIEN (Orcid ID : 0000-0002-0845-0845)

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Clinical and Epidemiological Characteristics of 1,420 European Patients with mild-to-moderate Coronavirus Disease 2019.

Jerome R. Lechien, MD, PhD, MSc[1-4#], Carlos M. Chiesa-Estomba MD, MS[1,5#], Sammy Place, MD[1,6], Yves Van Laethem, MD, PhD,[7] Pierre Cabaraux MD[1,8], Quentin Mat, MD[1,8], Kathy Huet, PhD[1,2], Jan Plzak MD, PhD[9,10], Mihaela Horoi, MD[1,4], Stéphane Hans, MD, PhD, MS[1,3], Maria Rosaria Barillari MD, PhD, MS[1,11], Giovanni Cammaroto MD, PhD[1,12], Nicolas Fakhry MD, PhD[1,13], Delphine Martiny, PhD[14], Tareck Ayad MD, FCRCS[1,15], Lionel Jouffe, PhD[1,16], Claire Hopkins, MD, PhD[17,18], Sven Saussez, MD, PhD[2,4,19], COVID-19 Task Force of YO-IFOS*.

*Collaborators: Serge Blecic, MD, Daniele R. De Siati, MD, Pierre Leich MD, Christel Souchay MD, Camelia Rossi MD, Fabrice Journe PhD, Julien Hsieh MD, MS, Laurence Ris PhD, Fahd El Afia, MD, Bernard Harmegnies, PhD, Lea Distinguin, MD, MS, Younes Chekkoury-Idrissi, MD, Marta Circiu, MD, Philippe Lavigne MD, Irene Lopez Delgado MD, Christian Calvo-Henriquez MD, Chiara Falanga MD, Frederique Coppee PhD, Serge D. Le Bon, MD, Alexandra Rodriguez, MD, Didier Dequanter, MD, PhD, Jean-Philippe Cornelis, MD, Sebastien Vergez, MD, PhD, Lukas Koenen MD, Mannelli Giuditta MD, Gabriele Molteni MD, Manuel Tucciarone MD, Thomas Radulesco MD, Mohamad Khalife MD, Anne-Francoise Fourneau, MD, Soraya Cherifi, MD, PhD, Mario Manto, MD, PhD, Justin Michel MD, PhD, Thomas Radulesco MD, PhD, Gabriele Molteni, MD, PhD, Manuel Tucciarone, MD, Giuditta Mannelli, MD, PhD, Giovanna Cantarella, MD, PhD.

*These authors contributed equally to this article.

Institutions:

1. COVID-19 Task Force of the Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies (YO-IFOS).
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

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3. Department of 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 Internal Medicine, Infectiology, EpiCURA Hospital, Baudour, Belgium.
7. Department of Internal Medicine, Infectiology, CHU Saint-Pierre, Brussels, Belgium.
8. Department of Medicine, Neurology, CHU de Charleroi, Charleroi, Belgium.
9. Department of Statistics, Language Sciences, University of Mons, Belgium.
10. Department of Otolaryngology – Head & Neck Surgery, 1st Faculty of Medicine, University Hospital Motol, Prague, Czech Republic.
11. Confederation of European Otorhinolaryngology-Head & Neck Surgery, Vienna, Austria.
12. Department of Mental and Physical Health and Preventive Medicine, University of L. Vanvitelli, Naples, Italy.
13. Department of Otolaryngology-Head & Neck Surgery, Morgagni Pierantoni Hospital, Forli, Italy.
14. Department of Otorhinolaryngology— Head & Neck Surgery, APHM, Aix Marseille University, La Conception University Hospital, Marseille, France.
15. Department of Microbiology, Laboratoire Hospitalier Universitaire de Bruxelles - Universitair Laboratorium Brussel (LHUB-ULB), Brussels, Belgium; Faculté de Médecine et Pharmacie, Université de Mons (UMONS), Mons, Belgium.
16. Division of Otolaryngology-Head & Neck Surgery, Centre Hospitalier de l'Université de Montréal, Montreal, Québec, Canada.
17. BayesiaLab, Changé, France.
18. Guy's and St Thomas NHS Foundation Trust, London, UK.
19. British Rhinological Society (President), London, UK.
20. Department of Surgery, EpiCURA Hospital, Hornu, Belgium.

*Dr Lechien & Dr Chiesa have equally contributed to this work and should be regarded as *joint first authors.*

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Correspondence to:

Dr. Jay R. Lechien, M.D., Ph.D., M.S.

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.

Department of Human Anatomy and Experimental Oncology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium.
Email: Jerome.Lechien@umons.ac.be
Telephone: +32 65 37 35 84

Abstract:

Background: The clinical presentation of European patients with mild-to-moderate Covid-19 infection is still unknown.

Objective: To study the clinical presentation of Covid-19 in Europe.

Methods: Patients with positive diagnosis of Covid-19 were recruited from 18 European hospitals. Epidemiological and clinical data were obtained through a standardized questionnaire. Bayesian analysis was used for analyzing the relationship between outcomes.

Results: 1,420 patients completed the study (962 females, 30.7% of health care workers). The mean age of patients was 39.17±12.09 years. The most common symptoms were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%). Fever was reported by on 45.4%. The mean duration of Covid-19 symptoms of mild-to-moderate cured patients was 11.5±5.7 days. The prevalence of symptoms significantly varied according to age and sex. Young patients more frequently had ear, nose, and throat complaints, whereas elderly individuals often presented fever, fatigue and loss of appetite. Loss of smell, headache, nasal obstruction and fatigue were more prevalent in female patients. The loss of smell was a key symptom of mild-to-moderate Covid19 patients and was not associated with nasal obstruction and rhinorrhea. Loss of smell persisted at least 7 days after the disease in 37.5% of cured patients.

Conclusion: The clinical presentation of mild-to-moderate Covid-19 substantially varies according to the age and the sex characteristics of patients. Olfactory dysfunction seems to be an important underestimated symptom of mild-to-moderate Covid-19 that needs to be recognized as such by the WHO.

Key words: covid-19; coronavirus; clinical; epidemiological; symptoms; Europe; patients; medicine.

Introduction:

Since the first case of pneumonia related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], the coronavirus disease 2019 (Covid-2019) has spread rapidly worldwide. In Europe, the first cases have been identified in Italy, dating back January, 19, 2020 [2]. As of April 4, a total of 840,246 European citizens have been diagnosed through laboratory testing, with 70,583 corresponding deaths [3]. European data regarding clinical presentation and epidemiological factors of laboratory-confirmed Covid-2019 are limited by a paucity of diagnostic tests in many European countries. A recent study suggests 3 distinct variants of Covid-19, representing clusters of infection in the United States and Australia (Type A), China and East Asia (Type B) and Europe (Type C) [4].

Therefore, it seems that there may be significant epidemiological differences between Asian and European disease regarding, for example, the spread rate of the disease and the mortality [5].

The aim of this European multicenter study is to investigate the clinical and epidemiological characteristics of patients with mild-to-moderate Covid-2019 infection.

Materials and Methods:

This observational study was initiated by the Covid-19 Task Force of the International Federation of Otorhinolaryngological Societies (World Otolaryngological Federation, YO-IFOS). At the onset of the pandemic, the European otolaryngologists of the Task force have started collaborations with Internal Medicine physicians, infectious diseases specialists, microbiologists and clinical biologists of their respective hospitals to conduct this multicenter study. The institutional ethics committees of five European Hospitals approved the study protocol (HAP2020-011; CHUSP20032020; EpiCURA-2020-2303, CHUC,P20/30-24/03-B325-2020; J.Bordet Institute: CE3137). Patient informed consent was obtained electronically in light of the urgent need to collect data.

Data Collection

More than 50 European physicians have collected clinical data from patients with laboratory-confirmed Covid-19 infection. The data have been collected from March 22 to April 10 by physicians from 18 Hospitals from French (Paris, Marseille), Italian (Milan, Verona, Naples, Genova, Florence, Forli), Spanish (Sevilla, Santiago de Compostela, San Sebastian), Belgian

(Mons, Brussels, Charleroi, Saint-Ghislain), and Swiss (Geneva) cities.

In these European centers, the nasal or throat swabs were made for the following patients: 1) patients suspected on the basis on a consultation in the family physician, 2) patients who consulted specialists (internal medicine physician, pulmonologist, cardiologist, otolaryngologist, etc.), and 3) patients admitted/consulting in the Emergency Department for mild-to-moderate complaints.

The diagnosis of Covid-19 infection was based on the WHO interim guidance [6]. Viral RNA extraction was performed by m2000 mSample Preparation SystemDNA Kit (Abbott) using 1000µl manually lysed sample (700µl sample + 800µl lysis buffer from kit) eluted in 90µl elution buffer. A qRT-PCR internal control was added at each extraction. qRT-PCR was performed using 10µl of extracted sample in the RealStar®SARS-CoV-2 RT-PCR Kit from Altona-diagnostics with a cut-off set at 40 Ct.

Patients with positive RT-PCR were identified through the database of the laboratories of the hospitals. The hospital admittance records were used to identify additional patients who realized the RT-PCR in an external Lab. Patients requiring intensive care admission were not included due to their health status and the inability to answer to the questions. Thus, we mainly included mild-to-moderate Covid-19 patients, defined as patients without need of intensive care. To avoid some bias, the methodology was similar for all centers.

Study Outcomes

The clinical and epidemiological outcomes data were obtained using a standardized questionnaire in the patient's room; or over the phone for house-bound patients or infected health professionals. For confined patients, the same questionnaire was created with Professional Survey Monkey (San Mateo, California, USA), so that each participant could complete the survey only once. This online collection method allowed the automatic extraction of data, simplifying the realization of statistic matrixes. Note that investigators had access to the medical records of hospitalized patients for completing some data (comorbitities).

The selection of the relevant epidemiological and clinical features included in the questionnaire was carried out by the Covid-19 Task Force members. These included demographic data, medical history, tobacco addiction, comorbidities, general symptoms, otolaryngological symptoms, and treatments. The disease onset was defined as the first day of symptoms. The length of symptoms was defined as the number of days where the patients had >1 general or ear, nose and throat symptoms associated with the Covid-19 infection. The length of the disease was assessed on

patients who have a resolution of general symptoms for at least a week.

Statistical Methods

Bayesian networks used in the present study included a qualitative model based on Directed Acyclic Graph (DAG) indicating the dependencies, and a quantitative model based on local probability distributions, specifying the probabilistic relationships [7]. DAG consisted of nodes and directed links. Nodes were variables on interest, such as loss of smell, sex, age, whereas directed links represented statistical dependencies among the variables.

The local probability distributions were either marginal, for nodes without incoming links, or conditional, for nodes with incoming links. In this case, the dependencies were quantified by conditional probability tables (CPT) for each node given the nodes associated with the incoming links in the graph. Once fully specified, a Bayesian network compactly represented the joint probability distribution (JPD) and, thus, was used for computing the posterior probabilities of any subset of variables given evidence about any other subset. The Bayesian networks presented in this article were machine learned with BayesiaLab (Changé, France, Europe). The algorithms minimized the Minimum Description Length (MDL) score. Basically, the MDL score manages the trade-off between complexity and information, allowing the addition of arcs only when the additional cost in model representation is offset by the reduction in uncertainty.

Results:

Demographic data

We collected the data of 1,566 patients over the study period, including 1,420 patients who completed the full evaluation (962 females). The mean age of patients was 39.17 ± 12.09 years (median: 37.00) ; 94% of those patients were under 60 years of age. The cohort included 436 health care workers (30.7 % of cohort). Irrespective to the country, less than 10% of patients required hospitalization (N=116). The main ethnicities represented in our cohort were European/caucasian (91.4%), and, in lower proportions, North African (2.9%) and South American (2.6%) (Table 1).

Clinical outcomes

Symptoms

The most prevalent symptoms were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%) (Table 1, Figure 1). Fever was reported by on 45.4%. Some patients added the following: conjunctivitis (N=9), visual acuity reduction (N=6), rotatory vertigo (N=6), tinnitus (N=5), cutaneous rash (N=4), cervical lymphadenopathies (N=2), and parotiditis (N=1). The mean duration of Covid-19 symptoms of mild-to-moderate cured patients (N=264) was 11.5 ± 5.7 days (Figure 2).

Comorbidities

Allergic rhinitis (13.4%), hypertension (9.2%), gastroesophageal reflux disease (6.9%) and asthma (6.5%) were the most prevalent comorbidities (Table 1).

Age

The Bayesian analysis revealed that prevalence of symptoms significantly varied according to age. The clinical presentation of young Covid-19 patients more frequently included ear, nose, and throat symptoms, i.e. loss of smell, nasal obstruction, rhinorrhea, facial pain, headache, throat pain, compared with elderly individuals, who more frequently presented fever, fatigue, loss of appetite and diarrhea ($p<0.010$).

Sex

The following symptoms were proportionally more prevalent in females compared with males: loss of smell, headache, nasal obstruction, throat pain and fatigue ($p<0.001$). Males more frequently suffered from cough and fever ($p<0.001$). There was no significant difference in the duration of the disease regarding sex.

Key Symptoms

The Bayesian analysis identified that loss of smell is a key symptom in Covid-19 infection (Figure 3). Loss of smell was significantly influenced by both sex and age of patients. Excluding patients with current or history of chronic rhinosinusitis, 29.4% and 38.5% of patients with loss of smell had no nasal obstruction or rhinorrhea, respectively. Similarly, dysgeusia, which was defined as partial or total loss of the following four taste modalities: salty, sweet, bitter and sour, was more frequently found in young patients and in female patients ($p=0.001$). Gustatory dysfunction was

present in 23.4%, 49.8%, and 61.6% of patients without smell disorder, partial and total loss of smell, respectively. A total of 429 patients did not have gustatory dysfunction but had olfactory disorders (30.2%). According to the Bayesian analysis, the developments of olfactory and gustatory dysfunctions were linked ($p<0.001$), while many patient patterns have been identified regarding the development of one or both dysfunctions.

Among cured patients, 37.5% (N=99) reported that olfactory dysfunction persisted at least 7 days after the end the disease. The mean duration of loss of smell within the patients who recovered olfaction was 8.41 ± 5.05 days. The recovery of olfaction was not significantly linked to recovery of taste.

Treatment outcomes

The majority of patients received oral treatment for the Covid-19 infection (N=1005; 70.8%) whereas 29.1% of patients did not receive any treatment. Depending on the symptoms, patients received analgesic drugs (e.g. paracetamol (86.1%), nonsteroidal anti-inflammatory drugs (7.3%)), oral corticosteroids (1.4%), mucolytics (8.7%), hydroxychloroquine (12.4%), antibiotics (e.g. macrolides (3.1%) and beta-lactam antibiotic (4.5%)), and antiviral drugs (1.1%). Pulmonary aerosols and nasal treatments have been used in 2.2% and 9.4% of cases, respectively.

Discussion:

The majority of patients with Covid-19 infection are thought to be paucisymptomatic and do not require hospitalization. These patients remain potentially infectious individuals who must be identified and confined in order to reduce transmission. To date, there is no clinical study describing the epidemiological and clinical features of European mild-to-moderate Covid-19 patients.

The clinical presentation of mild-to-moderate patients in Europe mainly consists of headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%) and asthenia (63.3%). Interestingly, young patients presented more frequently with ear, nose, and throat symptoms than the elderly. The European clinical presentation appears different from that reported in Asian. According to recent studies, the Covid-19 infection of both hospitalized and non-hospitalized patients in Asia was mainly associated with fever, cough, dyspnea, and fatigue [8-12]. Precisely, in the study of Huang *et al*., the most prevalent symptoms were fever (98%), cough (76%) and dyspnea (55%) [8]. The authors only included hospitalized patients. In the study of Zou *et al*., the main prevalent

symptoms of hospitalized patients were fever (94%) and cough (79%) [10]. The symptom presentation appeared to be similar among elderly Asian patients with fever, cough and dyspnea as the most prevalent complaints [13]. Interestingly, Wu *et al*. provided substantial information about the proportion of mild-to-moderate patients in China, accounting for 81% of covid-19 patients but they did not study the clinical presentation of these patients [9]. Note that according to the China regions, 3.8 to 63.0% of infected patients were health care workers [9]. Surprisingly, only one Asian study reported olfactory and gustatory dysfunctions, accounting for 5.1% and 5.8% of patients, respectively [14]. The differences between our data and the Asian population may be explained by three main hypotheses. First, the Asian studies only included hospitalized patients who were probably more affected by the disease (moderate-to-severe patients). Thus, the pulmonary infection and the related symptoms (dyspnea, fever) would be more prevalent in moderate-to-severe patients. Currently, there is no Asian study that analyzed the data of mild-to-moderate patients, who are however more numerous than the hospitalized patients. Second, as proposed by Li *et al*. [15] and Forster *et al.*[4], the differences between both world regions, especially about olfactory and gustatory dysfunctions, could be related to differences in the genetic pattern of virus (potential mutations). Third, the well-established polymorphism in the angiotensin converting enzyme 2 (ACE2) expression in the human tissues may also explain clinical differences [16]. A recent comparison of the 15 expression quantitative trait loci (eQTLs) variants of the ACE2 gene suggested different ACE2 polymorphisms and expression levels between Asian and European populations [17].

The clinical presentation seems to be influenced by the sex. Our data may corroborate the researches demonstrating the differences between males and females in the immune response to Covid-19 infection and inflammatory diseases. Thus, it seems that females, compared to males, are less susceptible to have complications related to viral infections based on a different innate immunity, steroid hormones and factors related to sex chromosomes [18]. Precisely, the immune regulatory genes encoded by female X chromosome may cause lower viral load levels, and, therefore, less inflammation compared with male patients [18]. Our data revealed that gender differences may particularly concern the development of olfactory dysfunction. Females are more susceptible to develop post-infectious olfactory dysfunction in viral infections related to parainfluenza, Epstein-Barr virus or previous form of coronavirus [19].

The different patterns of development and recovery of gustatory and olfactory dysfunctions found in our cohort rejects the hypothesis that reported loss of taste would reflect only loss of flavor due

to olfactory dysfunction, and suggests true gustatory dysfunction. Olfactory and gustatory disorders could be related to the SARS-CoV-2 neuroinvasive potential [20], which may be more prevalent in European patients due to higher ACE2 expression in nasal mucosa [21].

Regarding treatment, our data showed that analgesics were the most commonly used drugs. Non-steroidal drugs (NDAIDs) were not used often, perhaps reflecting early thoughts that ibuprofen may exacerbate disease severity. However, the published evidence for or against the use of NSAIDs in Covid-19 patients are currently lacking [22]. Interestingly, hydroxychloroquine was empirically prescribed in 12% of patients despite a lack of large randomized controlled data demonstrating efficacy.

The present study has several limitations. First, our patiens were young and had few comorbidities. The lack of studies focusing on mild-to-moderate Covid-19 patients limits the comparison with the current literature. The comorbidity rates of some Asian studies focusing on all types of hospitalized patients is slightly higher to ours [23]. Second, as for many other studies, the lack of sensitivity of RT-PCR and the potential country-related differences in the indications for performing swabs may lead to a selection bias. Furthermore, we are reliant on self-reported reduction in loss of taste and smell and were unable to confirm this with objective testing. Third, we observed a high rate of health care workers in our population, which reflects likely exposure to the infection without protective material (e.g. FFP2/3 masks) in many places. While the proportion in our study suggests high rates of infection in health care workers than the study of Guan *et al*., [23] we are unable to provide true estimates of incidence. Fourth, regarding the lack of tests in Europe, it is probable that some swabs have been realized in moderate or –at risk- patients in some European centers, which may consist of another selection bias.

It seems important to emphasise that this study does not assume the prevalence of Covid-19 in the European population, which is still unknown, but aimed to describe the clinical characteristics of mild-to-moderate Covid-19 patients, defined as patients who did not require hospitalization in intensive care units. Considering the patients of intensive care units, the prevalence of some symptoms, such as fever or dyspnea, would be higher. According to the clinical observation of many investigators of the present study, future studies would focus on the clinical presentation of patients regarding their disease severity. Thus, it would be possible that loss of smell may be more frequent in mild-to-moderate patients, especially younger and female patients, compared with severe forms where cough and fever are more common. Future epidemiological are needed to elucidate this point.

Conclusion

The clinical presentation of mild-to-moderate Covid-19 substantially varies according to the age and the sex characteristics of patients. Olfactory dysfunction seems to be an important underestimated symptom of mild-to-moderate Covid-19 infection since the majority of studies focused on hospitalized patients. Loss of smell needs to be recognized as such by the WHO.

Conflict of interest statement: The authors have no conflicts of interest.

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References:

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497-506.

2. Giovanetti M, Benvenuto D, Angeletti S, Ciccozzi M. The first two cases of 2019-nCoV in Italy: Where they come from? *J Med Virol*. 2020; 92(5):518-521. doi: 10.1002/jmv.25699.

3. World Health Organization Data. https://who.maps.arcgis.com. Consulted April 11, 8:00 P.M.

4. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. *Proc Natl Acad Sci U S A*. 2020. pii: 202004999. doi: 10.1073/pnas.2004999117.

5. Yuan J, Li M, Lv G, Lu ZK. Monitoring Transmissibility and Mortality of COVID-19 in Europe. *Int J Infect Dis*. 2020. pii: S1201-9712(20)30182-X. doi: 10.1016/j.ijid.2020.03.050.

6. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (2019- nCoV) infection is suspected: interim guidance. January 28, 2020 (https://www .who.int/docs/default-source/coronaviruse/ clinical-management-of-novel-cov.pdf).

7. Conrady S, Jouffe L. Bayesian Networks & BayesiaLab - A Practical Introduction for Researchers, 2015, ISBN: 0996533303

8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
9. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020 Feb 24. doi: 10.1001/jama.2020.2648.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395:1054-62.
11. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, Zhang HY, Sun W, Wang Y. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *J Med Virol*. 2020. doi: 10.1002/jmv.25757.
12. Cao Y, Liu X, Xiong L, Cai K. Imaging and Clinical Features of Patients With 2019 Novel Coronavirus SARS-CoV-2: A systematic review and meta-analysis. *J Med Virol*. 2020. doi: 10.1002/jmv.25822.
13. Wang L, He W, Yu X, Hu D, Bao M, Liu H, Zhou J, Jiang H. Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infec*t. 2020. pii: S0163-4453(20)30146-8. doi: 10.1016/j.jinf.2020.03.019.
14. Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. MedRXiv, in press. 2020.
15. Wang C, Liu Z, Chen Z, Huang X, Xu M, He T, Zhang Z. The establishment of reference sequence for SARS-CoV-2 and variation analysis. *J Med Virol*. 2020. doi: 10.1002/jmv.25762.
16. Li W, Zhang C, Sui J, Kuhn JH, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. *EMBO J*. 2005; 24(8):1634-43.
17. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov*. 2020; 6:11. doi: 10.1038/s41421-020-0147-1.
18. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. *J Biol Regul Homeost Agents*. 2020; 34(2). doi: 10.23812/Editorial-Conti-3.
19. Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope*. 2007; 117(2):272-7.

20. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020. doi: 10.1002/jmv.25728.
21. Long C, Xu H, Shen Q, Zhang X, Fan B, Wang C, Zeng B, Li Z, Li X, Li H. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? *Eur J Radiol*. 2020 Mar 25;126:108961. doi: 10.1016/j.ejrad.2020.108961.
22. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience*. 2020; 14:1023. doi: 10.3332/ecancer.2020.1023.
23. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020. doi: 10.1056/NEJMoa2002032.

Table 1: Epidemiological and Clinical Characteristics of Patients.

Characteristic	All patients (N=1420)	Cured patients (N=264)	15-39 yo (N=793)	40-59 yo (N=551)	>60 yo (N=76)
Age					
Mean (SD) - yo	39.17 ± 12.09	34.1 ± 12.4	30.14 ± 4.8	48.4 ± 5.5	66.9 ± 6.9
Gender (N - %)					
Male	458 (32.3)	168 (63.6)	231 (29.0)	190 (34.5)	37 (48.7)
Female	962 (67.7)	96 (36.4)	562 (71.0)	361 (65.5)	39 (51.3)
Ethnicity (N - %)					
European/Caucasian	1298 (91.4)	242 (91.7)	715 (90.2)	512 (92.9)	71 (93.4)
Asian	11 (0.8)	1 (0.4)	6 (0.8)	5 (0.9)	0 (0)
Black African	25 (1.8)	3 (1.1)	17 (2.1)	7 (1.3)	1 (1.3)
North African	41 (2.9)	15 (5.7)	27 (3.4)	12 (2.2)	2 (2.6)
North American	2 (<0.1)	1 (0.4)	2 (0.3)	0 (0)	0 (0)
South American	37 (2.6)	1 (0.4)	24 (3.0)	13 (2.4)	0 (0)
Oceanian	1 (<0.1)	1 (0.4)	0 (0)	0 (0)	1 (1.3)
Mixing	5 (0.4)	0 (0)	2 (0.3)	2 (0.4)	1 (1.3)
Addictions (N - %)					
Non-smoker	1,217 (85.7)	224 (84.8)	670 (84.4)	485 (87.8)	62 (81.6)
Mild smoker (1-10 cigarettes daily)	162 (11.4)	40 (15.2)	98 (12.4)	53 (9.6)	11 (14.5)
Moderate smoker (11-20 cigarettes daily)	36 (2.5)	2 (0.8)	21 (2.8)	12 (2.4)	3 (3.9)
Heavy smoker (>20 cigarettes daily)	5 (0.4)	0 (0)	4 (0.4)	1 (0.2)	0 (0)
Allergic patients	277 (19.5)	39 (14.8)	155 (19.5)	111 (20.1)	11 (14.5)
Symptoms (N - %)					
Headache	998 (70.3)	162 (61.4)	574 (72.4)	385 (69.9)	39 (51.4)
Loss of smell	997 (70.2)	168 (63.6)	600 (75.8)	367 (66.6)	30 (39.5)
Nasal obstruction	963 (67.8)	157 (59.5)	585 (73.8)	335 (60.8)	43 (56.6)
Asthenia	514 (63.3)*	200 (76.0)*	264 (59.7)*	215 (65.7)*	35 (81.4)*
Cough	897 (63.2)	146 (55.3)	501 (63.2)	350 (63.5)	46 (60.5)
Myalgia	887 (62.5)	154 (58.3)	480 (60.5)	370 (67.2)	37 (48.7)
Rhinorrhea	854 (60.1)	141 (53.4)	507 (63.9)	304 (55.2)	43 (56.6)
Taste dysfunction	770 (54.2)	107 (40.5)	434 (54.9)	298 (54.1)	38 (50.0)
Sore throat	751 (52.9)	118 (44.7)	440 (55.5)	281 (51.0)	30 (39.5)
Dyspnea	697 (49.1)	116 (43.9)	392 (49.4)	271 (49.2)	34 (44.7)
Postnasal drip	680 (47.9)	105 (39.8)	398 (50.2)	254 (46.1)	28 (36.8)
Loss of appetite	649 (45.7)	121 (45.8)	344 (43.4)	257 (46.6)	48 (63.2)
Fever (>38C)	645 (45.4)	135 (51.1)	330 (41.6)	263 (47.7)	52 (68.4)

Face pain/heaviness	644 (45.4)	82 (31.1)	393 (49.6)	232 (42.1)	19 (25.0)
Arthralgia	519 (36.5)	74 (28.0)	265 (33.4)	226 (41.0)	28 (36.8)
Diarrhea	473 (38.1)	90 (34.1)	253 (31.9)	184 (33.4)	36 (47.4)
Dysphonia	176 (28.4)*	74 (28.0)	80 (23.8)*	86 (32.2)*	10 (28.6)*
Chest pain	173 (27.2)*	72 (27.4)	85 (25.4)*	81 (5.5)*	7 (20.0)*
Ear pain	358 (25.2)	45 (17.0)	214 (27.0)	133 (24.1)	11 (14.5)
Dysphagia	274 (19.3)	39 (14.8)	163 (20.6)	97 (17.6)	14 (18.4)
Nausea, vomiting	272 (19.2)	46 (17.4)	143 (18.0)	109 (19.8)	20 (26.3)
Abdominal pain	270 (19.1)	40 (15.2)	140 (17.7)	112 (20.3)	18 (23.7)
Reduction of smell	201 (14.2)	40 (15.2)	99 (12.6)	86 (15.6)	16 (21.1)
Sticky mucus/phlegm	193 (15.6)	16 (6.1)	112 (14.1)	68 (12.3)	13 (17.1)
Comorbidities					
Diabetes	24 (1.7)	4 (1.5)	2 (0.3)	15 (2.72)	7 (9.2)
Hypertension	131 (9.2)	28 (10.6)	12 (1.5)	87 (15.8)	32 (42.1)
CRS with or without polyps	35 (2.5)	6 2.3)	12 (1.5)	22 (4.0)	1 (1.3)
History of Surgery for CRS	23 (1.6)	3 (1.1)	10 (1.3)	9 (1.6)	4 (5.3)
Hypothyroidism (treated)	79 (5.6)	17 (6.4)	31 (3.9)	42 (7.6)	6 (7.9)
Hypothyroidism (untreated)	8 (<0.1)	0 (0)	1 (0.1)	7 (1.3)	0 (0)
Allergic rhinitis	190 (13.4)	35 (13.3)	111 (14.0)	71 (12.9)	8 (10.5)
Renal failure	6 (0.4)	0 (0)	1 (0.1)	3 (0.5)	4 (5.3)
Hepatic insufficiency	8 (0.6)	0 (0)	0 (0)	4 (0.7)	4 (5.3)
Respiratory insufficiency	10 (0.7)	2 (0.8)	1 (0.1)	4 (0.7)	5 6.6)
GERD	58 (6.9)*	20 (8.6)*	15 (3.3)*	36 (10.4)*	7 (13.7)*
Asthma	93 (6.5)	12 (4.5)	46 (5.8)	44 (7.99)	3 (3.9)
Heart problems	25 (1.8)	5 (1.9)	7 (0.9)	10 (1.8)	8 (10.5)
Neurological diseases	13 (0.9)	0 (0)	3 (0.4)	4 (0.7)	6 (7.9)
Depression	36 (2.5)	7 (2.7)	17 (2.1)	15 (2.7)	4 (5.3)
Autoimmune diseases	18 (1.3)	2 (0.8)	5 (0.7)	8 (1.5)	5 (6.6)
Untreated cancer/cancer under treatment	22 (1.5)	3 (1.1)	9 (1.1)	11 (2.0)	22 (28.9)

Table 1 footnotes: *Some data was not available, and, therefore, the proportion was calculated on a reduced sample. Abbreviations: CRS=chronic rhinosinusitis; GERD=gastroesophageal reflux disease; SD=standard deviation.

Figure 1: Symptom Proportion

Figure 1 footnotes: The proportion of symptoms (%) in the European Mild-to-moderate COVID-19 population.

Figure 2: Symptom Duration Data.

Figure 2 footnotes: The proportion of patients (Y-axis) and the duration of the disease (X-axis, Days).

Figure 3: Overview of one Network.

Figure 3 footnotes: Network describing the association between symptoms and some demographic data.

Figure 1

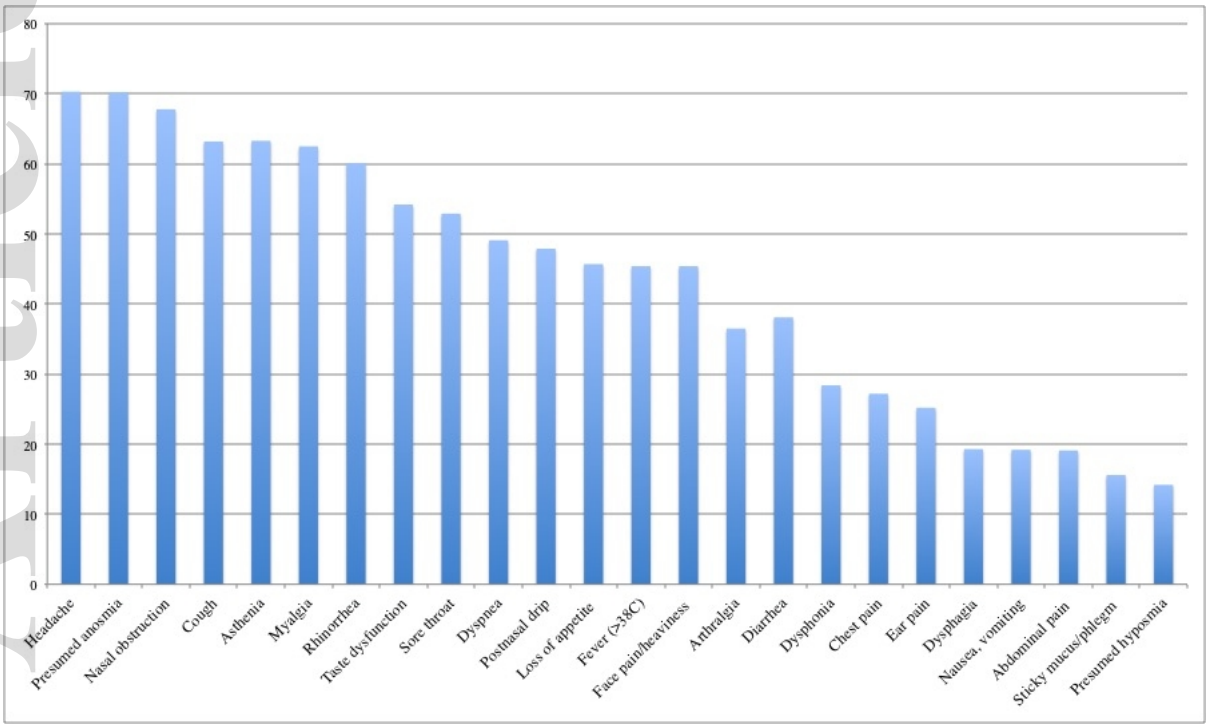

Figure 2

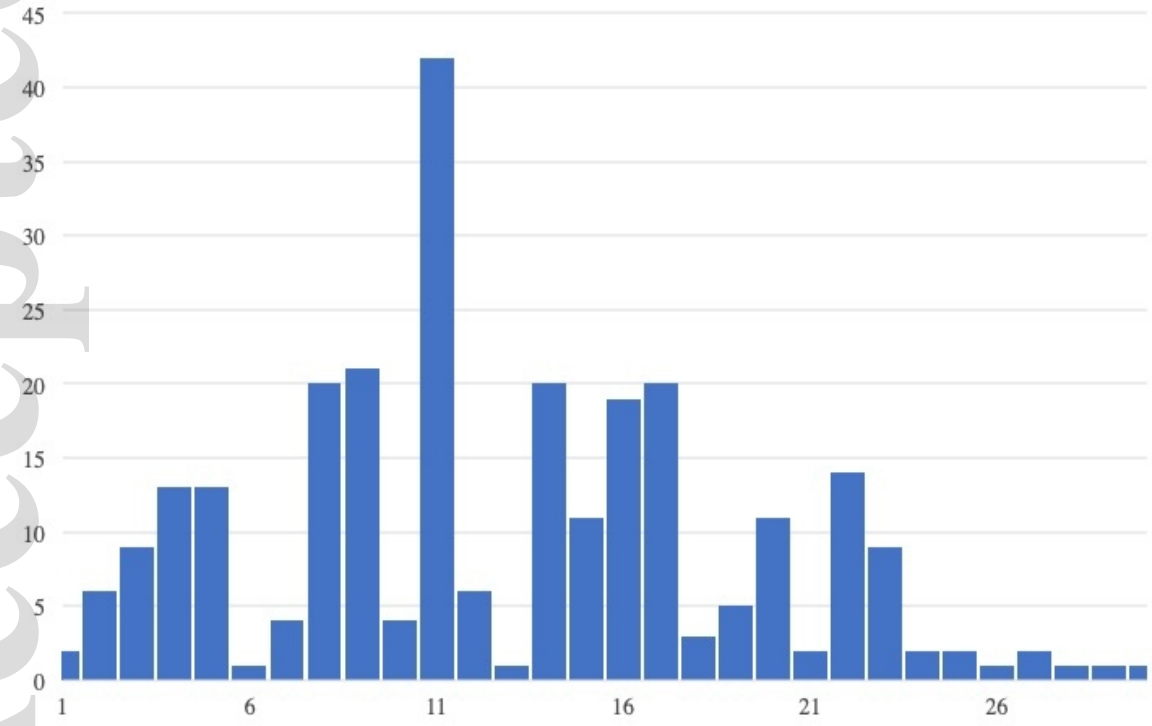

Figure 3