


Prospective Study in 355 Patients With Suspected COVID-19 Infection: Value of Cough, Subjective Hyposmia, and Hypogeusia

Eduardo Martin-Sanz, MD, PhD ; Juan Riestra, MD; Laura Yebra, MD; Alba Larran, MD; Fiorella Mancino, MD; Joaquin Yanes-Diaz, MD; Maria Garrote, MD; Marta Colmenero, MD; Esther Montiel, MD; Cristina Molina, MD; Daniel Moreno, MD; Antonio Rodriguez, MD, PhD; Gerardo Monedero, MD; Ricardo Sanz-Fernández, MD, PhD; Rocio Gonzalez, MD, PhD; Jonathan Esteban-Sanchez, MD

Objective: To evaluate the incidence of certain symptoms in a population of health workers exposed to coronavirus disease 2019 patients.

Study Design: Case-control study.

Methods: The study was conducted at a tertiary care hospital from March 1 to April 7, 2020. Health workers with suspected coronavirus disease 2019 (COVID-19) infection were included. The presence of COVID-19 was detected by using real-time polymerase chain reaction (RT-PCR) methods. Positive and negative RT-PCR patients were used as case and control groups, respectively.

This study analyzed the incidence of COVID-19 symptoms in both patient groups. Visual analog scales were used for self-assessment of smell and taste disorders, ranging from 0 (no perception) to 10 (excellent perception).

Results: There were 215 (60.6%) patients with positive RT-PCR and 140 (39.4%) patients with negative RT-PCR. The presence of symptoms such as hyposmia hypogeusia, dysthermia, and cough were strongly associated with a positive RT-PCR. The association of cough and subjective hyposmia had 5.46 times higher odds of having a positive test. The receiver operating characteristic (ROC) analysis showed that a fever higher than 37.45°C resulted in sensitivity and specificity of 0.65 and 0.61, respectively. A total of 138 cases (64.1%) and 114 cases (53%) had subjective hyposmia and hypogeusia, respectively. The 85.4% of these patients recovered olfactory function within the first 14 days of the onset of the symptoms.

Conclusion: There is a significant association between positive RT-PCR and subjective hyposmia. The association of subjective hyposmia and cough increase significantly the odds of having a positive RT-PCR. The measurement of fever as the only method for screening of COVID-19 infection resulted in a poor association.

Key Words: Hyposmia, hypogeusia, COVID-19, odds ratio, incidence, ROC.

Level of Evidence: 3

Laryngoscope, 130:2674–2679, 2020

INTRODUCTION

Since the first group of cases of coronavirus disease infection (COVID-19) was reported in Wuhan, China, in late December 2019, the disease has spread widely in the past 4 months, which has resulted in a global pandemic with an increasing number of deaths affecting practically every country in the world.¹

The spread from China was initially to other Asian countries, primarily to the Republic of Korea, then to the Middle East, most notably to Iran, then to southern Europe, especially Italy and Spain,² and then to the most recent epicenter, the United States.

From the Department of Otolaryngology (E.M.-S., J.R., L.Y., A.L., F.M., J.Y.-D., M.G., M.C., E.M., C.M., D.M., A.R., G.M., R.S.-FÁÑDEZ, R.G., J.E.-S.), University Hospital of Getafe, Madrid, Spain.

Editor's Note: This Manuscript was accepted for publication on July 16, 2020.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Eduardo Martin-Sanz, Department of Otolaryngology, Hospital Universitario de Getafe, Autovía de Toledo, km 12,500, 28905 Getafe, Madrid, Spain. E-mail: emartinsanz@gmail.com

DOI: 10.1002/lary.28999

Currently, there are fewer cases reported in low- and middle-income countries, but these are likely to increase dramatically in these countries, especially where medical care is limited and fewer diagnostic tests are performed.

Although there have been regular monitoring and reporting of total cases and deaths worldwide, the numbers of different types of workers exposed in the workplace are less known. Workers involved in healthcare are at the forefront for risk of infection and death, as has been the case during many previous infectious disease epidemics such as severe acute respiratory syndrome (SARS) and Ebola.³

In the management of the health crisis, the identification of paucisymptomatic patients is emerging as a crucial factor to interrupt the virus chain of transmission because this symptomatology may represent the only manifestation of the disease.

In health centers dealing with this emergency, a significant number of patients presenting hyposmia, hypogeusia,⁴ mild headache, diarrhea, or odynophagia⁵ associated with fever (> 37.5°C) are not correctly identified as potentially infected with COVID-19.

The actual incidence of these symptoms is not adequately described in the reviews that have been carried out, with very wide ranges according to the different authors. Odynophagia, for example, is present in 5% to 17.4% of patients with COVID-19.^{6,7} Hyposmia has been reported in 5.1% to 19.4% of cases.⁴

This large variation may be because most of the patients included in these reviews⁸ were drawn from studies that did not accurately describe the clinical presentation.^{6,9} The largest report on 44,672 confirmed patients with COVID-19 focused on critical cases and case fatality rate, without a detailed presentation of symptoms. In contrast, other studies that described the full spectrum of symptoms of COVID-19 found that sore throat or hyposmia was not uncommon.^{4,5}

Early reports have suggested that acute smell loss may be an early symptom associated with the worldwide pandemic known as COVID-19.¹⁰ Also, smell and/or taste loss has been noted in the absence of other known symptoms of the disease, but they have yet to be verified with hard data, including testing of both smell function and/or COVID-19.¹¹

Currently, polymerase chain reaction (PCR) is the standard for the detection of SARS-CoV-2 from nasal and oropharyngeal exudate.¹² The results of these tests could be affected by the variation of the viral RNA sequences or by the viral load in different anatomical sites during the evolution of the disease.¹²

A recent study of 1014 cases of COVID-19 found that only 59% of patients had positive PCR in cases of SARS-CoV-2 at the onset of symptoms, whereas chest computed tomography had a higher sensitivity for the diagnosis of COVID-19.¹³

Consequently, the clinical presentation could be useful in identifying suspected cases of COVID-19, and we believe that mild symptoms such as sore throat, hyposmia, or hypogeusia should not be considered a rare symptom.

METHODS

We performed a case-control study from March 15 to April 7, 2020. Inclusion criteria were health workers of the University Hospital of Getafe (Madrid, Spain) with suspicion of COVID-19 infection. Exclusion criteria were inconclusive PCR results.

The suspicion of COVID-19 was determined by the presence of either cough, fever (> 37.5°C), headache, or breathlessness of any health worker regardless of contact with a COVID-19 patient.

This project was approved by the institutional review board (CV20/24). Patient-informed consent was obtained in every patient.

We collected clinical data from the anamnesis, especially focused on every symptom associated with COVID-19 infection (Fig. 1). Visual analog scales (VAS) were used for self-assessment of smell and taste, ranging from 0 (no perception) to 10 (excellent perception).

Demographic data such as age and sex were reviewed. We reviewed the medical records of these patients to evaluate the incidence of other cranial neuropathies and possible predisposing factors of cranial nerve susceptibility, such as smoking, diabetes mellitus, hypertension, or dyslipidemia.

Fever was defined as a body temperature above 37.5°C, measured by an axillary digital thermometer.

The presence of COVID-19 in respiratory specimens obtained from nasal and pharyngeal swabs was detected by next-generation sequencing or real-time (RT)-PCR methods. Allplex 2019 -nCoV Assay (Seegene, Seoul, South Korea) is a multiplex RT-PCR assay for simultaneous detection of three target genes of SARS-CoV-2 in a single tube. The assay is designed to detect RdRP, N genes specific for SARS-CoV-2, and E gene for all Sarbecovirus including SARS-CoV-2.

Cases were defined as those patients with a positive RT-PCR, whereas patients with a negative test were the controls.

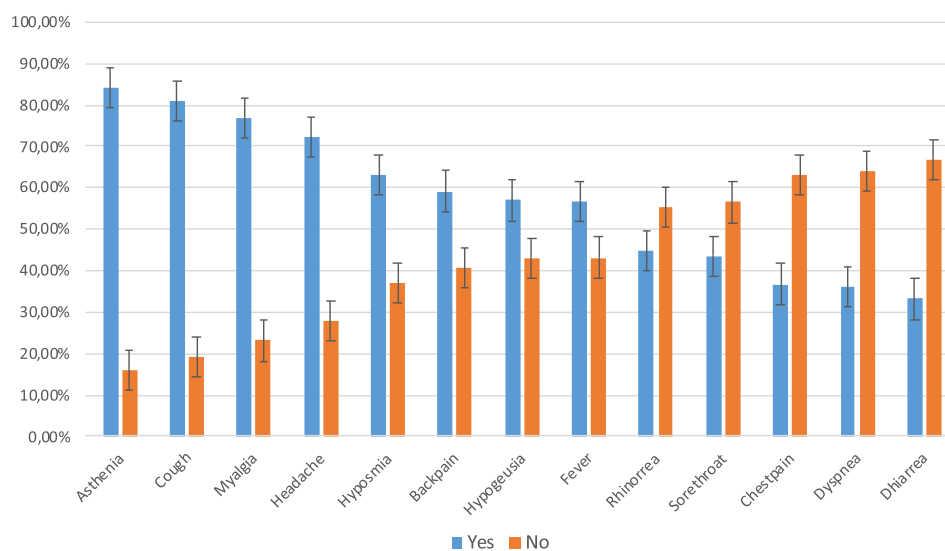


Fig. 1. Symptoms associated with COVID-19 infection. The ordinate axis consists of percentages of patients. COVID-19 = coronavirus disease 2019. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Every case was subsequently evaluated at the 2-week follow-up with a new anamnesis and RT-PCR.

Statistical Analysis Statistical Package for the Social Sciences for Windows (SPSS version 25.0; IBM Corp, Armonk, NY) was used to perform the statistical analyses. The potential associations between epidemiological, clinical, and olfactory and gustatory outcomes have been assessed through cross-tab generation between two variables (binary or categorical variables) and Chi-square test. Categorical variables between both age- and sex-matched groups were summarized by counts and frequencies and compared using odds ratio (OR) with 95% confidence intervals. The relationship between VAS variables was investigated using Spearman correlation coefficient.

A receiver operating characteristic (ROC) curve was used to determine the cutoff values of the degrees Centigrade and positive RT-PCR patients. The area under the ROC curve (AUC) varies from 0.5 for random performance to 1.0 for perfect performance.

The normally distributed variables were presented with means and standard deviations.

RESULTS

Demographic Data

A total of 355 patients participated in this study. The mean age of patients was 42.9 ± 0.67 years (range 18–65). There were 287 (80.8%) females and 154 (19.2%) males.

There were 215 (60.6%) patients with positive RT-PCR and 140 (39.4%) patients with a negative RT-PCR as part of the control group.

The most prevalent comorbidities of patients were hypertension, dyslipidemia, asthma, and hypothyroidism. There were no significant differences in baseline demographic characteristics, including age, sex, or comorbidities, between both cases and controls groups.

The mean time between the onset of the symptoms and the evaluation was 7.8 ± 0.51 days and 7.27 ± 0.60 days in cases and controls, respectively, with no statistically significant differences.

Association Between General Symptoms and COVID-19 Infection

The general symptoms of patients are described in Figure 1. Asthenia, cough, myalgia, headache, subjective hyposmia, hypogeusia, back pain, and dysthermia were the most prevalent symptoms, accounting for more than 50% of patients.

The presence of certain symptoms such as subjective hyposmia (OR 4.88), hypogeusia (OR 3.51), dysthermia (OR 2.38), and cough (OR 1.83) was strongly associated with a positive RT-PCR. The association of cough and subjective hyposmia had 5.46 times higher odds of having a positive test. In the same way, patients with both dysthermia and subjective hyposmia had 3.91 times higher odds of having an RT-PCR (Table I).

Other symptoms such as myalgia, asthenia, rhinorrhea, back and chest pain, dyspnea, diarrhea,

TABLE I.
Description of Case and Control Groups.

Symptoms	Odds Ratio (95% CI)	Significance (P)
Cough + hyposmia	5.46 (3.02–9.88)	.000
Hyposmia	4.88 (2.89–8.24)	.000
Dysthermia + hyposmia	3.91 (2.08–7.30)	.000
Hypogeusia	3.51 (2.09–5.89)	.000
Dysthermia	2.38 (1.49–3.79)	.000
Cough	1.83 (1.08–3.11)	.029
Myalgia	1.53 (0.91–2.58)	.10
Asthenia	1.19 (0.64–2.14)	.56
Rhinorrhea	1.04 (0.64–1.70)	.85
Back pain	0.92 (0.56–1.5)	.74
Chest pain	0.88 (0.54–1.44)	.62
Dyspnea	0.86 (0.53–1.39)	.54
Diarrhea	0.77 (0.49–1.21)	.26
Headache	0.74 (0.42–1.29)	.29
Sore throat	0.59 (0.36–0.95)	.03

CI = confidence interval.

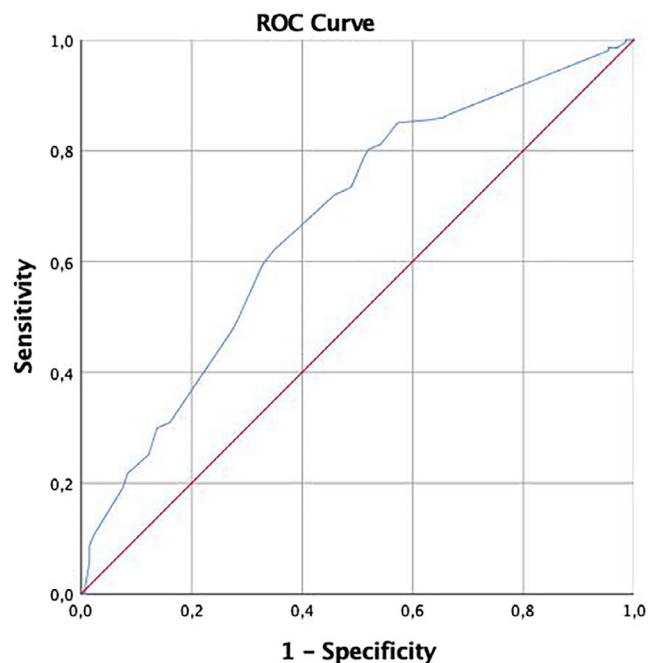


Fig. 2. ROC curve showing the capacity of degrees centigrade increase in predicting a positive PCR for COVID-19. The area under the curve was 0.671. The analysis showed that a fever higher than 37.45°C results in sensitivity and specificity of 0.65 and 0.61, respectively. COVID-19 = coronavirus disease 2019; PCR = polymerase chain reaction; ROC = receiver operating characteristic. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

headache, and sore throat were not associated with increased odds of being infected with COVID-19.

Finally, the presence of fever (measured temperature greater than 37.5°C) had 3.13 times higher odds of having a positive RT-PCR than afebrile patients.

TABLE II.
Symptoms of Cases and Controls.

Variable	Positive RT-PCR No.(%)	Negative RT-PCR No.(%)	Significance (P)
Sex			0,43
Male	44 (20,5%)	24 (17,1%)	
Female	171 (79,5%)	116 (82,9%)	
Hyposmia	138 (64.1%)	30 (24,8%)	< .001
VAS 0–2	78 (56.5%)	12 (40%)	< .001
VAS 3–5	33 (23.9%)	11 (36,7%)	< .001
VAS 6–8	20 (14.4%)	2 (6,7%)	< .001
VAS 9–10	7 (5.1%)	5 (16,6%)	< .001
Rinorrhea	61 (51,3%)	14 (53,8%)	0,811
Hypogeusia	114 (53%)	25 (17,9%)	< .001
VAS 0–2	65 (57%)	9 (36%)	< 0,001
VAS 3–5	31 (27,2%)	5 (20%)	0,003
VAS 6–8	15 (13,1%)	7 (28%)	< 0,001
VAS 9–10	3 (2,6%)	4 (16%)	< 0,001
Rinorrhea	54 (51,4%)	14 (28,3%)	.541

COVID-19 = coronavirus disease 2019; RT-PCR = real-time polymerase chain reaction; VAS = visual analog scale.

To assess the optimal cutoff point between the degrees centigrade and a positive RT-PCR, we performed a ROC analysis with an AUC of 0.671 ($P = .001$). The ROC analysis showed that a fever higher than 37.45°C results in sensitivity and specificity of 0.65 and 0.61, respectively (Fig. 2).

Subjective Hyposmia and Hypogeusia

Regarding olfactory and taste function, a total of 138 cases (64.1%) and 114 cases (53%) had subjective hyposmia and hypogeusia, respectively. The cases presented significantly lower olfactory and taste VAS scores compared to controls ($P < .001$), as observed in Table II. There was a significant positive association between both symptoms ($P < .001$), and their VAS were highly correlated ($r_2 = 0.714$).

Regarding the association of any other symptom to the subjective hyposmia or hypogeusia, 159 (70.9%) patients associated more than two symptoms; 50 (22.3%) patients had at least two symptoms; 12 (5.3%) patients associated one symptom; and three patients (1.3%) did not associate any symptom.

There was no significant association between comorbidities and the development of subjective hyposmia or hypogeusia. Olfactory dysfunction was not significantly associated with rhinorrhea or nasal obstruction.

Residual Symptoms

Fourteen patients (3.94%) developed pneumonia or severe symptoms that required hospitalization. One hundred and sixty-four patients (76.3%) totally recovered

from their symptoms at the 2 week follow-up. The mean time of recovery was 10.66 ± 0.44 days.

We did not observe any significant association between comorbidities or any symptom with the time to recover.

Considering the patients with a clinically resolved infection at the 2 week follow-up, 51 patients (23.8%) still had residual symptoms. The most frequently reported residual symptom was cough (11.2%), followed by subjective hyposmia (10.7%) and headache (1.9%).

The short-term olfaction recovery rate was assessed in 123 clinically cured patients. 85.4% of these patients recovered olfactory function within the first 14 days of the onset of the symptoms.

DISCUSSION

This is the first case control study that analyzes the odds of patients having a positive RT-PCR.

Our healthcare personnel are essential workers defined as paid persons serving in our healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials.

Worldwide, as millions of people stay at home to minimize the transmission of severe acute respiratory syndrome coronavirus, healthcare workers prepare to do the exact opposite. They go to clinics and hospitals, putting themselves at high risk for COVID-2019.²

In addition to healthcare workers, there are many other types of workers who are at increased risk of infection, generally because they are close to being infected. These include emergency services personnel, workers employed in nursing homes, daycare or education workers, cleaners, the hotel industry, public transportation, and drivers, to name a few. The importance of our results lies in the fact that they can be extrapolated to those other types of workers.

The safety of that personnel is essential to provide the best possible services for infected persons. It is therefore crucial to identify those positive health workers to isolate them in their homes.

It is widely recognized that screening is an imperfect barrier to spread,¹⁴ usually due to the lack of detectable symptoms during the incubation period, variation in the detectability of symptoms, and imperfect performance of screening equipment or personnel.¹⁵

Concerning the prevalence of general symptoms, our results are similar to other recent studies.^{7,10} Nevertheless, those studies do not predict or estimate the possibility of having a COVID-19 infection. For example, symptoms such as myalgia, asthenia, back and chest pain, diarrhea, or headache, which were present in a large percentage of our cases, did not have a significant result in predicting a COVID-19 infection because they were also highly present in our control group.

In the same way, the detection of measured fever, usually employed as a screening method, had an AUC of 0.671 and a sensitivity and specificity of 0.65 and 0.61, respectively, which are far from being optimal. In our opinion, this should be considered when creating

screening plans, or in case diagnostic tests are not completely available for the general population.

Coronavirus has already been identified as a family of viruses that may be associated with anosmia,¹⁶ and it has been demonstrated on transgenic mice that SARS-CoV may enter the brain through the olfactory bulb, leading to rapid transneuronal spread.¹⁷

International reports are accumulating from otolaryngologists and other healthcare workers on the front lines that anosmia, with or without dysgeusia, are symptoms frequently associated with COVID-19 infection.¹⁸ The American Academy of Otolaryngology–Head and Neck Surgery and the British Association of Otorhinolaryngology are now recommending that these symptoms be added to the list of primary screening symptoms for COVID-19.

Although the onset of the viral associated olfactory loss is sudden, patients rarely pay attention to this symptom given the common co-occurrence of other associated symptoms.¹⁹ Therefore, is often a delay between the onset of the olfactory loss and the patient's perception.²⁰

Recent retrospective studies¹⁰ reported more than 80% of patients having olfactory dysfunction, which supports the role of otolaryngologists as the first-line physicians for some COVID-19 patients. In our population, 64.1% and 53% of our cases had subjective hyposmia and hypogeusia, respectively, which is a significantly lower percentage, probably due to the retrospective design of their study.

In our prospective study, there was a significant association between the positive PCR and subjective hyposmia. This seems to represent the fact that, based on the odds ratio, the odds of patients having a positive RT-PCR were 4.88 times higher if they had subjective hyposmia. Interestingly, if we consider the association of subjective hyposmia and cough, the odds increase significantly to 5.46, which may be of interest when designing clinical tools to identify COVID-19 patients. The novelty of this finding is now diminished in that the World Health Organization has already adopted this finding. However, these data do provide another analysis in a specific population of at-risk subjects.

Regarding the association with other symptoms, the incidence of isolated subjective hyposmia or hypogeusia was present in just 1.3% of our population. Therefore, we consider that clinical scenario as marginal. The differences with other reports are probably related to a lack of awareness of those mild symptoms among both patients and clinicians.^{11,20}

In most cases, these episodes of smell loss are self-limiting. In our population, 85.4% of these patients recovered olfactory function within the first 14 days of the onset of the symptoms.

The fact of persistent subjective hyposmia is presumed to occur through a more direct olfactory insult by the virus.¹¹

However, given the scale of this pandemic, if COVID-19 does cause a chronic olfactory loss in even a small portion of those infected, the overall population prevalence could be quite large. It is important to highlight that results from olfactory testing of subjects may

impact these conclusions because there is known to be a poor correlation between subjective reporting and objective chemosensory testing.²¹

Our population of cases should be considered paucisymptomatic patients due to the benign evolution of the disease. 76.3% of our cases had total recovery of their symptoms at the 2 week follow-up, which represents the majority of our cases. Less than 4% of our patients developed pneumonia, and just 23.8% of our cases still had minor residual symptoms such as cough, subjective hyposmia, or headache. It is precisely those paucisymptomatic and asymptomatic patients, who represent the major challenge to the medical system, to identify them and avoid further spread of the pandemic.

The main limitation of our study results from our health workers' population. Because they were attended in case of suspicion of a COVID-19 infection, our percentage of totally asymptomatic subjects is probably abnormally low. In the same way, we should emphasize that our high percentage of the female population (81%) should prevent generalizing our results to other male populations.

Case-control studies usually are limited by issues with the identification of controls and the possible biases this may introduce, as well as reporting bias. In a prospective case-control study, this bias is usually limited and is unlikely to have affected our results.

Despite the limitations, the data presented here may constitute a valuable help for future prospective studies with longer follow-up periods investigating these associations. In the same way, performing objective smell testing on these patients may give us new information and conclusions that would add value to the scientific literature.

CONCLUSION

There is a significant association between positive PCR and subjective hyposmia.

If we consider the association of subjective hyposmia and cough, the odds of having a positive RT-PCR increase significantly.

The measurement of fever as the only method for screening of COVID-19 infection results in a poor association.

ACKNOWLEDGMENT

Concepción Campos Asensio for her support in information sources and bibliographic search strategies. Dr. David Molina Arana for his help in the analysis of the RT-PCR tests.

BIBLIOGRAPHY

1. Sim MR. The COVID-19 pandemic: major risks to healthcare and other workers on the front line. *Occup Environ Med* 2020;77:281–282.
2. Rubino S, Kelvin N, Bermejo-Martin JF, Kelvin D. As COVID-19 cases, deaths and fatality rates surge in Italy, underlying causes require investigation. *J Infect Dev Ctries* 2020;14:265–267.
3. The Lancet. COVID-19: protecting health-care workers. *Lancet* 2020; 395:922.
4. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and ageusia: common findings in COVID-19 patients. *Laryngoscope* 2020;130:1787.

5. Lovato A, Rossetini G, de Filippis C. Sore throat in COVID-19: comment on “clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis”. *J Med Virol* 2020;92:714–715.
6. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395:507–513.
7. Chu J, Yang N, Wei Y, et al. Clinical characteristics of 54 medical staff with COVID-19: a retrospective study in a single center in Wuhan, China. *J Med Virol* 2020;92:807–813.
8. Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis. *J Med Virol* 2020;92:612–617.
9. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. *J Clin Med* 2020;9:941.
10. Lechien JR, Chiesa-Estomba CM, De Siati DR, 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. *Eur Arch Otorhinolaryngol* 2020;277:2251–2261.
11. Soler ZM, Patel ZM, Turner JH, Holbrook EH. A primer on viral-associated olfactory loss in the era of COVID-19. *Int Forum Allergy Rhinol* 2020;10: 814–820.
12. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiology* 2020;296:E32–E40.
13. Wang Y, Kang H, Liu X, Tong Z. Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak. *J Med Virol* 2020;92:538–539.
14. Quilty BJ, Clifford S, Flasche S, Eggo RM, CMMID nCoV Working Group. Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV). *Euro Surveill* 2020;25(5):252000080.
15. Prem K, Liu Y, Russell TW, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *Lancet Public Health* 2020;5:e261–e270.
16. Suzuki M, Saito K, Min WP, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope* 2007;117:272–277.
17. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol* 2008;82:7264–7275.
18. Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, et al. Smell and taste dysfunction in patients with COVID-19. *Lancet Infect Dis* 2020;20 [https://doi.org/10.1016/S1473-3099\(20\)30293-0](https://doi.org/10.1016/S1473-3099(20)30293-0).
19. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol* 2008;63: 159–166.
20. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology* 2020;58:299–301.
21. Liu G, Zong G, Doty RL, Sun Q. Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the US population: a cross-sectional study. *BMJ Open* 2016;6:e013246.