ANOSMIA SYMPTOMS AND RT-PCR SWAB RESULTS IN COVID-19 DIAGNOSTICS

Vincent Geraldus Enoch Lusida[1], Nabilah Puspa Utami[1], Jihan Qonitatillah[1], Fabilla Faiz Arifin[1], Nida' Fahima Amatullah[1], Denillia Limawan[1], Raudhatuzzahra Kesuma[1], Subur Prajitno[2]

[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Public Health-Preventive Medicine, Faculty of Medicine Universitas Airlangga, Indonesia

ABSTRACT

Coronavirus Disease-19 (Covid-19) is an infectious disease that has become a pandemic since March 11, 2020. PCR (Polymerase chain reaction) swab is a definitive diagnostic tool for Covid-19, because it has a high level of sensitivity and specificity. One of the symptoms of this infection is anosmia. This study aimed to determine the relationship between the symptoms of anosmia and the positive RT-PCR swab results in Covid-19 diagnostics. This study used a systematic review and meta-analysis method that was in accordance with PRISMA. From 16 articles that met the inclusion and exclusion criteria, we selected 12 articles through EPHPP that reported smell disorder among Covid-19 patients. Four reports studied whether smell disorder was independently associated with Covid-19 diagnosis. The frequency of anosmia ranged between 7,5-95%. Anosmia has high specificity for detecting Covid-19 but has low sensitivity. There was a strong relationship between anosmia symptoms and positive RT-PCR swab results. This showed that anosmia can be a marker for patients to carry out further investigations.

ARTICLE HISTORY

Received: August 03, 2021
Revised: August 12, 2021
Accepted: September 08, 2021
Published: June 30, 2022 (Online)

doi: 10.20473/jcmphr.v3i1.28915

KEYWORDS
COVID-19, swab RT-PCR, anosmia, smell disorder

CORRESPONDING AUTHOR
Vincent Geraldus Enoch Lusida
✉vinlusida@gmail.com
Medical Program, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital Jl. Mayjend Prof. Dr. Moestopo 4-6, Surabaya, Indonesia

INTRODUCTION

Coronavirus Disease-2019 (Covid-19) is a dangerous disease that has already affected almost all countries in the world. Since March 11, 2020, WHO had declared Covid-19 as a pandemic event which was supported by the number of new world cases that increase from 4.5 million to 5.2 million for eight consecutive weeks starting in April 2021. Transmission of the virus is fairly easy through droplets or saliva and the air which is able to be transmitted in no time. To cope with the number of Covid-19 cases, layered prevention was needed, including screening, testing, and surveillance. Currently, the PCR (Polymerase Chain Reaction) test is a definitive diagnostic tool for Covid-19, since this test has a high level of sensitivity and specificity for diagnosing infection (Paltiel et al., 2020).

Covid-19 patients may experience several symptoms, one of which is anosmia or decreasing sense of smell. In a 2020 study, 54

patients (47%) of the 114 confirmed Covid patients had anosmia. Anosmia is caused by a virus that attacks several receptors in the body's organs, one of which is through the nasal epithelium to the olfactory nerve (olfactory bulb). People without symptoms, and people with mild or not easily suspected symptoms will think and assume these symptoms are something not dangerous so they are often the biggest contributors to the spread of the Covid-19 virus in society. Therefore, the authors compiled this systematic review to explore the relationship between symptoms of anosmia and positive RT-PCR swab results.

MATERIALS AND METHODS

Data Sources and Literature Search Strategies

This study used the PRISMA (Preferred Reporting Items for Systematic Reviews and meta-Analysis) method. Seven authors comprehensively, independently, and systematically examined articles published in Pubmed, Google Scholar, PubMed Center, and Sciencedirect from January 1, 2019 to April 24, 2021. MeSH keywords used were "anosmia" and "Covid-19 RT-PCR". Unpaid article searches were also conducted to increase the search scale.

Eligibility Criteria

After eliminating duplicates, the authors individually assessed the feasibility of the study by evaluating the title, abstract, and the full text. Different opinions were resolved by deliberation. These are the inclusion criteria: (1) Patients screened for and/or confirmed Covid-19 using RT-PCR, (2) Articles including clinical symptoms, (3) Free full-text articles, (4) Studies published within 2 years, (5) Articles were in Indonesian or English.

Quality Assessment

The tool used to assess the quality of the literature in this study was an assessment tool from the Effective Public Health Practice Project (EPHPP). This tool assessed the quality of the literature through six components from each literature; selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. The final result of the literature quality assessment was divided into three; strong, moderate, and weak. Articles with weak quality were excluded from this study.

Data Analysis

The collected data were analyzed using Meta-Synthesis. The collection of qualitative data was used to form new interpretations of the research to build new theories.

RESULTS

The authors obtained 353 articles from four databases: PubMed (n = 20), Google Scholar (n = 278), PMC (n = 40), and ScienceDirect (n = 15). The duplicate articles were removed, and 314 articles were obtained. Then, the authors excluded 297 studies with details of 16 paid studies, 7 studies not in English/Indonesian, 113 studies that did not meet the desired research method, 98 studies that were not on topic, 3 studies that were not accessible, and 68 studies with incomplete data. Finally, 16 studies were included in the systematic and metanalytic review. The screening and selection process of these articles is presented in Figure 1.

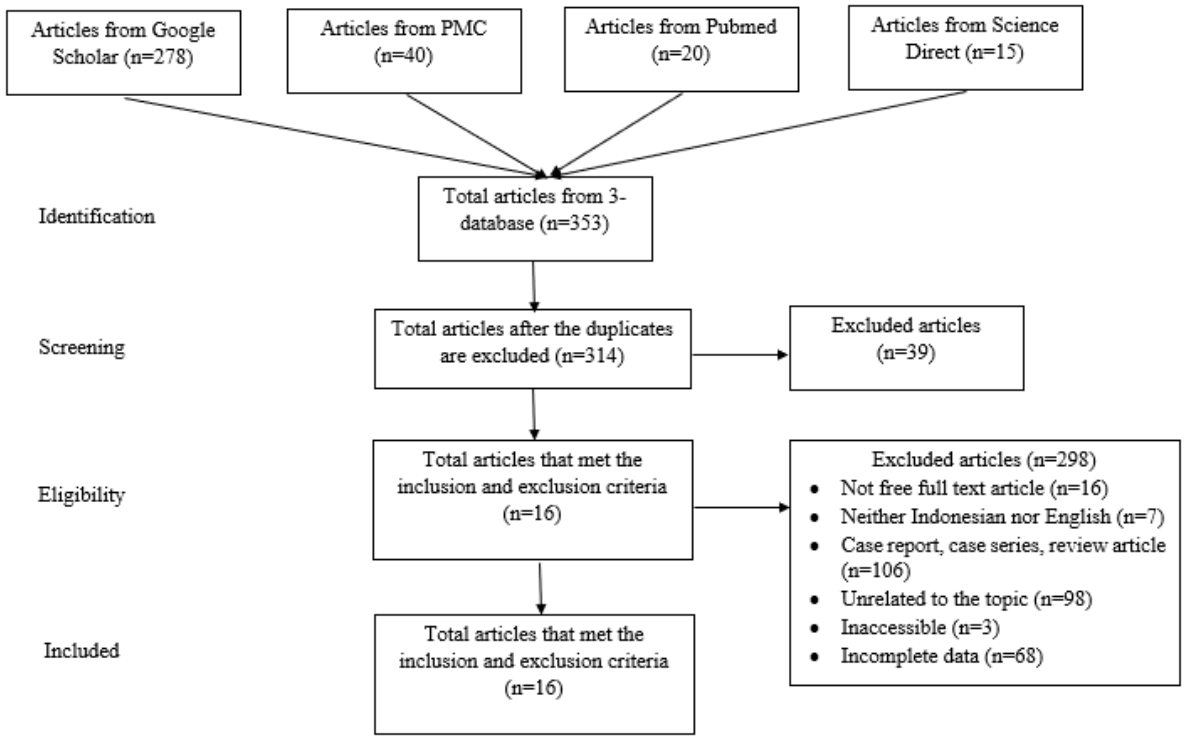

Figure 1. PRISMA Method

The studies were collected based on the similarity of questions to achieve a similar research goal, to find the relationship between anosmia symptoms and positive RT-PCR results. After being assessed using the EPHPP and Quality Assessment Tool on 16 literatures within the inclusion criteria, 12 literatures were obtained and were further reviewed. The characteristics of each study involved in this systematic review can be seen in Table 1.

Table 1. Data Extraction

Author	Article Title	Location	Study design	Time frame	Participant	Result
Basu B., et al, 2020	Covid-Anosmia Checker: A rapid and low-cost alternative tool for mass screening of Covid-19	India	*Cohort study*	2020	188	Loss of smell can be used as a reliable marker for COVID-19 screening. It shows that anosmia/parosmia/hyposmia in smell tests increased the likelihood of positive for COVID-19 by 3.8 times.
Jeyashree, K. et al., 2021	Self-reported and clinically identified loss of smell and taste among persons tested for Covid-19 in Chennai, southern	Chennai	*Analytic cohort study*	2021	277	Loss of smell or taste was higher among COVID-19 positives (n = 13; 22%) than negative people (n = 23; 11%) [p = 0.02].

	India, July-August 2020: A cross sectional study					
Ceron et al., 2020	Self-reported loss of smell without nasal obstruction to identify Covid-19. The multicenter Coranosmia cohort study	Paris	*Cohort study*	17 - 25 March 2020	(i) 55 ; (ii) 1824	Self-reported loss of smell has a high positive predictive value for identifying COVID-19 so it can be used as a screening for potential contacts.
Leal et al, 2021	Clinical features and natural history of the first 2073 suspected Covid-19 cases in the Corona São Caetano primary care programme: a prospective cohort study	São Caetano do Sul, Brazil	*Cohort Study*	6 April - 4 June 2020	1048	Patients who were positive for SARS-CoV-2 (RT-PCR or serology) had the strongest association with anosmia (OR 3.3, 95% CI 2.6 to 4.4).
Zayet et al., 2020	Contribution of anosmia and dysgeusia for diagnostic of Covid-19 in outpatients	France	*Retrospective study*	30 March - 3 April 2020	217	The sensitivity and specificity of anosmia for positive RT-PCR results were 63% and 85%. The positive predictive value (PPV) and negative predictive value (NPV) of anosmia were 76.9% and 74.8%.
Eyheramendy et al., 2021	Improved screening of Covid-19 cases through a Bayesian network symptoms model and psychophysical olfactory test	Santiago, Chili	*Cohort analytic*	2021	2291	Olfactory disorders are discriminant symptoms for predicting Covid-19 infection; AUC = 0.785; 95% CI [0.754;0.816]; 76% accuracy
Miller D. et al, 2021	Covid-19 test positivity: predictive value of various symptoms in a large community-based testing program in California	California	*Cohort study*	March - May 2021	547,018	The major symptom of COVID-19 with the highest predictive value was loss of taste or smell; OR 5.75 (95% CI 5.47-6.06)

Callejon-Leblic et al., 2021	Loss of Smell and Taste Can Accurately Predict Covid-19 Infection: A Machine-Learning Approach	Seville and Cadiz, Spanyol	*Case control study*	March-April 2020	777	Loss of smell is an accurate predictor of a COVID-19 diagnosis; OR = 10.85; 95% CI: 7.47–15.77; p < 0.0001. AUC=0.76
Trubiano J. et al, 2020	COVID-MATCH65-A prospectively derived clinical decision rule for severe acute respiratory syndrome coronavirus 2	Melbourn, Australia	*Cohort study*	11 March - 22 April 2020	2935	Internal validation showed an AUC of 0.836. A cut-off of ≥ 1.5 points was associated with a 92.6% sensitivity and 99.5% negative predictive value (NPV) for COVID-19.
Antonelli et al., 2021	Optimal symptom combinations to aid Covid-19 case identification: analysis from a community-based, prospective, observational cohort	UK and USA	*Cohort study*	September - October 2020	125.467	Cough, shortness of breath, fever and anosmia are significant symptoms of COVID-19 for triggering PCR; with sensitivity: 17.85%; specificity: 95.9%
Michael owusu et al 2020	Epidemiological profile of SARS-CoV-2 among selected regions in Ghana: A cross-sectional retrospective study.	Kumasi Centre for Collaborative Research in Tropical Medicine (KCCR), Ghana	*Cross-sectional retrospektif*	February - July 2020	72,434	Among all clinical presentations, anosmia was the strongest predictor of SARS-CoV-2 infection (Adj. OR (95%CI): 24.39 (20.18, 29.49).
Feehan AK et. al, 2021	The importance of anosmia, ageusia and age in community presentation of symptomatic and asymptomatic SARS-CoV-2 infection in Louisiana, USA; a cross-sectional prevalence study	USA	*Cross sectional*	9 May dan 11–15 May 2020, 15–31 July 2020	4778	Anosmia/ageusia appears to be a hallmark of COVID-19 both in people with symptoms and even in clusters of symptoms with low or no symptoms.

The Meta-analysis of this systematic review was carried out using the Review Manager application 5.4.1 version. Statistical analysis was carried out in 8 out of 12 studies because in 4 studies there were no data needed to perform statistical analysis. The research designs in the six studies were 3 cohorts, 1 cross-sectional, 1 retrospective study, and 2 case controls. Eight studies on forest plots that showed a relationship between symptoms of anosmia and positive RT-PCR swab results.

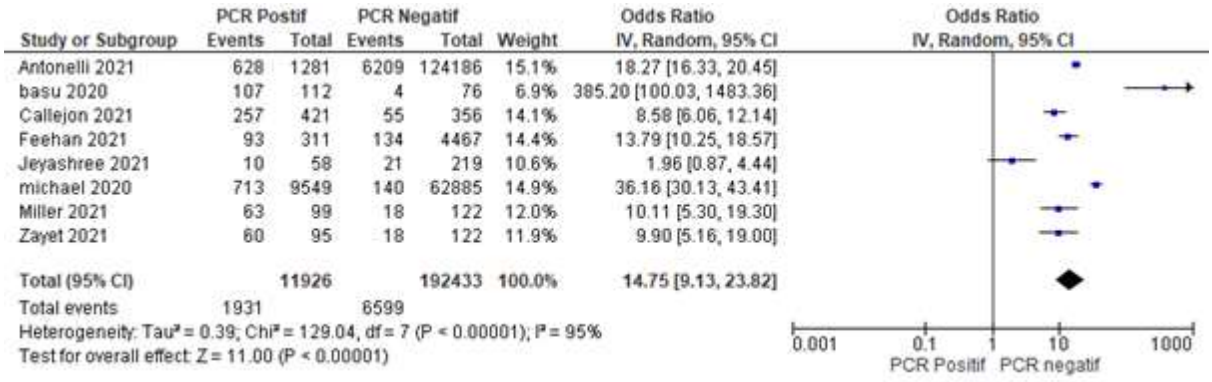

Figure 2. Forest Plot

In Figure 2, the value of I^2 in the heterogeneity test is 95%. This shows that the research used in this systematic study had a large heterogeneity.

The results of statistical analysis in this systematic study showed that symptoms of anosmia led to the risk of a positive RT-PCR result (OR = 14.75; 95% CI = 9.13 - 23.82). In addition, there was a significant relationship between anosmia symptoms and an increase in RT-PCR positive results. It is proven by the p-value obtained by <0.00001.

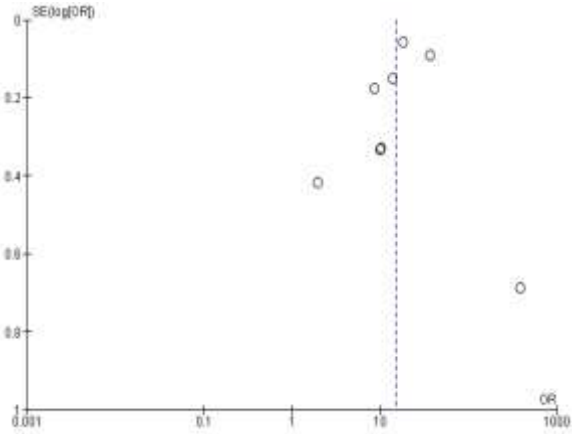

Figure 3. Funnel Plotting

In the funnel plotting (Figure 3) of this study, it was found that the distribution of the studies was uneven and asymmetrical and there were studies that were located far from the center area. This could be due to the lack of studies used and the differences in research methods in each of the studies we analyzed, thus allowing the risk of publication bias to be found in this study.

DISCUSSION

In this systematic review, there were 12 journals regarding the relationship of anosmia with the risk of positive RT-PCR results in Covid-19. Anosmia is the loss of a person's ability to smell. A person infected with Covid-19 has typical symptoms compared to other SARS (Severe Acute Respiratory Syndrome) infections, which is called anosmia (Hwang, 2006). In the results of this study, it was found that the symptoms of anosmia increased the possible risk of a positive result on RT-PCR with OR = 14.75; 95% CI = 9.13 - 23.82. In addition, there was a significant relationship between anosmia and an increase in RT-PCR positive results. It is proven by the p-value obtained by <0.00001.

Anosmia is one of the symptoms of Covid-19 that has been reported in the literature. Anosmia in Covid-19 patients is thought to be caused by four main pathways, namely nasal obstruction, damage to the olfactory receptor nerves, infiltration in the central nervous system to the olfactory nerves, and damage to supporting cells in the olfactory epithelium (Butowt and Bartheld, 2020). Anosmia is an important sign of SARS-CoV-

2 infection. Covid-19 patients may or may not experience other symptoms such as dry coughs before anosmia. Dysgeusia is often present with anosmia (Meng *et al.*, 2020).

A total of 12 studies were used consisting of 9 cohort study designs, 2 cross-sectional, 1 case-control, and 1 retrospective study. With a total of 759,309 participants, there was a relationship between the symptoms of anosmia and the results of the RT-PCR swab in the Covid-19 diagnostic. In a study with 188 participants, an olfactory acuity test using 6 test strips showed that nearly 95% of Covid-19 positive patients showed some degree of olfactory dysfunction ranging from hyposmia to complete or anosmia (Basu *et al.*, 2020). Research conducted in Chennai, India in July-August 2020 with 277 participants to assess anosmia as a tool for early detection of Covid-19 disease also stated that anosmia in independently assessed Covid-19 patients was significantly ($p<0.05$) higher than the anosmia in non-Covid-19 patients. In addition, this study also assessed the symptoms of anosmia in Covid-19 patients objectively and obtained the same results. The same results were stated in a study by Feehan et al (2020) with 4778 population. It was found that anosmia or ageusia is a hallmark of Covid-19 in people with severe, moderate, or no symptoms. In a study by Zayet et al (2020) using a retrospective study model on 217 patients aimed at comparing the patient's symptoms with positive and negative SARS-CoV-2 RT-PCR results and to determine the sensitivity, specificity, positive predictive value (PPV), and negative prediction (NPV) for each symptom with SARS-CoV-2 RT-PCR results, anosmia was found to have high specificity for detecting Covid-19 but had low sensitivity.

In this study, it can be assumed that there was a strong relationship between anosmia symptoms and positive RT-PCR swab results. This shows that anosmia can be a marker for patients to carry out further investigations. However, further research is needed on the pathophysiology of anosmia in Covid-19.

CONCLUSION

This systematic study of the relationship between anosmia symptoms and the Covid-19 RT-PCR concluded that there was a relationship between anosmia symptoms and positive RT-PCR swab results in Covid-19 diagnostics.

ACKNOWLEDGEMENT

The authors' gratitude goes to Dr. Widati Fatmaningrum, Subur Prajitno, dr., MS., AKK, Atika, S.Si., M.Kes., who are willing to assist our research in the field of statistics, All lectures of Department of Public Health and Preventive Medicine who have provided knowledge and guidance for this research, and all parties that we cannot mention one by one who have contributed to the making of this research.

REFERENCES

1. Antonelli, M. *et al*. (2021). Optimal symptom combinations to aid Covid-19 case identification: Analysis from a community-based, prospective, observational cohort. *Journal of Infection*, 82(3), pp.384-390. doi:10.1016/j.jinf.2021.02.015. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7881291/
2. Basu, B. *et al*. (2020). Covid-Anosmia Checker: A rapid and low-cost alternative tool for mass screening of Covid-19. doi:10.1101/2020.10.28.20221200. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.28.20221200v2>

3. Butowt, R. and Bartheld, C., 2020. Anosmia in Covid-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. *The Neuroscientist*, doi:10.1177/1073858420956905. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7488171/
4. Callejon-Leblic, M., *et al* (2021). Loss of Smell and Taste Can Accurately Predict Covid-19 Infection: A Machine-Learning Approach. *Journal of Clinical Medicine*, 10(4), p.570. doi:10.3390/jcm10040570. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7913595/
5. Eyheramendy, S. *et al* (2021). Improved screening of Covid-19 cases through a Bayesian network symptoms model and psychophysical olfactory test. doi:10.1101/2021.01.18.21249821. Available at: https://www.medrxiv.org/content/10.1101/2021.01.18.21249821v3.full
6. Feehan, A. *et al* (2021). The importance of anosmia, ageusia and age in community presentation of symptomatic and asymptomatic SARS-CoV-2 infection in Louisiana, USA; a cross-sectional prevalence study. *Clinical Microbiology and Infection*, 27(4), pp.633.e9-633.e16. doi: 10.1016/j.cmi.2020.12.029. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7787079/
7. Miller, D. *et al* (2021). Covid-19 test positivity: predictive value of various symptoms in a large community-based testing program in California. doi:10.1101/2021.03.03.21252014. Available at: https://www.medrxiv.org/content/10.1101/2021.03.03.21252014v1.full
8. Hwang, CS (2006) 'Olfactory neuropathy in severe acute respiratory syndrome: report of a case', *Acta Neurol Taiwan*. 15(1), pp. 26–28.
9. Jeyashree, K. *et al*. (2021) 'Self-reported and clinically identified loss of smell and taste among persons tested for Covid-19 in Chennai, southern India, July-August 2020: A cross sectional study', *Clinical epidemiology and global health*, 11: p. 100718. doi:10.1016/j.cegh.2021.100718
10. Leal, FE., Mendes-Correa, MC., Buss, LF., Costa, SF., Bizario, JCS., de Souza, SRP., Thomaz, O., Tozetto-Mendoza, TR., Villas-Boas, LS., de Oliveira-da Silva, LC., Grespan, RMZ., Capuani, L., Buccheri, R., Domingues, H., Alexander, N., Mayaud, P., Sabino, EC, (2021) 'Clinical features and natural history of the first 2073 suspected Covid-19 cases in the Corona São Caetano primary care programme: a prospective cohort study', *BMJ Open.* 11(1) p. e042745. doi: 10.1136/bmjopen-2020-042745. PMID: 33436471; PMCID: PMC7805372.
11. Miller, D., Morrow, S., Califf, R., Kaiser, C., Kapur, R., Starsiak, C., Mega, J. and Marks, W., (2021) 'COVID-19 test positivity: predictive value of various symptoms in a large community-based testing program in California', *BMJ*. doi: https://doi.org/10.1101/2021.03.03.21252014
12. Meng, X., Deng, Y., Dai, Z. and Meng, Z., (2020) 'Covid-19 and anosmia: A review based on up-to-date knowledge', *American Journal of Otolaryngology*, 41(5).
13. Owusu, M., Sylverken, AA., Ankrah, ST., El-Duah, P., Ayisi-Boateng, NK., Yeboah, R., Gorman, R., Asamoah, J., Binger, T., Acheampong, G., Bekoe, FA., Ohene, SA., Larsen-Reindorf, R., Awuah, AA., Amuasi, J., Owusu-Dabo, E., Adu-Sarkodie, Y., Phillips, RO, (2020)

'Epidemiological profile of SARS-CoV-2 among selected regions in Ghana: A cross-sectional retrospective study', *PLoS One*, 15(12), doi: 10.1371/journal.pone.0243711. PMID: 33301533; PMCID: PMC7728229.

14. Paltiel, AD., Zheng, A., Walensky, RP., (2020) 'Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States', *JAMA Netw Open*. 3(7), doi:10.1001/jamanetworkopen.
15. Ceron, DS. et al. (2020) 'Self-reported loss of smell without nasal obstruction to identify COVID-19, The multicenter Coranosmia cohort study', *J Infect*. 2020 Oct;81(4):614-620. doi: 10.1016/j.jinf.2020.07.005. Epub 2020 Jul 7. PMID: 32650110; PMCID: PMC7338860. Available at: https://pubmed.ncbi.nlm.nih.gov/32650110/
16. Trubiano, JA. et al. (2020) ' Covid-MATCH65-A prospectively derived clinical decision rule for severe acute respiratory syndrome coronavirus 2', *PLoS One*. 2020 Dec 9;15(12):e0243414. doi: 10.1371/journal.pone.0243414. PMID: 33296409; PMCID: PMC7725390. Available at: https://pubmed.ncbi.nlm.nih.gov/33296409/
17. von Bartheld, CS. Hagen, MH. Butowt, R. (2020) 'Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences'. *Preprint. medRxiv*. 2020;2020. 06.15.20132134. Published 2020 Jun 17. doi:10.1101/2020.06.15.20132134. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7310651/
18. WHO. (2020) 'Coronavirus disease (Covid-19)'. *Who.int.* Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-Covid-19#:~:text=symptoms
19. WHO. (2020) 'Weekly Epidemiological Update on Covid-19' *Who. int.* Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-Covid-19---20-april-2021
20. Zayet, S. et al. (2021) 'Contribution of anosmia and dysgeusia for diagnostic of Covid-19 in outpatients'. *Infection.* 2021;49(2):361-365. doi:10.1007/s15010-020-01442-3 Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7221233/