Anosmia/Hyposmia is a Good Predictor of Coronavirus Disease 2019 (COVID-19) Infection: A Meta-Analysis

Timotius Ivan Hariyanto1, Niken Ageng Rizki2, Andree Kurniawan3

1 Faculty of Medicine, Pelita Harapan University, Karawaci, Tangerang, Indonesia
2 Department of Otorhinolaryngology, Faculty of Medicine, Pelita Harapan University, Karawaci, Tangerang, Indonesia
3 Department of Internal Medicine, Faculty of Medicine, Pelita Harapan University, Karawaci, Tangerang, Indonesia

Introduction The number of positive cases and deaths from the coronavirus disease 2019 (COVID-19) is still increasing. The early detection of the disease is very important. Olfactory dysfunction has been reported as the main symptom in part of the patients.

Objective To analyze the potential usefulness of anosmia or hyposmia in the detection of the COVID-19 infection.

Data Synthesis We systematically searched the PubMed Central database using specific keywords related to our aims until July 31st, 2020. All articles published on COVID-19 and anosmia or hyposmia were retrieved. A statistical analysis was performed using the Review Manager (RevMan, Cochrane, London, UK) software, version 5.4. A total of 10 studies involving 21,638 patients were included in the present analysis. The meta-analysis showed that anosmia or hyposmia is significantly associated with positive COVID-19 infections (risk ratio [RR]: 4.56; 95% confidence interval [95% CI]: 3.32–6.24; p < 0.00001; I² = 78%, random-effects modeling).

Conclusion The presence of anosmia or hyposmia is a good predictor of positive COVID-19 infections. Patients with onset of anosmia or hyposmia should take the test or undergo screening for the possibility of COVID-19 infection.
dysfunction, such as anosmia and hyposmia. These symptoms become more prominent in patients with COVID-19 infection.\(^5\) However, the usefulness of the symptoms of olfactory dysfunction in the prediction of COVID-19 infection is still unclear, and the analysis of this issue is the aim of the present study.

**Review of the Literature**

**Eligibility Criteria**
We included all research articles on adult patients diagnosed with COVID-19 with information on symptoms of anosmia or hyposmia and clinical grouping of the clinically-validated COVID-19 test positivity (positive and negative COVID-19 patients). The following types of articles were excluded: articles that were not original research (such as review articles, letters, or commentaries); case reports; articles not in English; articles on pediatric populations (17 years of age or younger); and articles on pregnant women.

**Search Strategy and Study Selection**
We conducted a systematic search of the literature published in English on PubMed Central (PMC) using the keywords “anosmia” OR “hyposmia” AND “coronavirus disease 2019” OR “COVID-19,” until July 31st, 2020. Duplicate results were removed. The title, abstract, and full text of all articles identified that matched the search criteria were assessed by two authors (TIH and NAR), and were included in the present meta-analysis. The references of all studies retrieved were also analyzed (forward and backward citation tracking) to identify other potentially-eligible articles. The present study was performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.\(^6\)

**Data Extraction and Quality Assessment**
Data extraction was performed independently by two authors (TIH and NAR); we used standardized forms that include author, year, study design, number of participants, age, gender, number of patients with symptoms of anosmia/hyposmia, and COVID-19 test results. The outcome of interest was the positivity of the COVID-19 test, which was defined as a positive SARS-CoV-2 RT-PCR test from respiratory-tract samples.

Two investigators (TIH and AK) independently evaluated the quality of the included cohort and case-control studies using the Newcastle–Ottawa Scale (NOS).\(^7\) The selection, comparability, and exposure of the studies included were broadly assessed, and they were assigned a score from zero to nine. Studies with scores \(\geq 7\) were considered of good quality.

**Statistical analysis**
A meta-analysis was performed using the Review Manager (RevMan, Cochrane, London, UK) software, version 5.4. Dichotomous variables were calculated using the Mantel-Haenszel formula with random-effects models. We used the \(I^2\) statistic to assess the heterogeneity, and values < 25%, between 26% and 50%, and > 50% were considered low, moderate, and high degrees of heterogeneity respectively. The effect estimate was reported as the risk ratio (RR) along with its 95% confidence intervals (95%CIs) for the dichotomous variables. The \(p\)-value was two-tailed, and the statistical significance was set at \(\leq 0.05\). A funnel plot was adopted to statistically assess the publication bias.

**Study Selection and Characteristics**
A total of 1,125 records were obtained through systematic electronic searches, and 827 records remained after the removal of duplicates. In total, 810 records were excluded after screening the title/abstracts because they did not match our inclusion criteria. After evaluating 17 full-texts for eligibility, 7 full-text articles were excluded because they did not have a control/comparison group, and 10 studies\(^8\)–\(^17\) with a total of 21,638 COVID-19 and non–COVID-19 patients were included in the meta-analysis (\(\rightarrow\) Fig. 1). Among the included studies, 5 were prospective cohorts, 4 were case-control studies, while the remaining 1 study was a retrospective cohort. The essential characteristics and the methods used to detect anosmia/hyposmia in each study included are summarized in \(\rightarrow\) Table 1. Most of the included studies use the patients’ self-report as a method to detect the presence of anosmia/hyposmia. Each of the remaining studies used a different tool, such as the “Sniffin’ Sticks” test, The University of Pennsylvania Smell Identification Test (UPSIT), The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Anosmia Reporting Tool, and the Subjective Olfaction Score to evaluate the presence of anosmia/hyposmia.

**Assessment of the Quality of the Studies**
Studies with various designs, including cohorts and case series were, included in the present review and assessed accordingly with the appropriate scale or tool. The NOS was used to assess the cohort and case-control studies (\(\rightarrow\) Table 2). All included studies were rated ‘good’.

**Outcomes**
The individual and pooled RRs for anosmia or hyposmia predicting COVID-19 positivity are shown in \(\rightarrow\) Fig. 2. Our pooled analysis showed a significant association of anosmia or hyposmia with COVID-19 positivity, with high heterogeneity (RR: 4.56; 95%CI: 3.32–6.24; \(p < 0.00001\); \(I^2 = 78%\), random-effects modeling).

**Publication Bias**
The funnel-plot analysis showed a relatively symmetrical inverted funnel plot for anosmia/hyposmia predicting the COVID-19 test positivity, suggesting no indication of publication bias (\(\rightarrow\) Fig. 3).

**Discussion**
To our knowledge, the present is the first meta-analysis which analyzes the usefulness of anosmia/hyposmia in the prediction of the positivity of the COVID-19 test. Several previous meta-analysis only analyze the prevalence of...
Table 1 Characteristics of the included studies

| Study         | Sample size | Design           | Methods to detect anosmia/hyposmia | COVID-19 positive patients | COVID-19 negative patients |
|---------------|-------------|------------------|------------------------------------|----------------------------|---------------------------|
|               |             |                  | Anosmia/hyposmia (n) | Age (years) | Anosmia/hyposmia (n) | Age (years) |
| Altin et al.  | 121         | Case-control     | “Sniffin’ Sticks” test      | 50 (61.7%)   | 54.1 ± 16.9          | 0 (0%)       | 55 ± 15.3 |
| Beltrán-Corbellini et al. | 119     | Case-control     | Patients’ self-report       | 25 (31.6%)   | 61.6 ± 17.4          | 4 (10%)      | 61.1 ± 17.1 |
| Bénézit et al. | 257       | Prospective cohort | Patients’ self-report      | 31 (45%)     | N/A                 | 19 (10%)     | N/A |
| Menni et al.  | 18,401      | Prospective cohort | Patients’ self-report      | 4,668 (65%)  | 41.2 ± 12.1          | 2,436 (21.7%)| 41.8 ± 12.1 |
| Moein et al.  | 120         | Case-control     | UPSIT scoring system       | 59 (98.3%)   | 46.5 ± 12.1          | 1 (1.7%)     | 46.5 ± 12 |
| Sayin I et al.| 128         | Case-control     | AAO-HNS Anosmia Reporting Tool | 52 (81.2%)  | 37.7 ± 11.3          | 15 (23.4%)   | 39.4 ± 8.6 |
| Trubiano et al.| 1236      | Prospective cohort | Patients’ self-report      | 7 (25%)      | 54.8 ± 12.9          | 62 (5.1%)    | 43 ± 18.5 |
| Wee et al.    | 870         | Prospective cohort | Patients’ self-report      | 35 (22.7%)   | N/A                 | 9 (1.2%)     | N/A |
| Yan et al.    | 262         | Prospective cohort | Subjective olfaction score | 40 (67.8%)   | 44.5 ± 12.5          | 33 (16.3%)   | 38.7 ± 14.6 |
| Zayet et al.  | 124         | Retrospective cohort | Patients’ self-report      | 37 (52.9%)   | 56.7 ± 19.3          | 9 (16.7%)    | 61.3 ± 18.8 |

Abbreviations: AAO-HNS, American Academy of Otolaryngology-Head and Neck Surgery; N/A, not available; UPSIT, University of Pennsylvania Smell Identification Test.
symptoms of anosmia/hyposmia in COVID-19 positive patients, but do not compare these symptoms regarding COVID-19 positive and negative patients. Based on the present meta-analysis of available data, the presence of anosmia/hyposmia seems to be associated with an enhanced risk of testing positive for COVID-19. Several reasons can be proposed to explain this result. First, Angiotensin Converting Enzyme 2 (ACE2), the receptor for SARS-CoV-2, the pathogen causing COVID-19 infection, is expressed in the nasal mucosa. The virus can enter the nasal mucosa through ACE2 and cause damage to the supporting cells of the olfactory system, such as the olfactory epithelium sustentacular cells, microvillar cells, Bowman gland cells, horizontal basal cells, and olfactory bulb pericytes. These damages can alter the function of the olfactory neurons, contributing to the development of symptoms of olfactory dysfunction. Another possible mechanism is through the inflammatory blockage of the olfactory cleft in the COVID-19 infection, which contributes to the development of anosmia. Finally, it has been found that the sinonasal route is an important area of COVID-19 viral shedding; therefore, the presence of olfactory dysfunction may reflect the presence of infection and the early course of the disease.

The present study has several limitations. First, the presence of confounding factors such as age, comorbid conditions, and the immunity status of patients, which can affect the relationship between anosmia or hyposmia and the positivity for COVID-19 infection must still be considered. Second, the studies included used different methods to detect the presence of anosmia or hyposmia, and most of them used subjective or unvalidated methods. However, we hope that the present study can still provide good insights on the early detection of COVID-19 infections.

### Final Comments

Patients with onset of anosmia or hyposmia in whom another ear, nose, and throat (ENT) diagnosis is unlikely should be
advised to take the test or undergo screening for the possibility of COVID-19 infection. Physicians should also be more cautious when encountering patients with onset of anosmia or hyposmia to be able to make an early diagnosis and protect themselves better to minimize the risk of exposure to COVID-19. Previous history of anosmia or hyposmia should also be addressed to screen for other risk factors of olfactory dysfunction. The alcohol-sniffing test can be used to make a rapid clinical evaluation of COVID-19 patients with olfactory dysfunction. Finally, the presence of anosmia or hyposmia shall be regarded as one of the important symptoms, besides fever and respiratory symptoms, when screening for COVID-19.

Conflict of Interests
The authors have no conflict of interests to declare.

References
1. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. Int J Infect Dis 2020; 99:47–56. Doi: 10.1016/j.ijid.2020.07.029
2. Hariyanto TI, Kurniawan A. Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr 2020;14(05):1463–1465. Doi: 10.1016/j.dsx.2020.07.054
3. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. J Infect 2020;80(04):388–393. Doi: 10.1016/j.jinf.2020.02.016
4. Kwenandar F, Japar KV, Damay V, et al. Coronavirus disease 2019 and cardiovascular system: A narrative review. Int J Cardiol Heart Vasc 2020;29:100557. Doi: 10.1016/j.jchiva.2020.100557
5. Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. Am J Otolaryngol 2020;41(05): 102581. Doi: 10.1016/j.amjoto.2020.102581
6. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(07):e1000097. Doi: 10.1371/journal.pmed.1000097
7. Margulis AV, Pladevall M, Riera-Guardia N, et al. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank. Clin Epidemiol 2014;6:359–368. Doi: 10.2147/CLEP.S66677
8. Altin F, Cingi C, Uzun T, Bal C. Olfactory and gustatory abnormalities in COVID-19 cases. Eur Arch Otorhinolaryngol 2020;277(10): 2775–2781. Doi: 10.1007/s00405-020-06155-9
9. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. Eur J Neurol 2020. Doi: 10.1111/ene.14273
10. Bénézit F, Le Turnier P, Declerck CR. AN COVID Study Group, et al. Utility of hyposmia and hypoguesia for the diagnosis of COVID-19. Lancet Infect Dis 2020;20(09):1014–1015. Doi: 10.1016/S1473-3099(20)30297-8
11. Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med 2020;26(07):1037–1040. Doi: 10.1038/s41591-020-0916-2
12. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol 2020;10(08):944–950. Doi: 10.1002/air.22587
13. Sayin I, Yaşar KK, Yazici ZM. Taste and Smell Impairment in COVID-19: An AAO-HNS Anosmia Reporting Tool-Based Comparative Study. Otolaryngol Head Neck Surg 2020;163(03):473–479. Doi: 10.1177/0194599820931820
14. Trubiano JA, Vogrinc S, Kwong JC, Holmes NE. Alterations in smell or taste – Classic COVID-19? Clin Infect Dis 2020:ciaa655. Doi: 10.1093/cid/ciaa655
15. Wee LE, Chan YF, Teo NY, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. Eur Arch Otorhinolaryngol 2020;277(08): 2389–2390. Doi: 10.1007/s00405-020-09599-5
16. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020;10(07):806–813. Doi: 10.1002/air.22579
17. Zayet S, Kadiane-Oussou NJ, Lepiller Q, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect 2020;25:4789–4799(20). Doi: 10.1016/j.micinf.2020.05.016
18. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis. Otolaryngology Neck Surg 2020;163(01):3–11. Doi: 10.1177/0194599820926473
19. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. Mayo Clin Proc 2020;95(08):1621–1631. Doi: 10.1016/j.mayocp.2020.05.030
20. Vaira LA, Salzano G, Fois AG, Piombino P, De Riu G. Potential pathogenesis of ageusia and anosmia in COVID-19 patients. Int Forum Allergy Rhinol 2020;10(09):1103–1104. Doi: 10.1002/air.22593
21. Gengler I, Wang JC, Speth MM, Sedaghat AR. Sinonasal pathogenesis of SARS-CoV-2 and COVID-19: A systematic review of the current evidence. Laryngoscope Investig Otolaryngol 2020;5(03):354–359. Doi: 10.1002/lio2.384
22. Davidson TM, Murphy C. Rapid clinical evaluation of anosmia. The alcohol sniff test. Arch Otolaryngol Head Neck Surg 1997;123(06):591–594. Doi: 10.1001/archotol.1997.0190060033005