SPECIAL ARTICLE COVID-19

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

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Abstract

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; $p < 0.00001$; $I^2 = 78\%$, 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.

Keywords
- coronavirus disease 2019
- COVID-19
- anosmia
- hyposmia
- olfactory dysfunction

Introduction

Five months have passed since the coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO). This disease has caused a significant burden in all aspects of life, especially health and the economy. The number of positive cases and deaths is still increasing. Several comorbidities have been demonstrated to be associated with severe COVID-19 infection, such as hypertension, diabetes, dyslipidemia, cardiovascular disease, and pulmonary disease.[1,2] Patients with COVID-19 can report a wide variety of clinical manifestations, from mild symptoms, such as fever and cough, to severe symptoms, such as shortness of breath, arrhythmia, and loss of consciousness.[3,4] Part of the patients are also reporting the presence of symptoms of olfactory

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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 researches (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 ≥ 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 ≤ 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 (►**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 ►**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 (►**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 ►**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 (►**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

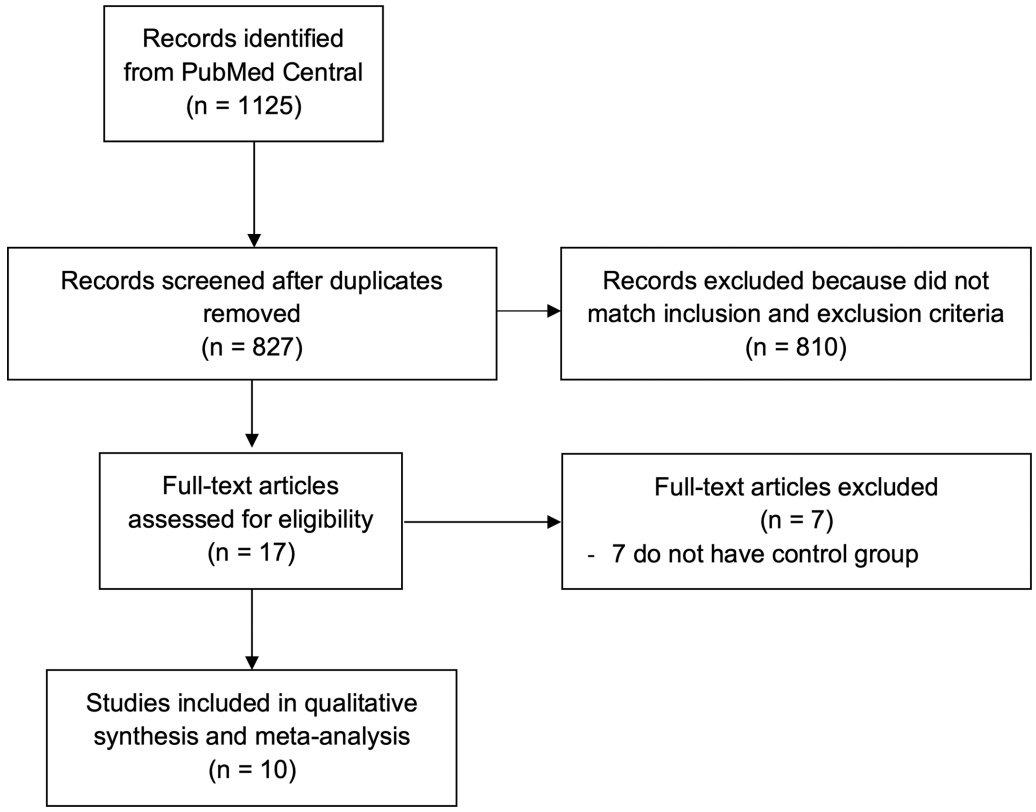

Fig. 1 PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

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.,[8] 2020	121	Case-control	"Sniffin' Sticks" test	50 (61.7%)	54.1 ± 16.9	0 (0%)	55 ± 15.3
Beltrán-Corbellini et al.,[9] 2020	119	Case-control	Patients' self-report	25 (31.6%)	61.6 ± 17.4	4 (10%)	61.1 ± 17.1
Bénézit et al.,[10] 2020	257	Prospective cohort	Patients' self-report	31 (45%)	N/A	19 (10%)	N/A
Menni et al.,[11] 2020	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.,[12] 2020	120	Case-control	UPSIT scoring system	59 (98.3%)	46.5 ± 12.1	1 (1.7%)	46.5 ± 12
Sayin I et al.[13] 2020	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.,[14] 2020	1236	Prospective cohort	Patients' self-report	7 (25%)	54.8 ± 12.9	62 (5.1%)	43 ± 18.5
Wee et al.,[15] 2020	870	Prospective cohort	Patients' self-report	35 (22.7%)	N/A	9 (1.2%)	N/A
Yan et al.,[16] 2020	262	Prospective cohort	Subjective olfaction score	40 (67.8%)	44.5 ± 12.5	33 (16.3%)	38.7 ± 14.6
Zayet et al.,[17] 2020	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.

Table 2 Newcastle–Ottawa quality assessment of observational studies

First author, year	Study design	Selection	Comparability	Outcome	Total score	Result
Altin et al.,[8] 2020	Case-control	***	**	***	8	Good
Beltrán-Corbellini et al.,[9] 2020	Case-control	***	**	***	8	Good
Bénézit et al.,[10] 2020	Cohort	**	**	***	7	Good
Menni et al.,[11] 2020	Cohort	***	**	***	8	Good
Moein et al.,[12] 2020	Case-control	***	**	***	8	Good
Sayin et al.,[13] 2020	Case-control	***	**	***	8	Good
Trubiano et al.,[14] 2020	Cohort	**	**	***	7	Good
Wee et al.,[15] 2020	Cohort	**	**	***	7	Good
Yan et al.,[16] 2020	Cohort	***	**	***	8	Good
Zayet et al.,[17] 2020	Cohort	***	**	***	8	Good

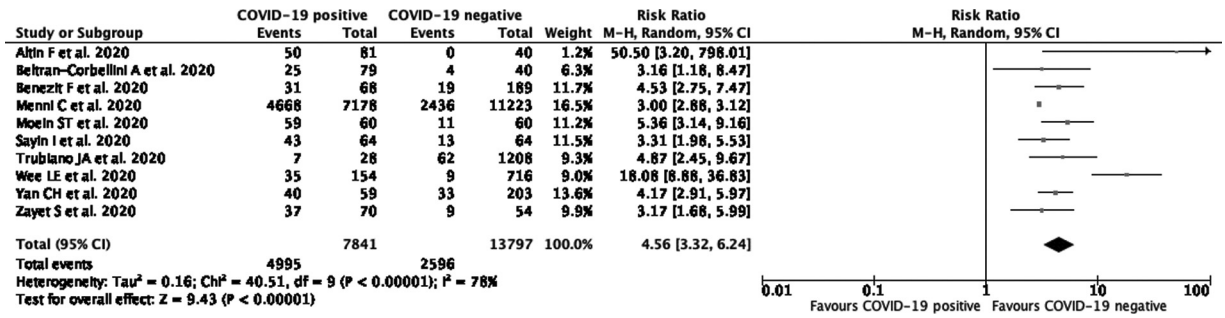

Fig. 2 Forest plot demonstrating the association of anosmia/hyposmia with COVID-19 positivity. Events means the presence of symptoms of anosmia/hyposmia.

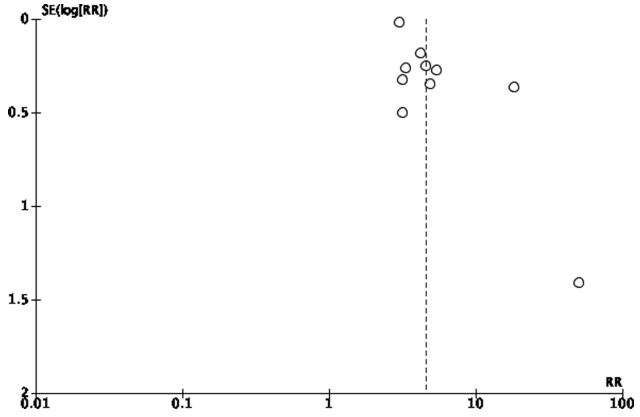

Fig. 3 Funnel-plot analysis of symptoms of anosmia/hyposmia predicting the positivity of the COVID-19 test.

symptoms of anosmia/hyposmia in COVID-19 positive patients, but do not compare these symptoms regarding COVID-19 positive and negative patients.[18,19]

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.[20] Another possible mechanism is through the inflammatory blockage of the olfactory cleft in the COVID-19 infection, which contributes to the development of anosmia.[5] 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.[21]

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.[22] 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.

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