REVIEW ARTICLE

Asian Pacific Journal of
Allergy and Immunology

APJAI

Olfactory and gustatory dysfunctions in COVID-19 patients: A systematic review and meta-analysis

Minh P Hoang,[1,2,3] Jesada Kanjanaumporn,[1,2] Songklot Aeumjaturapat,[1,2] Supinda Chusakul,[1,2] Kachorn Seresirikachorn,[1,2] Kornkiat Snidvongs[1,2]

Abstract

Olfactory and gustatory dysfunctions (OGD) are pathognomonic symptoms in patients with Coronavirus Disease 2019 (COVID-19). This study reviews the associations of OGD with COVID-19 which will be useful for early diagnosis and self-isolation. Systematic searches of PubMed, Ovid Medline, Scopus, and EMBASE electronic databases were performed. Studies reporting OGD in COVID-19 patients were included. Data were pooled for meta-analysis. The outcomes were odds ratios (OR) of OGD in COVID-19 patients. Proportions of smell and/or taste dysfunctions in the COVID-19 patients were assessed. Fourteen studies (21,515 participants, age 49.12 years, 26% male) were included. The OR of olfactory and/or gustatory dysfunctions in COVID-19 patients were 11.26 (95% confidence interval (CI) 5.41 to 23.4) when compared with acute respiratory infection (ARI) without detectable virus and 6.46 (95% CI 2.79 to 14.97) in patients with other respiratory viruses. The OR of olfactory dysfunction in COVID-19 patients were 11.67 (95% CI 6.43 to 21.17) when compared with the ARI patients without detectable virus and 4.17 (95% CI 1.34 to 12.98) with other respiratory viruses. The OR of gustatory dysfunction in COVID-19 patients were 12.70 (95% CI 7.9 to 20.44) when compared with the ARI patients without detectable virus and 4.94 (95%CI 1.59 to 15.31) with other respiratory viruses. Fifty percent (95% CI 36.7 to 63.3%) of COVID-19 patients had olfactory and/or gustatory dysfunctions. In summary, there are associations between OGD and COVID-19 patients. Patients presenting with ARI should be assessed for olfactory and gustatory functions.

Key words: COVID-19, olfactory, gustatory, smell, taste

From:
[1] Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[2] Endoscopic Nasal and Sinus Surgery Excellence Center, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[3] Department of Otolaryngology, Hue University of Medicine and Pharmacy, Hue University, Vietnam

Corresponding author:
Kornkiat Snidvongs
Department of Otolaryngology
Medical School, Chulalongkorn University
1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand
E-mail: drkornkiat@yahoo.com

Introduction

Because of the rapid spreading of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the Coronavirus disease 2019 (COVID-19) outbreak was characterized as a pandemic by the WHO on March 11, 2020.[1] Early diagnosis is essential because asymptomatic carriers and patients with mild symptoms are sources of infection, in other words super spreaders.[2] While most presenting symptoms of COVID-19 are non-specific such as fever, cough, and tiredness,[3] there are anecdotal reports suggesting olfactory and gustatory dysfunctions (OGD) as the early symptoms of paucisymptomatic patients.[4-6] Although the sudden onset of anosmia accompanying with a taste disorder pattern is acknowledged as a presenting symptom of COVID-19, the true prevalence of OGD is not conclusive.

Using The University of Pennsylvania Smell Identification Test (UPSIT) for evaluation, Moein et al.[7] demonstrated that ninety-eight percent of COVID-19 patients had olfactory dysfunction. Thus, disposable olfactory measures might be used for screening COVID-19 patients in the countries with the high incidence of COVID-19 with limited resources for performing real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2.

This systematic review aims to assess the associations of olfactory and/or gustatory dysfunctions with COVID-19 and to estimate the proportion of the patients with smell and taste dysfunctions among the COVID-19 patients.

Recent findings

Search strategy

The study was registered with the international prospective register of systematic reviews PROSPERO (reference number CRD42020182107). This systematic review followed The Preferred Reporting Items for Systematic Reviews and Meta -Analyses (PRISMA).[8] Electronic searches with PubMed, Ovid Medline, Scopus, and EMBASE were conducted. References of the included studies and additional sources were manually searched. The date of the last search was April 30, 2020. Combination of MESH terms and keywords were "smell"; "olfaction disorders", "smell disorder", "anosmia", "hyposmia", "olfactory dysfunction", "olfactory loss function", "taste", "taste disorders", "ageusia", "dysgeusia", "gustatory dysfunction", "hypogeusia", "SARS-CoV-2", "COVID-19", "2019 Novel Coronavirus", "2019-nCoV", "coronavirus disease". The search was limited to human studies and English language publications.

Eligibility criteria

Studies assessing olfactory and/or gustatory functions in patients with COVID-19 were identified. Only studies which confirmed the diagnosis of COVID-19 by a positive result of RT-PCR were included. OGD was assessed by either subjective evaluation (e.g. self-report questionnaires or surveys) or objective test (e.g. smell identification test or threshold test). Case series were excluded when only selected cases having OGD were reported. Primary outcomes were odds ratios (OR) of olfactory and/or gustatory dysfunctions in patients with COVID-19 compared to three control groups: normal subjects, acute respiratory infection (ARI) patients without detectable virus and ARI patients with other respiratory viruses. Secondary outcomes were proportions of the number of patients with OGD; olfactory and/or gustatory dysfunctions, olfactory dysfunction and gustatory dysfunction; among the COVID-19 patients.

Study selection process

Two review authors (MPH and KSe) independently screened the titles and abstracts based on predetermined eligibility criteria. Full texts of the selected articles were then reviewed by MPH and JK. Any disagreements in study selection were resolved by consulting the corresponding author (KSn) and a debate until getting a consensus.

Data extraction

Data sought by the review authors included study design, COVID-19 diagnostic method, sample size, number of COVID-19 patients and control, sex, mean age, methods of OGD evaluation, and characteristics of the control group.

Risk of bias in individual studies

Quality of studies was independently assessed by 2 reviewers (MPH and JK) following the modified Newcastle-Ottawa Scale (NOS) for non-randomised studies adapted for cross-sectional studies.[9] The modified NOS is presented in Supplement 1, https://figshare.com/articles/NOS/12233456. Four domains were assessed: selection, comparability, exposure, and outcome. The total score of modified NOS was 10. The quality of the studies was determined according to the score: low quality (score 0 to 4), medium quality (score 5 to 7) and high quality (score 8 to 10).

Data synthesis and statistical analysis

Data were pooled for meta-analysis. OR and 95% confidence interval (CI) were used for dichotomous data. Discrepancies in odds ratio among different studies were assessed using a heterogeneity (I^2) statistic. An I^2 of < 40%, 40-60% and > 60% represented low, moderate and substantial heterogeneity, respectively. When the heterogeneity was not substantial, a fixed-effect model (Mantel–Haenszel method) was used. A random-effects model was used for a more conservative estimate of the differences when the heterogeneity was substantial. Statistical assessments were performed using Open Meta Analyst version 10.10 and Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).[10]

Study selection

Sixty-five studies from electronic searches and two from manual searches were identified. Fifty irrelevant articles were excluded during title and abstract screening. Three articles were excluded after full-text review. Two articles were survey studies without RT-PCR diagnostic confirmation.[6,11] One article reported 11 cases of isolated sudden onset anosmia but the RT-PCR was performed in only one case.[5] Flow diagram of the study selection and reasons for exclusion are displayed in **Figure 1**. Finally, 14 studies were included in the qualitative synthesis and quantitative synthesis.[7,12-24] Seven (50%) articles had one or more control groups, there were two case-control studies and five cross-sectional studies.[7,12,13,18,20,22,23] In the two case-control studies, the study group was COVID-19 patients while the control group was normal subjects in one study and ARI patients with influenza in the other study.[7,12] In the five cross-sectional studies, Wee et al. reported two control groups of ARI without detectable virus and ARI with other respiratory viruses (ORV).[22] The other four studies assessed ARI patients without detectable virus as a control.[13,18,20,23] Seven (50%) articles were case series assessing olfactory and gustatory functions in COVID-19 patients.[14-17,19,21,24] Characteristics of the selected studies are shown in **Table 1**.

Participants

There were 8,871 COVID-19 patients in a total of 21,515 participants. Twenty-six percent were male.[7,12,14-19,21,23,24] The mean age of the participants was 49.12 years.[7,12,14-19,21,24]

Olfactory and gustatory evaluation

Two studies evaluated olfactory dysfunction using objective tests.[7,21] One study used the UPSIT.[7] The other study used the Connecticut Chemosensory Clinical Research Center test (CCCRC). The latter study used an odor identification test using common odors and a butanol threshold assessment. One study evaluated gustatory dysfunction by using a taste score which ranged from 0 to 4: Normal (score 4), mild hypogeusia (score 3), moderate hypogeusia (score 2), severe hypogeusia (score 1), and ageusia (score 0). The score was given according

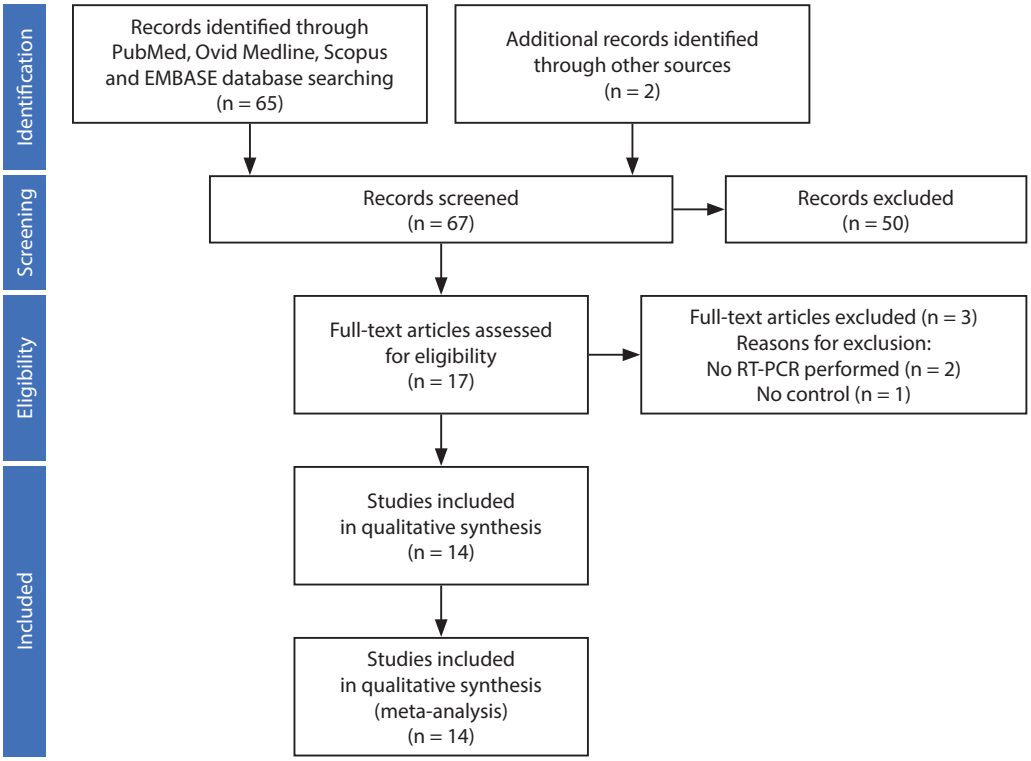


Figure 1. Flow diagram of study selection for the systematic review and meta-analysis.

Table 1. Characteristics of included studies.

First author	Year	Study design	Sample size (n)	Mean Age (Year)	Male (%)	COVID-19 testing	Olfactory function test	Gustatory function test	Control group	Quality of study
Beltrán-Corbellini[12]	2020	Case-control	119	61.35	56.3	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	ARI with ORV	Medium
Bénézit[13]	2020	Cross-sectional	257	NR	NR	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	ARI without detectable virus	Medium
Giacomelli[14]	2020	Case series	59	60	67.8	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	NR	Low
Klopfenstein[15]	2020	Case series	54	47	33.3	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	NR	Medium
Lechien[16]	2020	Case series	417	36.9	36.9	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	NR	Medium
Mao[17]	2020	Case series	214	52.7	40.7	RT-PCR	Structured interview	Structured interview	NR	Low
Menni[18]	2020	Cross-sectional	18401	43.72	26	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	ARI without detectable virus	Medium
Moein[7]	2020	Case-control	120	46.55	66.7	RT-PCR	Identification test	Self-reported questionnaire	Normal subject	Medium
Spinato[19]	2020	Case series	202	56	48	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	NR	Medium
Tostmann[20]	2020	Cross-sectional	269	NR	NR	RT-PCR	Self-reported questionnaire	NR	ARI without detectable virus	Medium
Vaira[21]	2020	Case series	72	49.2	37.5	RT-PCR	1. BTT 2. Identification test	Taste score	NR	Medium

Table 1. (Continued)

First author	Year	Study design	Sample size (n)	Mean Age (Year)	Male (%)	COVID-19 testing	Olfactory function test	Gustatory function test	Control group	Quality of study
Wee[22]	2020	Cross-sectional	941	NR	NR	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	ARI with ORV ARI without detectable virus	Low
Yan (a)[23]	2020	Cross-sectional	262	NR	37.4	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	ARI without detectable virus	Medium
Yan (b)[24]	2020	Case series	128	48.25	47.6	RT-PCR	Self-reported questionnaire	Self-reported questionnaire	NR	Medium

NR = not reported. ORV = other respiratory viruses, ARI = acute respiratory infection, BTT = butanol threshold test, RT-PCR = reverse transcription polymerase chain reaction.

to the ability to perceive four primary tastes (sweet, salty, sour, and bitter).[21] The other twelve studies used questionnaires, surveys or phone calls for olfactory and gustatory function assessments.[12-20,22-24]

Association between olfactory and/or gustatory dysfunctions and patients with COVID-19

When compared to normal subjects, patients with COVID -19 had significantly higher odds of olfactory and/or gustatory dysfunctions (OR 65.86, 95% CI 3.88 to 1118.69, $p < 0.01$, 1 study, 120 patients).[7] When compared to ARI patients without detectable virus, patients with COVID-19 had significantly higher odds of olfactory and/or gustatory dysfunctions (OR 11.26, 95% CI 5.41 to 23.4, $p < 0.01$, 3 studies, 19,528 patients).[13,18,22] An I^2 of 84% represented substantial heterogeneity. Data are displayed in **Figure 2A**. When compared to ARI patients with ORV, patients with COVID-19 had significantly higher odds of olfactory and/or gustatory dysfunctions (OR 6.46, 95% CI 2.79 to 14.97, $p < 0.01$, 2 studies, 344 patients).[12,22] An I^2 of 0% represented no heterogeneity. Data are displayed in **Figure 2B**.

Association between olfactory dysfunction and patients with COVID-19

When compared to normal subjects, patients with COVID -19 had significantly higher odds of olfactory dysfunction (OR 48.68, 95% CI 2.85 to 831.50, $p < 0.01$, 1 study, 120 patients).[7] When compared to ARI patients without detectable virus, patients with COVID-19 had significantly higher odds of olfactory dysfunction (OR 11.67, 95% CI 6.43 to 21.17, $p < 0.01$, 3 studies, 788 patients).[13,20,23] An I^2 of 50% represented moderate heterogeneity. Data are displayed in **Figure 3**. When compared to ARI patients with ORV, patients with COVID-19 had significantly higher odds of olfactory dysfunction (OR 4.17, 95% CI 1.34 to 12.98, $p = 0.01$, 1 study, 119 patients).[12]

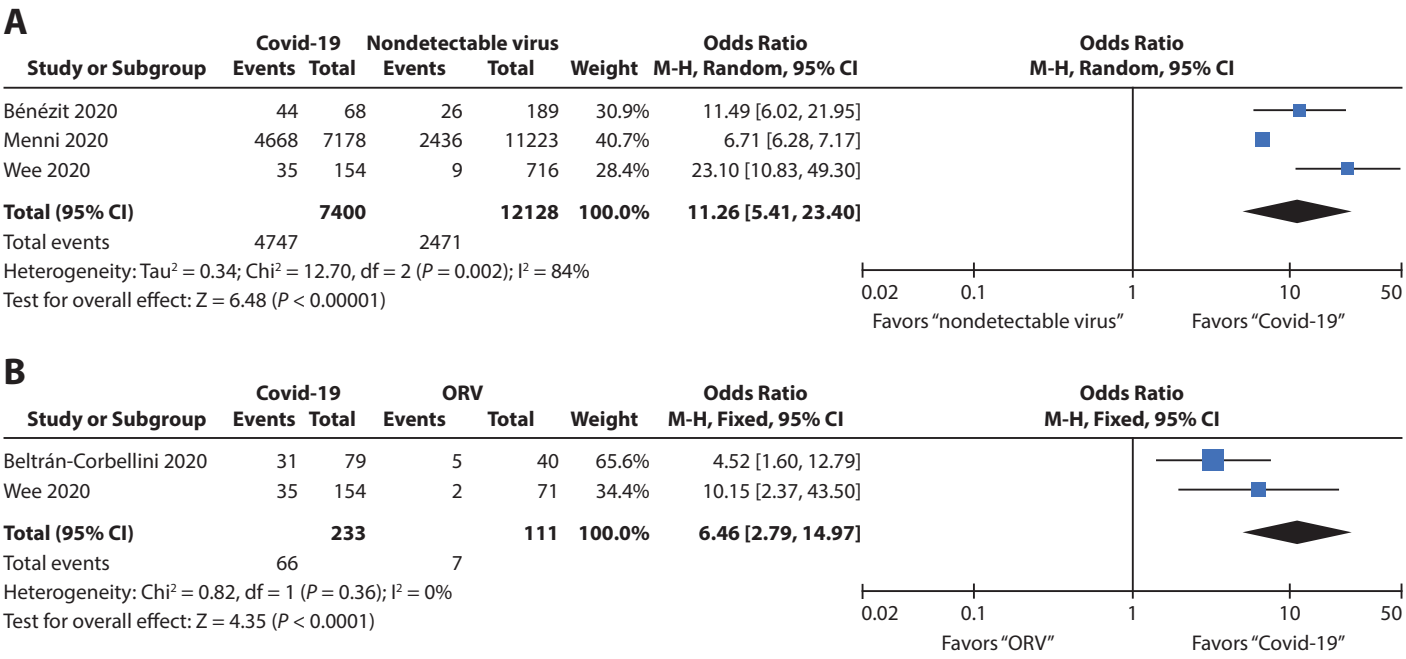


Figure 2. Odds ratios in association with olfactory and/or gustatory dysfunctions: (A) COVID-19 patients versus ARI patients with no detectable virus. (B) COVID-19 patients versus ARI patients with other respiratory viruses.

COVID-19 = coronavirus disease 2019, ARI = acute respiratory infection, nondetectable virus = ARI patients with no detectable virus, ORV = ARI patients with other respiratory viruses, M-H = Mantel–Haenszel method, random = random effects, fixed = fixed effects, CI = confidence interval, df = degrees of freedom.

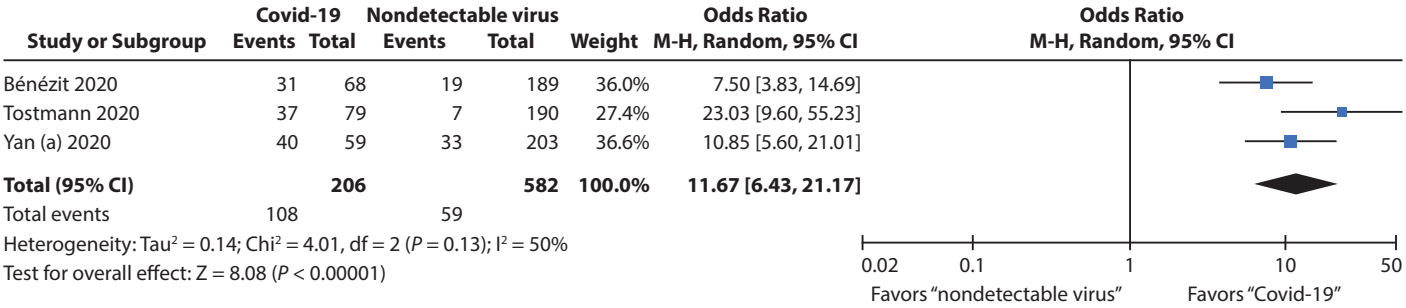


Figure 3. Odds ratio in association with olfactory dysfunction: COVID-19 patients versus ARI patients with no detectable virus.
COVID-19 = coronavirus disease 2019, ARI = acute respiratory infection, nondetectable virus = ARI patients with no detectable virus, M-H = Mantel–Haenszel method, random = random effects, CI = confidence interval, df = degrees of freedom.

Association between gustatory dysfunction and patients with COVID-19

When compared to normal subjects, patients with COVID -19 had significantly higher odds of gustatory dysfunction (OR 37.73, 95% CI, 2.19 to 649.03, p = 0.01, 1 study, 120 patients).[7] When compared to ARI patients without detectable virus, patients with COVID-19 had significantly higher odds of gustatory dysfunction (OR 12.70, 95% CI 7.90 to 20.44, p < 0.01, 2 studies, 519 patients).[13,23] An I^2 of 0% represented no heterogeneity. Data are displayed in **Figure 4**. When compared to ARI patients with ORV, patients with COVID-19 had significantly higher odds of gustatory dysfunction (OR 4.94, 95% CI 1.59 to 15.31, p < 0.01, 1 study, 119 patients).[12]

Proportions of olfactory and gustatory dysfunctions in COVID-19 population

When data of patients with COVID-19 were pooled for analysis, the proportion of olfactory and/or gustatory dysfunctions among the COVID-19 patients was 0.5 (95% CI 0.36 to 0.63, p < 0.01, 8 studies, I^2 = 96.83%);[7,13,14,17-22] olfactory dysfunction was 0.45 (95% CI 0.22 to 0.69, p < 0.01, 11 studies, I^2 = 99.2%);[7,12-17,20,21,23,24] and gustatory dysfunction was 0.47 (95% CI 0.17 to 0.76, p < 0.01, 9 studies, I^2 = 99.47%).[7,12-14,16,17,21,23,24] Heterogeneity was substantial for all analyses. Data are displayed in **Figure 5**.

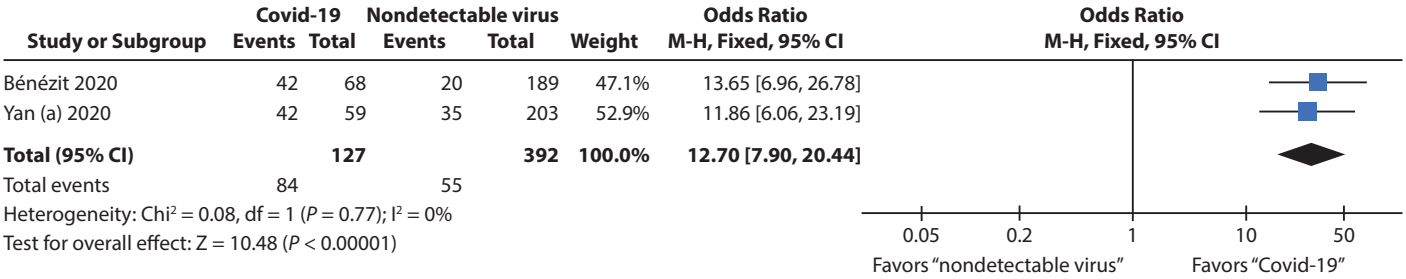


Figure 4. Odds ratio in association with gustatory dysfunction: COVID-19 patients versus ARI patients with no detectable virus.
COVID-19 = coronavirus disease 2019, ARI = acute respiratory infection, nondetectable virus = ARI patients with no detectable virus, M-H = Mantel–Haenszel method , fixed = fixed effects, CI = confidence interval, df = degrees of freedom.

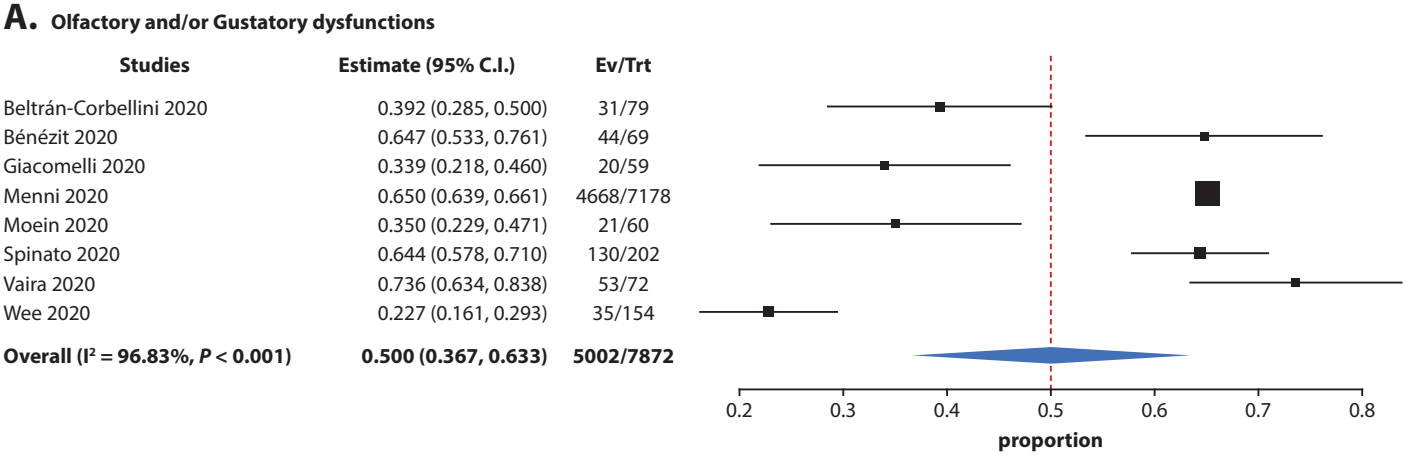
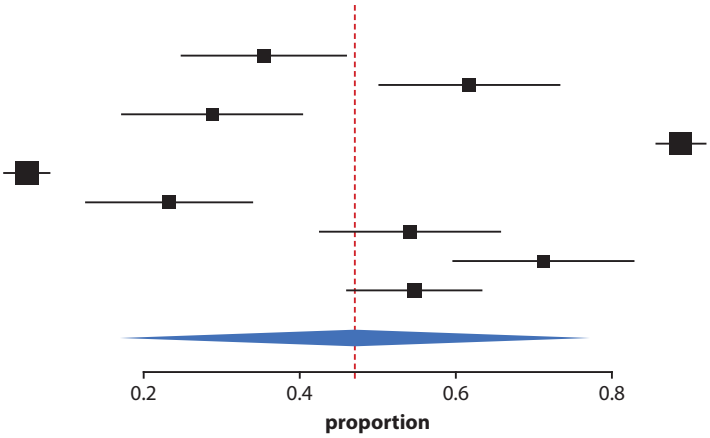


Figure 5. Proportions of patients with olfactory and gustatory dysfunctions in the patients with COVID-19: (A) Olfactory and/or Gustatory dysfunctions. (B) Gustatory dysfunction. (C) Olfactory dysfunction.
COVID-19 = coronavirus disease 2019, C.I. = confidence interval, Ev = event, Trt = total.

B. **Gustatory dysfunction**

Studies	Estimate (95% C.I.)	Ev/Trt
Beltrán-Corbellini 2020	0.354 (0.249, 0.460)	28/79
Bénézit 2020	0.618 (0.502, 0.733)	42/68
Giacomelli 2020	0.288 (0.173, 0.404)	17/59
Lechien 2020	0.888 (0.857, 0.920)	342/385
Mao 2020	0.051 (0.022, 0.081)	11/214
Moein 2020	0.233 (0.126, 0.340)	14/60
Vaira 2020	0.542 (0.427, 0.657)	39/72
Yan (a) 2020	0.712 (0.596, 0.827)	42/59
Yan (b) 2020	0.547 (0.461, 0.633)	70/128
Overall (I^2 = 99.47%, P < 0.001)	**0.470 (0.173, 0.768)**	**605/1124**



C. **Olfactory dysfunction**

Studies	Estimate (95% C.I.)	Ev/Trt
Beltrán-Corbellini 2020	0.316 (0.214, 0.419)	25/79
Bénézit 2020	0.456 (0.338, 0.574)	31/68
Giacomelli 2020	0.237 (0.129, 0.346)	14/59
Klopfenstein 2020	0.474 (0.382, 0.565)	54/114
Lechien 2020	0.856 (0.822, 0.890)	357/417
Mao 2020	0.056 (0.025, 0.087)	12/214
Moein 2020	0.283 (0.169, 0.397)	17/60
Tostman 2020	0.468 (0.358, 0.578)	37/79
Vaira 2020	0.611 (0.499, 0.724)	44/72
Yan (a) 2020	0.678 (0.559, 0.797)	40/59
Yan (b) 2020	0.586 (0.501, 0.671)	75/128
Overall (I^2 = 99.2%, P < 0.001)	**0.457 (0.220, 0.693)**	**706/1349**

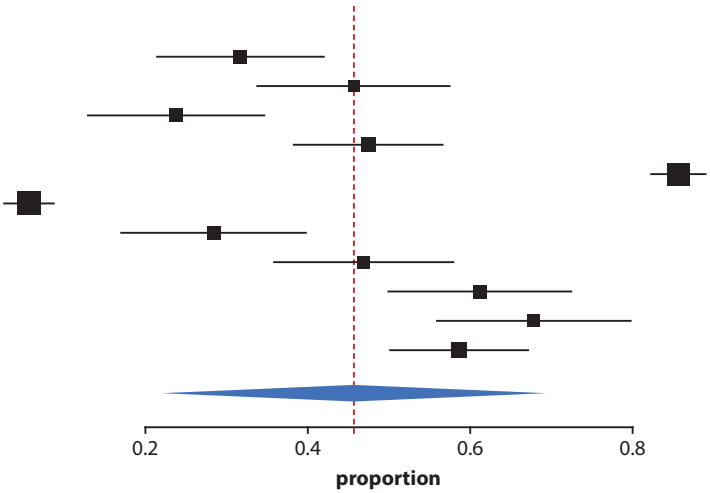


Figure 5. (Continued)

Risk of bias of the included studies

Eleven of the included studies had medium quality [7,12,13,15,16,18-21,23,24] and three studies had low quality.[14,17,22] In general, the included studies had low scores on selection domain because most studies used self-report as ascertainment of outcome except the studies from Moein et al. and Vaira et al.[7,21]

Discussion

To the best of our knowledge, this is the first meta-analysis that assessed the associations between OGD and COVID-19 patients. Although recent reports noticed a high incidence of isolated sudden anosmia without other signs and symptoms in a large group of patients, the quality of the evidence was low.[6,11] Patients with COVID-19 tend to have mild severity of nasal and pharyngeal symptoms or asymptomatic condition which make some of them become super spreaders.[25] Thus, an assessment of initial pathognomonic symptoms and signs for early detection is essential to help preventing the spreading of the virus. Evidence based on a pooled data analysis is required in order to help physicians identify the suspect patients such as patients with ARI and OGD as patients under investigation.

Viral infection has long been known as one of the key etiologies of smell disorder along with trauma, chronic rhinosinusitis, aging and neurological diseases.[26] Viral olfactory dysfunction, known as post-viral olfactory loss, may result from nerve impairment.[27] Based on our findings, the odds ratio of olfactory dysfunction in SAR-CoV-2 infection was 11.67 (95% CI 6.43 to 21.17). The odds ratio of chronic rhinosinusitis with polyps having hyposmia was 2.38 (95% CI 1.34 to 4.23) and anosmia was 13.21 (95% CI 5.68 to 30.70).[28] Unlike patients with nasal mucosal congestion and conductive olfactory loss, the COVID-19 patients had mild nasal congestion.[29,30] Mechanism of action for developing OGD in the infected SARS-CoV-2 patients is not known. The pathogenesis of OGD in population with COVID-19 was postulated. Angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) are located on the surface of non-neuro cells, including nasal and oral epithelial cells.[31] When SARS-CoV-2 entered the nasal and oral epithelium through the ACE2 and TMPRSS2, it might cause damages to olfactory and gustatory receptor cells and infiltrate the brain leading to impaired central nervous system (CNS).[31-34] Another hypothesis indicated that SARS-CoV2 may degrade CNS by demyelination and stimulation of T cell-mediated autoimmune reactions against CNS antigens. Consequently, impaired nerves can result in the alteration of olfactory and gustatory functions.[35]

The recent article by Mao et al.[17] showed central and peripheral neurologic manifestations, including smell and taste impairments in the hospitalized COVID-19 patients. Evidence from a previous study in SARS-CoV revealed that the cerebral

involvement of the virus might happen during the early and late phase of infection.[36] Moreover, the impaired cranial nerves (VII, IX, X), gustatory system (N. glossopharyngeus, N. facialis, and N. vagus) and receptors cease the taste transportation and lead to gustatory dysfunction. Amongst gustatory dysfunction patterns, dysgeusia is the most common impairment.[26] Jang et al.[37] reported an asymptomatic COVID patient who initially complained of the metallic taste during his quarantine. Our meta-analysis showed a higher odds of having OGD in COVID-19 patients compared to ORV patients. Thus, these findings elicited the different pathogenesis of OGD between the two groups.

The prevalence of OGD in our meta-analysis was around fifty percent based on eight studies. The 95% CI range was wide and the heterogeneity was substantial. This is in line with previously published articles showing that the prevalence of OGD ranged from 23.7% to 85.6%.[14,16] The great variety of the proportions should be due to a substantial heterogeneity which includes the differences in COVID-19 severity, clinical diagnostic criteria and the methods for olfactory and gustatory evaluation. Although OGD is not a common finding, it is strongly associated with COVID-19. This finding might help the COVID-19 diagnosis. Yan et al.[24] revealed that anosmia had a strong association with the outpatient with COVID-19 while pulmonary signs and symptoms were strongly associated with the hospitalized patients with COVID-19.

This study had several limitations. Most included studies were conducted in Europe and America, and therefore, it might not represent the epidemiological picture of OGD in the whole COVID-19 population. Further, just a small number of patients were studied by these fourteen articles. This could be due to a serious situation which patients were isolated or admitted in quarantine wards. To conduct research was complicated and patients did not volunteer to participate in the studies. Objective tools for chemosensory testing during the COVID-19 pandemic were not suggested due to a high risk of the SARS-CoV-2 spreading. Thus, self-report seems to be practical. In addition, there was a possibility of negative publication bias to report COVID-19 patients with normal smell function.

Conclusion

This study showed associations of OGD with COVID-19 patients. Not only individual sense was altered but the risk of impairment of both senses was also high. Patients presenting with ARI should be assessed for olfactory and gustatory functions.

Conflicts of interest

- Kornkiat Snidvongs received Honoraria for speaking at symposia from Merck Sharp & Dohme and Menarini.
- Minh P Hoang, Jesada Kanjanaumporn, Songklot Aeumjaturapat, Supinda Chusakul, and Kachorn Seresirikachorn declare that they have no conflict of interest.

Authorship contribution

- Minh P Hoang: conception, study design, search, study selection, data collection, data analysis, drafting the article, and final approval
- Jesada Kanjanaumporn: study selection, data collection, data analysis, drafting the article, and final approval
- Songklot Aeumjaturapat: manuscript edits and final approval
- Supinda Chusakul: manuscript edits and final approval
- Kachorn Seresirikachorn: search, study selection, data collection, data analysis, drafting the article, and final approval
- Kornkiat Snidvongs: conception, study design, data analysis, drafting the article, and final approval

Funding

This is an unfunded project.

References

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020;91:157-60.
2. Gandhi M, Yokoe DS, Havlir DV. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19. N Engl J Med. 2020;382:2158-60.
3. Whitcroft KL, Hummel T. Olfactory Dysfunction in COVID-19: Diagnosis and Management. JAMA. 2020. doi.org/10.1001/jama.2020.8391
4. Russell B, Moss C, Rigg A, Hopkins C, Papa S, Van Hemelrijck M. Anosmia and ageusia are emerging as symptoms in patients with COVID-19: What does the current evidence say? Ecancermedicalscience. 2020;14:ed98.
5. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome?. Rhinology. 2020. doi.org/10.4193/Rhin20.114
6. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. Laryngoscope. 2020. doi.org/10.1002/lary.28692
7. Moein ST, Hashemian SMR, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol. 2020. doi.org/10.1002/alr.22587
8. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-5.
10. Review manager (Revman) [Computer program]. version 5.3. Copenhagen. The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
11. Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. Rhinology. 2020. doi.org/10.4193/Rhin20.116
12. Beltran-Corbellini A, Chico-Garcia JL, Martinez-Poles J, Rodriguez-Jorge F, Natera-Villalba E, Gomez-Corral J, et al. Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCR-based case-control study. Eur J Neurol. 2020. doi.org/10.1111/ene.14273
13. Benezit F, Le Turnier P, Declerck C, Paille C, Revest M, Dubee V, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. Lancet Infect Dis. 2020. doi.org/10.1016/S1473-3099(20)30297-8
14. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020. doi.org/10.1093/cid/ciaa330
15. Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. Med Mal Infect. 2020. doi.org/10.1016/j.medmal.2020.04.006
16. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, 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. doi.org/10.1007/s00405-020-05965-1

17. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020. doi.org/10.1001/jamaneurol.2020.1127
18. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020. doi.org/10.1038/s41591-020-0916-2
19. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. JAMA. 2020. doi.org/10.1001/jama.2020.6771
20. Tostmann A, Bradley J, Bousema T, Yiek WK, Holwerda M, Bleeker-Rovers C, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020. Euro Surveill. 2020;25:2000508.
21. Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head & Neck. 2020;1-7.
22. Wee LE, Chan YFZ, Teo NWY, Cherng BPZ, Thien SY, Wong HM, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. Eur Arch Otorhinolaryngol. 2020. doi.org/10.1007/s00405-020-05999-5
23. 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. doi.org/10.1002/alr.22579
24. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol. 2020. doi.org/10.1002/alr.22592
25. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet. 2020;395:514-23.
26. Hummel T, Landis BN, Huttenbrink KB. Smell and taste disorders. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2011;10:Doc04.
27. Seiden AM. Postviral olfactory loss. Otolaryngol Clin North Am. 2004;37:1159-66.
28. Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. Laryngoscope. 2008;118:2225-30.
29. Eliezer M, Hautefort C, Hamel AL, Verillaud B, Herman P, Houdart E, et al. Sudden and Complete Olfactory Loss Function as a Possible Symptom of COVID-19. JAMA Otolaryngol Head Neck Surg. 2020. doi.org/10.1001/jamaoto.2020.0832
30. Galougahi MK, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. Olfactory Bulb Magnetic Resonance Imaging in SARS-CoV-2-Induced Anosmia: The First Report. Acad Radiol. 2020;27:892-3.
31. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. ACS Chem Neurosci. 2020;11:1200-3.
32. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol. 2020;38:1-9.
33. Das G, Mukherjee N, Ghosh S. Neurological Insights of COVID-19 Pandemic. ACS Chem Neurosci. 2020;11:1206-9.
34. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). Asian Pac J Allergy Immunol. 2020;38:10-8.
35. Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due to the 2019 Novel Coronavirus; a hypothesis that needs further investigation. Maxillofac Plast Reconstr Surg. 2020;42:9.
36. 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;82:7264-75.
37. Jang Y, Son HJ, Lee S, Lee EJ, Kim TH, Park SY. Olfactory and taste disorder: The first and only sign in a patient with SARS-CoV-2 pneumonia. Infect Control Hosp Epidemiol. 2020;1.