REVIEW ARTICLE

PHILIPPINE JOURNAL OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY VOL. 36 NO. 1 JANUARY – JUNE 2021

Prevalence of Olfactory Dysfunction Among COVID-19 Patients with Self-Reported Smell Loss Versus Objective Olfactory Tests: A Systematic Review and Meta-Analysis

Joyce Anne F. Regalado, MD
Mariel Mae H. Tayam, MD
Romiena A. Santos, MD
January E. Gelera, MD

Department of Otorhinolaryngology
Head and Neck Surgery
'Amang' Rodriguez Memorial Medical Center

ABSTRACT

Background: Olfactory dysfunction (OD) in COVID-19 presents as a sudden onset smell loss commonly seen in mild symptomatic cases with or without rhinitis but can occur as an isolated symptom. The reported prevalence of OD among COVID-19 patients ranged from 5% to 98%. Although numerous studies have been conducted about their association, these were mainly based on self-reported cases and subjective questionnaires.

Objective: This study investigates whether there is a significant difference in the prevalence of olfactory dysfunction between self-reported and objective testing using validated objective olfactory tests among RT-PCR confirmed COVID-19 patients.

Methods: PubMed (MEDLINE), Cochrane, Web of Science, and Google Scholar were searched for studies investigating the prevalence of OD by using objective olfactory tests among patients who self-reported OD (November 1, 2019 to July 31, 2020). All studies were assessed for quality and bias using the Cochrane bias tool. Patient demographics, type of objective olfactory test, and results of self-reported OD and objective testing were reported.

Results: Nine studies encompassing 673 patients met the inclusion criteria. Validated objective olfactory tests used in the included studies were CCCRC, SST and SIT. Overall prevalence of OD among patients who self-reported was higher after objective testing (71% versus 81%). This was also seen in when we performed subgroup analysis based on the objective tests that were used. However, meta-analysis using random effects model showed no significant difference in the overall prevalence of OD (p-value=.479, 95% CI 56.6 to 84.0 versus 71.2 to 89.8) as well as in the subgroups.

Conclusion: To the best of our knowledge, this is the first meta-analysis that statistically reviewed articles that evaluated the difference between self-reported and objective tests done on the same patients. Results showing that self-reporting OD approximates the results of the objective tests among COVID-19 positive patients may imply that self-reporting can be sufficient in contact tracing and triggering swabbing and self-quarantine during the time of COVID-19 and objective

Correspondence: Dr. January E. Gelera
Department of Otorhinolaryngology
Head and Neck Surgery
'Amang' Rodriguez Memorial Medical Center
Sumulong Highway, Sto. Niño, Marikina City 1800
Philippines
Phone: +63 915 490 4673
Email: januarygelera@gmail.com

The authors declared that this represents original material that is not being considered for publication or has not been published or accepted for publication elsewhere in full or in part, in print or electronic media; that the requirements for authorship have been met by all the authors, and that each author believes that the manuscript represents honest work.

Disclosures: The authors signed a disclosure that there are no financial or other (including personal) relationships, intellectual passion, political or religious beliefs, and institutional affiliations that might lead to a conflict of interest.

Funding: No funding support was received for this study.

Presented at the Philippine Society of Otolaryngology Head and Neck Surgery COVID-19 Research Forum 2020 (1st Place). November 18, 2020.

Philipp J Otolaryngol Head Neck Surg 2021; 36 (1): 6-14

tests can be used as an adjunct in the diagnosis particularly in research. However, this study was limited by small sample size and articles done in European countries hence, interpretation and application of the results of this study must be approached with care. Further studies documenting the difference between self-reporting and objective test in large scale setting involving different countries may be helpful in establishing a definitive consensus.

Registration: PROSPERO ID CRD42020204063

Keywords: *anosmia; hyposmia; olfactory dysfunction; SARS-CoV-2; pandemic; 2019-NCoV; COVID-19*

Increasing reports of olfactory dysfunction (OD) during the current Coronavirus Disease 2019 (COVID-19) pandemic have been a point of interest for clinicians and authorities.[1-4] Olfactory dysfunction in COVID-19 presents as a sudden onset smell loss commonly seen in mild symptomatic cases with or without rhinitis but can occur as an isolated symptom.[5-6] The reported prevalence of OD among COVID-19 patients ranged from 5% to 98%,[7-23] where higher prevalence is seen in European countries. A large-scale meta-analysis of 38 cohorts involving 12,154 COVID-19 positive patients in 18 countries showed a 38% prevalence rate of smell loss.[24] Although numerous studies have been conducted about their association, these were mainly based on self-reported cases and subjective questionnaires.[25-27]

Due to patient biases that are inherent in self-reporting such as recall and social desirability bias, and the tendency of patients to exaggerate or understate their symptoms based on their expected gain, the question of the true association of COVID-19 and OD has been raised.[28-29] Furthermore, the poor correlation of subjective questionnaires to actual olfactory status and poor sensitivity in detecting dysfunction calls for the use of objective tools.[30] Olfactory status can be evaluated objectively using different methods such as olfactory threshold, odor discrimination and odor idenitification.[31] Tests such as the Connecticut Chemosensory Clinical Research Center (CCCRC), Sniffin' Stick Test (SST) and the University of Pennsylvania Smell Identification Test (UPSIT), are the most commonly used validated tools for objective olfactory testing.

Differences between self-reported OD and objective tests has been reported in the literature. Studies comparing the overall prevalence of OD among COVID-19 patients who self-reported OD with those who underwent olfactory tests showed a significant difference between the two groups. This was corroborated by meta-analyses that were recently conducted.[25-26] However, these meta-analyses compared the individual articles that were categorized into "self-reporting" and "objective testing" based on their final result. Upon review, analysis of studies that compare the prevalence of OD before and after using objective tests on same subjects has not yet been done.

The purpose of this study was to conduct a meta-analysis of the published literature to investigate if there is a significant difference in the prevalence of olfactory dysfunction between self-reported dysfunction and objective test results among RT-PCR confirmed COVID-19 patients. This will give an idea if simply asking patients about their history of smell loss is enough in establishing the association of OD in COVID-19, or if there is a need for an objective test to ascertain the accurate prevalence of OD. Furthermore, this study could help clinicians decide on how to evaluate patients with olfactory dysfunction during the COVID-19 pandemic.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy and Data Sources

To identify studies that are eligible for inclusion in our study, we conducted a computerized search using PubMed (MEDLINE), Cochrane, Web of Science, and Google Scholar from November 1, 2019 to July 31, 2020. The search terms used were (["COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" OR "coronavirus disease 2019"] AND ["anosmia" OR "hyposmia" OR "olfactory dysfunction" OR "smell loss"]). Searches were performed using the keywords as Medical Subject Headings (MeSH).

Inclusion and Exclusion Criteria

Two authors (JAR, MMT) independently selected studies for analysis according to the following inclusion criteria: 1) participants: patients with RT-PCR confirmed COVID-19 disease who self-reported smell loss, 2) clinical test: validated objective tests, 3) outcome measure: prevalence of olfactory dysfunction, 4) type of study: cross-sectional or cohort. Studies were excluded if they had: 1) incomplete and/or no proper outcomes data, 2) no full text available, 3) non-English language without available English version. Editorials, commentaries, case reports and literature reviews as well as animal experiments and cellular studies were excluded. Letters to the editor were reviewed for shared data and were included if data fit the inclusion criteria. Two independent authors (JAR, MMT) screened the studies and disagreements were resolved by a third author (RAS). The studies were identified by title, abstract, and text in the first screening, and then the full text of relevant studies was retrieved for validation before final inclusion in the present systematic review. A flow chart of the study selection process is shown in *Figure 1*.

Methodological Quality Assessment

The risk of bias in the selected studies was assessed using an adaptation of the Cochrane Collaboration risk-of-bias tool and the Risk-of-Bias Assessment Tool for Non-randomized Studies (ROBIS). The criteria involved assessing studies for selection bias caused by inadequate selection of participants or inadequate confirmation and consideration of confounding variables, performance bias caused by inadequate measurement of intervention, detection bias caused by inadequate blinding of outcome assessment, attrition bias caused by inadequate handing of incomplete outcome data, or reporting bias caused by selective outcome reporting. A judgment related to risk of bias was assigned to each study by answering a pre-specified question about the adequacy of the study in relation to the entry. A judgment of "green" indicated a low risk of bias, "red" indicated a high risk of bias, and "yellow" indicated an unclear or unknown risk of bias. The methodological quality of the included studies was independently assessed by two researchers (JAR and MMT) and disagreements were resolved by a third author (RAS).

Data Extraction

Independent data extraction was done by two investigators (JAR, RAS) and disagreements were resolved by discussion. Data extracted from each study were: 1) patient characteristics (mean age, gender, country, setting), 2) clinical test: (i.e. self-reporting, objective test), 3) outcome measure (with or without olfactory dysfunction). Due to variability in outcome presentation, patients were considered "with olfactory dysfunctions" when they: 1) report both olfactory and gustatory dysfunction, 2) reported as with anosmia, hyposmia, cacosmia or phantosmia. Other study data extracted included author, year of publication, research design, number of samples. Furthermore, articles having the same authors were examined further to avoid duplication of data.

Statistical Analysis

Using MedCalc Statistical Software version 16.4.3 2016 (*https://www.medcalc.org*) (MedCalc Software, Ostend, Belgium), point estimates for gender proportion and OD were calculated by dividing the number of cases by the total number of COVID-19 patients included in the studies. Prevalence rates of OD were reported based on the type of reporting as to self-reported and objective test. Forest plots were generated for visual representation to show variations between studies and pooled analyses. Test for heterogeneity was carried out using Cochran's Q and I^2. Significant Cochran Q-value with p-value less than .05 and $I^2 > 50\%$ was considered for high heterogeneity. For this case, a random effects model was used to provide a conservative prevalence estimate, otherwise fixed effect model was used. Subgroup analysis of specific objective tests CCCRC, Sniffin' Stick and Smell Identification Test, were done to further investigate the difference between the studies.

RESULTS

Search Characteristics

Initial literature search yielded 286 articles, 189 of which were duplicates. During screening, 83 studies were excluded based on selection criteria. Among the 14 remaining studies, 5 were excluded with reasons. *(Figure 1)* Thus, 9 studies (n=784) met the selection criteria and were eligible for qualitative analysis. *(Figure 1, Table 1)* Study sample sizes ranged from 18 to 345, all were RT-PCR confirmed COVID-19. The mean age of patients in the included studies was 47 ± 14 years, ranging from 28 to 63. All were cross-sectional studies and were published in 2020. Majority of the studies were conducted in Europe- 3 in Italy, 2 in Belgium, 2 in Germany, and the other 2 were done in Asia.

Methodological Quality and Risk of Bias

Assessment of risk of bias for the studies is presented in *Figure 2*. All the included studies showed adequate selection of participants and low risk of confounding. The risk of bias in classification of intervention was low in 8 studies (88%) included. Separately, the risk of bias due to deviations from intended intervention and measurement of outcome was low in 6 studies (66%) and unclear in four. The risk of bias due to missing data was low in 4 studies (44%). Overall, most of the included studies were classified as low risk for bias.

Prevalence of Olfactory Dysfunction: Combined Prevalence Estimates

Complaints of OD were reported by 33.3% to 65% of COVID-19 patients who were asked about their sense of smell. *(Table 1)* There were 3 studies[35,39,40] that had subjects who all had OD. Validated objective olfactory tests were used in all the articles. In 4 studies,[35,36,39,40] the authors failed to include all the subjects in the objective evaluation due to logistic issues. Hence, the number of data were adjusted prior to statistical analysis. In summary, there were 784 COVID-19 positive patients confirmed by RT-PCR, however only 673 were included in this meta-analysis.

Specific tests used were CCCRC in 3 studies,[32-34] Sniffin' Stick test in another 3 studies,[35-37] and Smell Identification Tests in 3 studies.[38,40] The detected OD among COVID-19 patients who underwent objective olfactory tests ranged from 33.3% to 98.3%, with 1 study[38] confirmed OD on all of the participants. The prevalence of OD after using CCCRC, Sniffin' Stick and SIT were 69% to 83.3%, 60% to 84% and 83.3% to 98.3%, respectively.

The difference in prevalence of OD between self-reporting and objective testing is summarized in *Table 1*. All studies showed a notable difference in the prevalence of OD after objective testing aside from one[40] which showed no difference. However, the characteristic differences between the studies were not the same. Five studies[32-34,38,40] using CCCRC and SIT, showed an increase in the prevalence of OD after objective testing which ranges from 4.9% to as high as70%. On the other hand, 2 studies[35,36] using Sniffin' Stick test showed a decreased incidence of OD among tested subjects at 14 to 25%. One study[37] had a different result from the Sniffin' Stick subgroup showing an increase in prevalence of OD after objective testing.

Substantial to considerable heterogeneity was seen on both self-reporting (I^2 = 91.9%) and objective olfactory testing (I^2 = 86.46%), hence random effects model was used. *(Figure 3)* Out of 673 pooled subjects, the prevalence proportions of self-reported OD were 71.3% and 81.4% after objective testing. The difference in point estimates between groups was 10% (p-value=.479, 95% CI 56.6 to 84.0 versus 71.2 to 89.8).

Table 1. Main characteristics of included studies

		Subject		Self-reported, n (%)		Objective test, n (%)			
First Author, Year Published	Country	No. (Male%)	Mean Age, yr±SD	(+)	(-)	(+)	(-)	Objective test	Difference†, n (%)
Vaira, 2020 (a)[32]	Italy	72 (37.5)	49.2 ±13.7	44 (61.1)	28 (38.9)	60 (83.3)	12 (16.7)	CCCRC	+16 (22.2)
Vaira, 2020 (b)[33]	Italy	345 (42.3)	48.5 ±12.8	224 (65)	121 (35)	241 (69.9)	104 (30.1)	CCCRC	+17 (4.9)
Vaira, 2020 (c)[34]	Italy	33 (33.3)	47.2 ±10	17 (51.5)	16 (48.5)	25 (75.8)	8 (24.2)	CCCRC	+8 (23.2)
Lechien, 2020 (a)[35]	Belgium	78 (41.0)	40.6 ±11.2	28 (100)*	0 (0)*	21 (75)*	7 (25)*	Sniffin' Stick	-7 (25)*
Lechien, 2020 (b)[36]	Belgium	86 (34.9)	41.7 ±11.8	52 (74.3)*	18 (25.7)*	42 (60.0)*	28 (40.0)*	Sniffin' Stick	-10 (14.3)*
Hornuss, 2020[37]	Germany	45 (55.6)	56 ±16.9	22 (48.9)	23 (51.1)	38 (84.4)	7 (15.6)	Sniffin' Stick	+16 (35.5)
Moein, 2020[38]	Iran	60 (66.7)	46.55 ±12.17	17 (28.3)	43 (71.7)	59 (98.3)	1 (1.7)	UPSIT	+42 (70.0)
Bertlich, 2020[39]	Germany	47 (72.3)	63.3 ±13.9	14 (100)*	0 (0)*	14 (100)*	0 (0)*	BSIT	0 (0)*
Chung, 2020[40]	Hong Kong	18 (38.9)	28 ±19	6 (100)*	0 (0)*	5 (83.3)*	1 (16.7)*	SIT	1 (16.7)*

* Sample size was reduced to 28 from 78 for meta-analysis since part of the subjects did not undergo objective test. The percentage was adjusted to the sample size.
† Difference in results after objective test interpretation: (+) = number of patients who self-reported a normal OD but was positive for OD after olfactory test; (-) = number of patients who self-reported having
OD but was negative for OD after olfactory test
CCCRC = Connecticut Chemosensory Clinical Research Center; UPSIT = University of Pennsylvania Smell Identification Test; SIT = Smell Identification Test; BSIT = Brief Smell Identification Test

Prevalence of OD based on specific objective olfactory test

Connecticut Chemosensory Clinical Research Center Test. Three studies[32-34] reported the prevalence of olfactory dysfunction using the CCCRC, which includes both threshold and identification measures. *(Figure 4A, B)* Olfactory threshold was performed using butanol placed in a squeezable bottle with decreasing concentration and another identical bottle containing deionized water. The threshold was identified when the subject gave the correct answer four times. The threshold was quantified for each of the two nostrils with a score from 0 to 8 corresponding to the less concentrated bottle that the patient was able to correctly detect. The average between values of the two nostrils expressed the overall score. The odor identification on the other hand used common odorants placed inside 180 ml opaque jars covered with gauze. One at a time, the samples were presented to the patient in the same way as the threshold test. Therefore, the patient was asked to identify the odorant on a list containing the 10 test items and 10 distractors. *(Table 1)* Score ranged from 0 to 10 and was obtained from the average of the two nostrils.

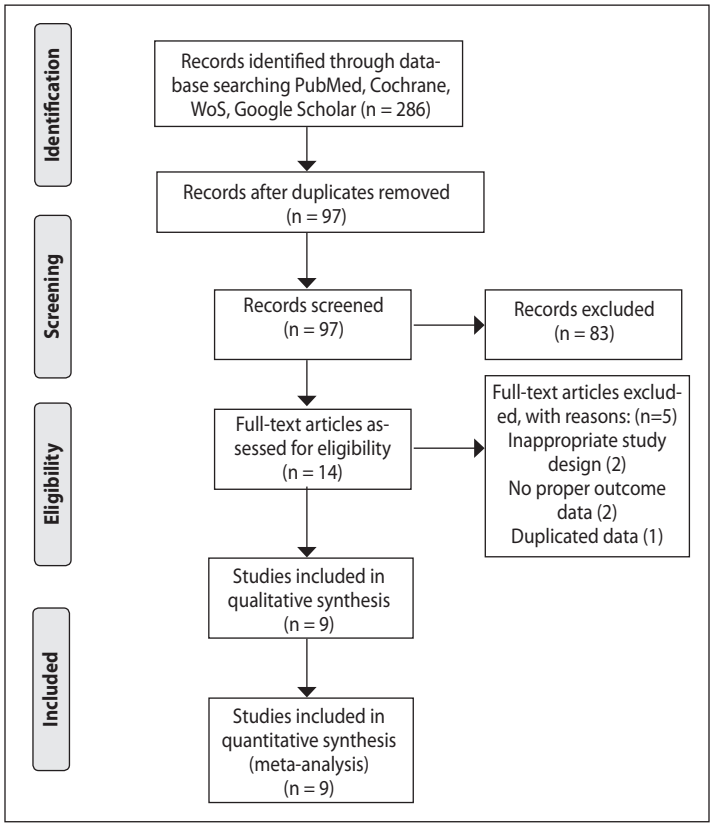


Figure 1. Flowchart of the process for selecting studies for systematic review and meta-analysis.

Olfactory status using CCCRC in the included studies was classified as a test composite score of 0-10 as anosmia, 20-80 as hyposmia and 90-100 as normal. In this study, anosmia and hyposmia are grouped as olfactory dysfunction. Self-reported OD among COVID-19 patients in the CCCRC group ranged from 51% to 65%. After the objective test, prevalence increased to 70% to 83%. Test of heterogeneity showed minimal heterogeneity in the self-reporting group and substantial heterogeneity in CCCRC, hence fixed effect and random model was used, respectively. Reported pooled prevalence of self-reported OD was 62% and 76% after CCCRC. The difference in point estimates between groups was 12% (p-value=.088, 95% CI 58.6 to 67.7 versus 65.8 to 83.9).

Sniffin' Sticks Test. Three studies[35-37] reported the prevalence of olfactory dysfunction using the Sniffin' Stick test, which comprised of odor threshold, odor discrimination, and odor identification. *(Figure 4. C, D)* Using the identification Sniffin' Sticks test (Medisense, Groningen, the Netherlands), a total of 16 scents were presented via a pen device to patients for 3 seconds followed by a forced choice from four given options with a total possible score of 16.

Self-reported OD occurred in 48% to 100%. Olfactory status using SST score was classified as normosmia (between 12 to 16), hyposmia (between 9 to 11), and anosmia (8 or below). Prevalence of OD after SST was 60% to 84% among COVID-19 patients. Substantial and considerable heterogeneity was seen in both group with I^2 of 94% and 76% hence random effects model was used. The combined prevalence of overall olfactory dysfunction in patients who self-reported smell loss was 79% and 73% after SST. The difference in point estimates between groups was 6% (p-value=.636, 95% CI 45.4 to 98.4 versus 56.3 to 86.4).

Smell Identification Test. Three studies[38-40] reported the prevalence of OD on COVID-19 patients using SIT which tests odor identification. *(Figure 4E, F)* One used the University of Pennsylvania Smell Identification Test (UPSIT), another one used Brief Smell Identification Test (B-SIT), and last used Smell Identification Test (SIT, Sensonics International Haddon Heights, NJ). These tests consist of odorants embedded per page of a test kit. Stimuli are contained in plastic microcapsules on a brown strip on the footnote. The examiner asks the patient to scrape the strip with a pencil, which releases the odor. The patient then marks the option that best describes the odor. The test score was the total of all correct answers.

Among the 80 subjects, prevalence of self-reported OD was 28% to 100% and 83% to 100% after testing. Test of heterogeneity showed a considerable heterogeneity in self-reporting group (I^2 =96%) and minimal in SIT group (I^2 = 27%) hence random and fixed effects model was used, respectively. Pooled prevalence of self-reported OD was 81% and SIT was 97%. The difference in point estimates between group was 16.2% (p-value=.636, 95% CI 45.4 to 98.4 versus 56.3 to 86.4).

	D1	D2	D3	D4	D5	D6	D7	Overall bias
Vaira, 2020 (a)	+	+	+	+	+	+	+	+
Vaira, 2020 (b)	+	+	+	?	?	+	+	+
Vaira, 2020 (c)	+	+	+	+	+	+	+	+
Lechien 2020 (a)	+	+	?	?	+	?	+	+
Lechien 2020 (b)	+	+	+	+	?	?	+	+
Hornuss 2020	+	+	+	?	?	+	+	+
Moein 2020	+	+	+	+	?	?	+	+
Bertlich 2020	+	+	+	?	?	+	+	+
Chung 2020	+	+	+	+	+	+	+	+

Figure 2. Assessment of risk of bias in the included clinical studies.
Domains:
D1: Bias due to confounding
D2: Bias in selection of participants into the study
D3: Bias in classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported results

X High
- Some concerns
+ Low

DISCUSSION

In this systematic review, the overall reported prevalence of OD in 637 COVID-19 patients who were asked about their sense of smell was 71%. After objective testing, the prevalence of OD increased to 81%. However, meta-analysis using random effects model found no significant difference between self-reporting and objective testing (p-value=.479, 95% CI 56.6 to 84.0 versus 71.2 to 89.8). Furthermore, subgroup analyses based on the type of objective test performed also showed no significant difference when compared to self-reporting.

The noted difference between the 2 groups in the overall and subgroup analysis is important to mention although the analysis of the point estimates was not significant. When objective tests were done in patients who self-reported smell loss, the prevalence of OD increased. The observed increase in the prevalence of OD after objective testing shows the tendency of self-reporting to underestimate olfactory dysfunction. This was also seen in the subgroup analysis using CCCRC. Interestingly, this was reversed when Sniffin Stick test and SIT were used wherein a decrease in the prevalence of OD were noted.

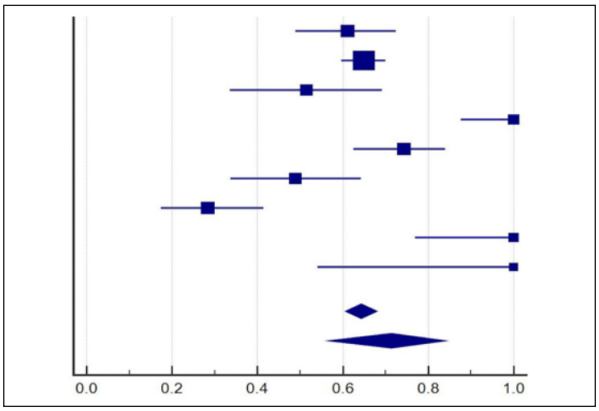
The accuracy of objective olfactory tests has been shown to increase when multiple components of olfaction were measured.[41] Hence, the discordance between the subgroups may be due to the

difference in the olfactory function that is being measured by a specific technique. The SIT measures odor identification at a suprathreshold level, whereas CCCRC (threshold and identification) and SST (threshold, discrimination, and identification) measures multiple components. Future research using objective olfactory tests that measure composite scores are needed.

In the clinical setting, olfactory tests are usually performed on both nostrils. However, the presence of side differences between the two nostrils, called lateral discrepancy, have been documented in literature.[42] Bi-rhinal testing has been shown to reflect the function of the better nostril resulting in a masked improvement of olfactory function compared to monorhinic testing.[42-43] Out of the 9 included studies, only 3 studies[32-34] that used CCCRC mentioned using a monorhinic method. They evaluated both nostrils separately and the average between the values of the two nostrils were taken as the overall score. This may explain the increase in the occurrence of OD in the CCCRC group compared to the other studies. Given these, it is important to consider the possibility of the discrepancy that may have occurred in the studies based on the methods of olfactory testing that were conducted which may have underestimated the prevalence of olfactory loss. Future studies that take these factors into consideration are needed.

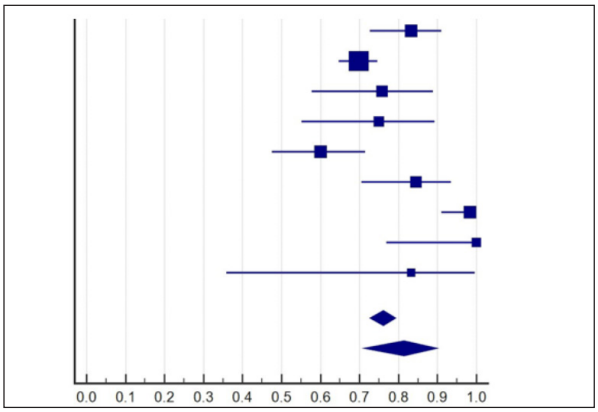
The timing of objective testing might have an effect on the results. Studies showed that OD in COVID-19 occurs early in the disease (approximately 3 days), and the majority resolve after 1-3 days, with highest rate of recovery seen in the first week from the time of onset.[44-45] Hence, the timing of the objective testing is important in documenting

A



Model	Study	Statistics for each study		
		Sample size	Proportion (%)	95% CI
Vaira, 2020 (a)		72	61.111	48.894 to 72.385
Vaira, 2020 (b)		345	64.928	59.636 to 69.961
Vaira, 2020 (c)		33	51.515	33.544 to 69.204
Lechien 2020 (a)		28	100.000	87.656 to 100.000
Lechien 2020 (b)		70	74.286	62.439 to 83.993
Hornuss 2020		45	48.889	33.703 to 64.226
Moein 2020		60	28.333	17.451 to 41.444
Bertlich 2020		14	100.000	76.836 to 100.000
Chung 2020		6	100.000	54.074 to 100.000
Fixed		673	64.269	60.544 to 67.871
Random		673	71.302	56.608 to 83.997

B

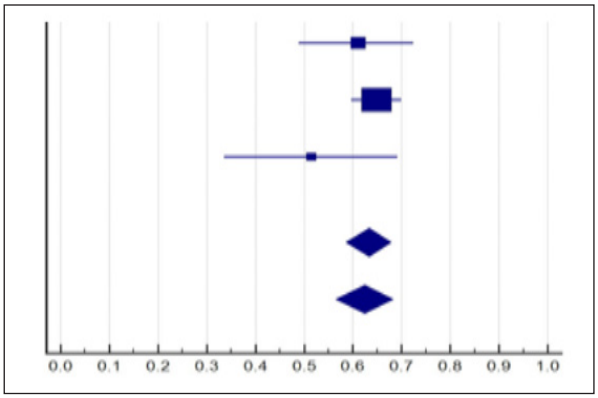


Model	Study	Statistics for each study		
		Sample size	Proportion (%)	95% CI
Vaira, 2020 (a)		72	83.333	72.696 to 91.080
Vaira, 2020 (b)		345	69.855	64.712 to 74.653
Vaira, 2020 (c)		33	75.758	57.741 to 88.908
Lechien 2020 (a)		28	75.000	55.128 to 89.309
Lechien 2020 (b)		70	60.000	47.593 to 71.533
Hornuss 2020		45	84.444	70.545 to 93.509
Moein 2020		60	98.333	91.060 to 99.958
Bertlich 2020		14	100.000	76.836 to 100.000
Chung 2020		6	83.333	35.877 to 99.579
Fixed		673	76.108	72.725 to 79.263
Random		673	81.447	71.239 to 89.831

Figure 3. Forest plots of meta-analysis comparing the prevalence of olfactory dysfunction between self-reporting (A) and objective olfactory test (B). CI = confidence interval; CCCRC = Connecticut Chemosensory Clinical Research Center; UPSIT = University of Pennsylvania

A. Self-reported OD

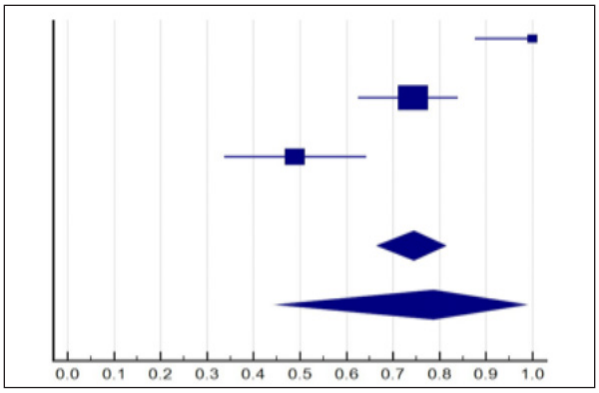
Std diff in means and 95% CI



Model Study	Statistics for each study		
	Sample size	Proportion (%)	95% CI
Vaira, 2020 (a)	72	61.111	48.894 to 72.385
Vaira, 2020 (b)	345	64.928	59.636 to 69.961
Vaira, 2020 (c)	33	51.515	33.544 to 69.204
Fixed	450	63.274	58.649 to 67.724
Random	450	62.457	56.546 to 68.188

C.Self-reported OD

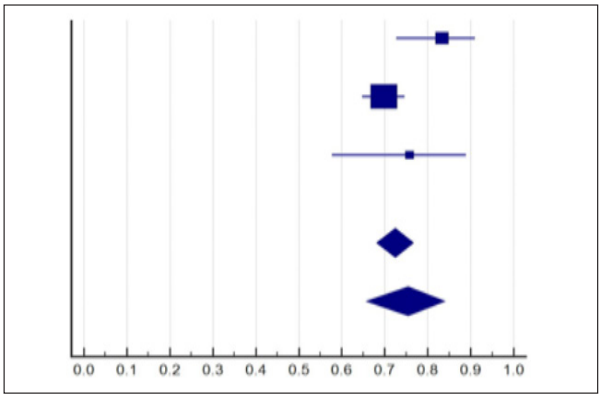
Std diff in means and 95% CI



Model Study	Statistics for each study		
	Sample size	Proportion (%)	95% CI
Lechien, 2020 (a)	28	100.000	87.656 to 100.00
Lechien, 2020 (b)	70	74.286	62.439 to 83.993
Hornuss, 2020	45	48.889	33.703 to 64.226
Fixed	143	74.450	66.578 to 81.302
Random	143	78.708	45.393 to 98.378

B. CCCRC

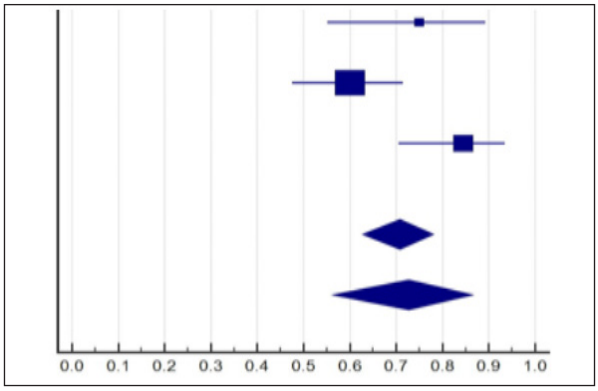
Std diff in means and 95% CI



Model Study	Statistics for each study		
	Sample size	Proportion (%)	95% CI
Vaira, 2020 (a)	72	83.333	72.696 to 91.080
Vaira, 2020 (b)	345	69.855	64.712 to 74.653
Vaira, 2020 (c)	33	75.758	57.741 to 88.908
Fixed	450	72.462	68.101 to 76.528
Random	450	75.393	65.795 to 83.861

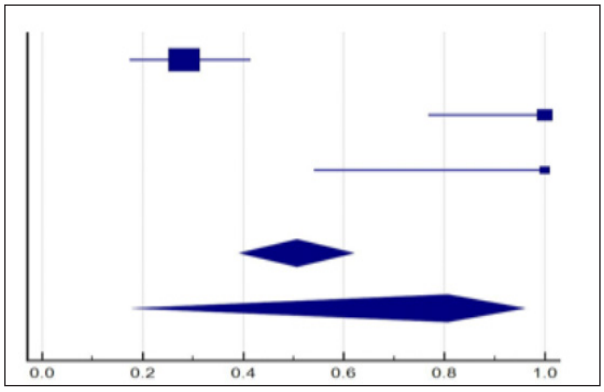
D. SST

Std diff in means and 95% CI



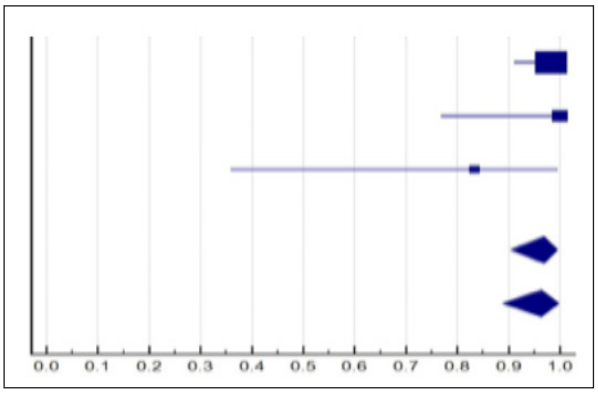
Model Study	Statistics for each study		
	Sample size	Proportion (%)	95% CI
Lechien, 2020 (a)	28	75.000	55.128 to 89.309
Lechien, 2020 (b)	70	60.000	47.593 to 71.533
Hornuss, 2020	45	84.444	70.545 to 93.509
Fixed	143	70.835	62.747 to 78.056
Random	143	72.700	56.323 to 86.411

E.Self-reported OD



Model Study	Statistics for each study		
	Sample size	Proportion (%)	95% CI
Moein,2020	60	28.333	17.451 to 41.444
Bertlich, 2020	14	100.000	76.836 to 100.000
Chung, 2020	6	100.000	54.074 to 100.000
Fixed	80	50.640	39.434 to 61.799
Random	80	80.693	19.130 to 95.725

F. SIT



Model Study	Statistics for each study		
	Sample size	Proportion (%)	95% CI
Moein,2020	60	98.333	91.060 to 99.958
Bertlich, 2020	14	100.000	76.836 to 100.000
Chung, 2020	6	83.333	35.877 to 99.579
Fixed	80	96.872	90.499 to 99.451
Random	80	96.311	88.810 to 99.794

Figure 4. Forest plots comparing the prevalence of olfactory dysfunction between self-reporting and specific objective test used: (A, B) Connecticut Chemosensory Clinical Research Center, (C, D) Sniffin' Stick Test (E, F) Smell Identification Test

the prevalence of OD in COVID-19. Unfortunately, due to logistical issues, there were difficulties in conducting timely testing. Majority of the studies that were included failed to indicate the timing of testing. The 2 studies[32,34] that mentioned the timing of objective test from the clinical onset of anosmia reported a time laps of 14 to 20 days. This time lag is important to note because the olfactory dysfunction of the patients who were evaluated may have already resolved or gradually improved by the time of assessment causing an underestimation of OD. Early olfactory evaluation of COVID-19 patients with OD is important in future studies. Moreover, the presence of the self-reported OD at the time of actual objective olfactory testing, which was not reported clearly by any of the studies included, must be taken into account to avoid errors in reporting.

This study has several limitations that is needed to be considered. First, due to novelty of the topic investigated, this study is limited by the small number of articles and sample size available for analysis which limits the authors to formulate a reliable conclusion. Difficulty in conducting objective olfactory testing during this time of the pandemic prevents researchers from conducting these kinds of studies. Studies using objective tests that were validated for home-settings would be helpful for future research. Furthermore, since olfactory tests are expensive, not readily available and a logistic problem, evaluation of validated olfactory questionnaires that would approximate objective tests would be advantageous as temporary replacement. Second, marked heterogeneity was seen between the studies which may be due to a large difference in the prevalence of OD seen in individual studies as well as the variability seen in the sample size. Lastly, the studies that were selected were limited to mostly European populations, which may mask the factor of cultural difference. Further studies that address these limitations are needed.

In conclusion, this meta-analysis indicates that self-reporting approximates objective testing in documenting the prevalence of OD among COVID-19 patients. When both groups were compared, no significant differences were seen in both the overall and subgroup analysis. Based on the results, self-reporting can be used as a threshold to test COVID-19 suspects and to advise self-quarantine. On the other hand, objective tests can be used as adjuncts in the diagnosis particularly in conducting research studies about the association of COVID-19 and olfactory dysfunction. However, due to the limitations mentioned, careful interpretation of our results is advised. Although self-reporting is valuable to assist in the initial screening of COVID-19 suspects, further studies evaluating the use of validated olfactory objective tests must be done.

ACKNOWLEDGEMENT
We would like to thank Mr. Roy Alvin J. Malenab for helping us with the statistical analysis for our study.

REFERENCES:

1. Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the covid-19 pandemic. *Rhinology.* 2020 Jun; 58(3): 295-298. DOI: 10.4193/Rhin20.116; Pubmed PMID: 32277751.
2. 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 Jul;10(7):821-831. DOI: 10.1002/alr.22592; Pubmed PMID: 32329222; PMCID: PMC7264572.
3. Joffily L, Ungierowicz A, David AG, Melo B, Brito CLT, dos Santos PSC, et al. The close relationship between sudden loss of smell and COVID-19. *Braz J Otorhinolaryngol.* Sep-Oct 2020;86(5):632-638. DOI: 10.1016/j.bjorl.2020.05.002; Pubmed PMID: 32561220; PMCID: PMC7247493.
4. Haehnera A, Drafa J, Dräger S, de Withb K, Hummel T. Predictive Value of Sudden Olfactory Loss in the Diagnosis of COVID-19. *ORL J Otorhinolaryngol Relat Spec.* 2020;82(4):175-180. DOI: 10.1159/000509143; Pubmed PMID: 32526759; PMCID: PMC7360503.
5. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope.* 2020 Jul;130(7):1787. DOI: 10.1002/lary.28692; Pubmed PMID: 32237238; PMCID: PMC7228304.
6. Gane S, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome?. *Rhinology.* 2020 Jun 1;58(3):299-301. DOI: 10.4193/Rhin20.114; Pubmed PMID: 32240279.
7. Al-Ani RM, Acharya D. Prevalence of Anosmia and Ageusia in Patients withCOVID-19 at a Primary Health Center, Doha, Qatar. *Indian J Otolaryngol Head Neck Surg.* 2020 Aug 19;1-7. DOI: 10.1007/s12070-020-02064-9; Pubmed PMID: 32837952; PMCID: PMC7435125.
8. 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 Jun 1;77(6):683-690. DOI: 10.1001/jamaneurol.2020.1127; Pubmed PMID: 32275288; PMCID: PMC7149362.
9. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med.* 2020 Jun 11;382(24):2302-2315. DOI: 10.1056/NEJMoa2006100; Pubmed PMID: 32289214; PMCID: PMC7175425.
10. Mishra P, Gowda V, Dixit S, Kaushik M. Prevalence of New Onset Anosmia in COVID-19 Patients: Is The Trend Different Between European and Indian Population? *Indian J Otolaryngol Head Neck Surg.* 2020 Jul 21;72(4):1-4. DOI: 10.1007/s12070-020-01986-8; Pubmed PMID: 32837939; PMCID: PMC7373335.
11. Wee LE, Chan YFZ, Teo NWY, Cherng BPZ, Thien SY, Wong HY, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected *Eur Arch Otorhinolaryngol.* 2020 Aug;277(8):2389-2390. DOI: 10.1007/s00405-020-05999-5; Pubmed PMID: 32328771; PMCID: PMC7180656.
12. 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 Jul 28;71(15):889-890. DOI: 10.1093/cid/ciaa330; Pubmed PMID: 32215618; PMCID: PMC7184514
13. Levinson R, Elbaz M, Ben-Ami R, Shasha D, Levinson T, Choshen G, et al. Anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. *Infect Dis (Lond).* 2020 Aug;52(8):600-602. DOI: 10.1080/23744235.2020.1772992; Pubmed PMID: 32552475.
14. Bénézit F, Le Turnier P, Declerck C, Paillé C, Revest M, Dubée V, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *Lancet Infect Dis.* 2020 Sep;20(9):1014-1015. DOI: 10.1016/S1473-3099(20)30297-8; Pubmed PMID: 32304632; PMCID: PMC7159866.
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 Aug;50(5):436-439. DOI: 10.1016/j.medmal.2020.04.006; Pubmed PMID: 32305563; PMCID: PMC7162775.
16. Menni C, Valdes A, Freidin M, Sudre C, Nguyen L, Drew D, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med.* 2020 Jul;26(7):1037-1040. DOI: 10.1038/s41591-020-0916-2; Pubmed PMID: 32393804; PMCID: PMC7751267.
17. 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 May 26;323(20):2089-2090. DOI: 10.1001/jama.2020.6771; Pubmed PMID: 32320008; PMCID: PMC7177631.
18. Heidari F, Karimi E, Firouzifar M, Khamushian P, Ansari R, Ardehali MM, et al. Anosmia as a prominent symptom of COVID-19 infection. *Rhinology.* 2020 Jun 1;58(3):302-303. DOI: 10.4193/Rhin20.140; Pubmed PMID: 32319971.
19. Yan CH, Faraji F, Prajapati DP, Boone CE, De Conde A. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol.* 2020 Jul;10(7):806-813. DOI: 10.1002/alr.22579; Pubmed PMID: 32279441; PMCID: PMC7262089
20. 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 Aug;277(8):2251-2261. DOI: 10.1007/s00405-020-05965-1; Pubmed PMID: 32253535; PMCID: PMC7134551.
21. Carignan A, Valiquette L, Grenier C, Musonera JB, Nkengurutse D, Marcil-Héguy A, et al. Anosmia and dysgeusia associated with SARS-CoV-2 infection: an age-matched case–control study. *CMAJ.* 2020 Jun 29;192(26):E702-E707. DOI: 10.1503/cmaj.200869; Pubmed PMID: 32461325; PMCID: PMC7828887.
22. Bagheri SHR, Asghari AM, Farhadi M, Shamshiri AR, Kabir A, Kamrava SK, et al. Coincidence of COVID-19 Epidemic and Olfactory Dysfunction Outbreak. *Med J Islam Repub Iran. 2020* Jun 15;34:62. DOI: 10.34171/mjiri.34.62; Pubmed PMID: 32974228; PMCID: PMC7500422.
23. Qiu C, Cui C, Hautefort C, Haehner A, Zhao J, Yao Q, et al. Olfactory and Gustatory Dysfunction as An Early Identifier of COVID-19 in Adults and Children: An International Multicenter Study. *Otolaryngol Head Neck Surg.* 2020 Oct; 163(4): 714–721. DOI: 10.1177/0194599820934376; PMCID: PMC7298561; PMID: 32539586.
24. von Bartheld CS, Hagen MM, Butowt R. Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences. *ACS Chem Neurosci.* 2020 Oct 7;11(19):2944-2961. DOI: 10.1021/acschemneuro.0c00460; Pubmed PMID: 32870641; PMCID: PMC7571048.
25. Hannum ME, Ramirez VA, Lipson SJ, Herriman RD, Toskala AK, Lin C, et al. Objective sensory testing methods reveal a higher prevalence of olfactory loss in COVID-19–positive patients compared to subjective methods: A systematic review and meta-analysis. *medRxiv.* 2020 Jul 6;2020.07.04.20145870. DOI: 10.1101/2020.07.04.20145870; Pubmed PMID: 32676608; PMCID: PMC7359533.
26. Tong J, Wong A, Zhu D, Fastenberg J, Tham T, The Prevalence of Olfactory and Gustatory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis *Otolaryngol Head Neck Surg.* 2020 Jul;163(1):3-11. DOI: 10.1177/0194599820926473; Pubmed PMID: 32369429
27. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Oforio-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. *Mayo Clin Proc.* 2020 Aug;95(8):1621-1631. DOI: 10.1016/j.mayocp.2020.05.030; Pubmed PMID: 32753137; PMCID: PMC7275152.
28. Philpott CM, Wolstenholme CR, Goodenough PC, Clark A, Murty GE. Comparison of Subjective Perception with Objective Measurement of Olfaction. *Otolaryngol Head Neck Surg.* 2006 Mar;134(3):488-90. DOI: 10.1016/j.otohns.2005.10.041; Pubmed PMID: 16500450.
29. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. *J Multidiscip Healthc.* 2016 May;9:211-217. DOI: 10.2147/JMDH.S104807; Pubmed PMID: 27217764; PMCID: PMC4862344.
30. Seok J, Shim YJ, Rhee CS, Kim JW. Correlation between olfactory severity ratings based on olfactory function test scores and self-reported severity rating of olfactory loss. *Acta Otolaryngol.* 2017 Jul;137(7):750-754. DOI: 10.1080/00016489.2016.1277782; Pubmed PMID: 28112015.
31. Doty RL, Laing DG. Psychophysical Measurement of Human Olfactory Function. *Handbook of Olfaction and Gustation.* 2015 Jun: 225–260. DOI: 10.1002/9781118971758.ch11.
32. 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: a single-center experience on 72 cases. *Head Neck.* 2020 Jun;42(6):1252-1258. DOI: 10.1002/hed.26204; Pubmed PMID: 32342566; PMCID: PMC7267244.
33. Vaira LA, Hopkins C, Salzano G, Petrocelli M, Melis A, Cucurullo M, et al. Olfactory and gustatory function impairment in COVID -19 patients: Italian objective multicenter-study. *Head & Neck.* 2020 Jul;42(7):1560-1569. DOI: 10.1002/hed.26269; Pubmed PMID: 32437022; PMCID: PMC7280583.
34. Vaira LA, Salzano G, Petrocelli M, Deiana G, Salzano FA, De Riu G. Validation of a self-administered olfactory and gustatory test for the remotely evaluation of COVID-19 patients in home quarantine. *Head Neck.* 2020 Jul;42(7):1570-1576. DOI: 10.1002/hed.26228; Pubmed PMID: 32357379; PMCID: PMC7267597.
35. Lechien JR, Cabaraux P, Chiesa-Estomba CM, Khalife M, Plzak J, Hans S, et al. Psychophysical Olfactory Tests and Detection of COVID-19 in Patients With Sudden Onset Olfactory Dysfunction: A Prospective Study. *Ear Nose Throat J.* 2020 Nov;99(9):579-583. DOI: 10.1177/0145561320929169; Pubmed PMID: 32469246.
36. Lechien JR, Cabaraux P, Chiesa-Estomba CM, Khalife M, Hans S, Calvo-Henriquez C, et al. Objective olfactory evaluation of self-reported loss of smell in a case series of 86 COVID -19 patients. *Head Neck.* 2020 Jul;42(7):1583-1590. DOI: 10.1002/hed.26279; Pubmed PMID: 32437033; PMCID: PMC7280665.
37. Hornuss D, Lange B, Schröter N, Rieg S, Kern WV, Wagner D. Anosmia in COVID-19 patients. *Clin Microbiol Infect.* 2020 Oct;26(10):1426-1427. DOI: 10.1016/j.cmi.2020.05.017; Pubmed PMID: 32447049; PMCID: PMC7242197.
38. 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 Aug;10(8):944-950. DOI: 10.1002/alr.22587; Pubmed PMID: 32301284; PMCID: PMC7262123.
39. Bertlich M, Stihl C, Weiss B, Canis M, Haubner F, Ihler F. Characteristics of Impaired Chemosensory Function in Hospitalized COVID-19 Patients. *SSRN Electron J.* 2020 Jan. DOI: 10.2139/ssrn.3576889.
40. Chung TWH, Sridhar S, Zhang AJ, Chan KH, Li HL, Wong FKC, et al. Olfactory Dysfunction in Coronavirus Disease 2019 Patients: Observational Cohort Study and Systematic Review. *Open Forum Infect Dis.* 2020 Jun 5;7(6):ofaa199. DOI: 10.1093/ofid/ofaa199; Pubmed PMID: 32548209; PMCID: PMC7284010.
41. Lotsch J, Reichmann H, Hummel T. Different Odor Tests Contribute Differently to the Evaluation of Olfactory Loss. *Chem Senses.* 2008 Jan;33(1):17-21. DOI: 10.1093/chemse/bjm058; Pubmed PMID: 17761724.
42. Gudziol V, Hummel C, Negoias S, Ishimaru T, Hummel, T. Lateralized Differences in Olfactory Function. *Laryngoscope.* 2007 May;117(5):808-11. DOI: 10.1097/MLG.0b013e3180330092; Pubmed PMID: 17473673.
43. Klimek L, Hummel T, Moll B, Kobal G, Mann WJ. Lateralized and Bilateral Olfactory Function in Patients With Chronic Sinusitis Compared With Healthy Control Subjects. *Laryngoscope.* 1998 Jan;108(1 Pt 1):111-4. DOI: 10.1097/00005537-199801000-00021; Pubmed PMID: 9432078
44. Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic – an observational cohort study. *J Otolaryngol Head Neck Surg.* 2020 May 4;49(1):26. DOI: 10.1186/s40463-020-00423-8; Pubmed PMID: 32366299; PMCID: PMC7196882.
45. Parente-Arias P, Barreira-Fernandez P, Quintana-Sanjuas A, Patiño-Castiñeira B. Recovery rate and factors associated with smell and taste disruption in patients with coronavirus disease 2019. *Am J Otolaryngol.* 2020 Jul 14 : 102648. DOI: 10.1016/j.amjoto.2020.102648; Pubmed PMCID: PMC7358151.