

Olfactory and Gustatory Symptoms of Coronavirus Disease 2019: A Systematic Review and Meta-analysis

SIVAKUMAR PRADEEP¹, KALPA PANDYA², VINAYAK KAMATH³, SIVAKUMAR VIDHYADHARAN⁴, NAVEEN HEDNE⁵



ABSTRACT

Introduction: There is increasing anecdotal evidence that olfactory and gustatory dysfunction may be associated with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).

Aim: The aim of this systematic review and meta-analysis was to find the association of olfactory and gustatory symptoms with Coronavirus Disease-19 (COVID-19) and estimate their pooled prevalence.

Materials and Methods: PubMed, Embase, EBSCO and Cochrane databases were searched for cross-sectional, cohort and case-control studies evaluating olfactory and gustatory symptoms in patients with COVID-19. The search terms included COVID-19, severe acute respiratory syndrome

coronavirus-2, coronavirus, olfaction disorders, anosmia, hyposmia, dysgeusia and ageusia. Random effects model was used to calculate a pooled Odds Ratio (OR) and pooled prevalence.

Results: Total 14 studies were included in qualitative synthesis and 13 studies were incorporated in quantitative synthesis, involving 3,125 patients. The pooled OR was 15.59 reflecting that smell and taste disorders were strongly associated with COVID-19. The pooled prevalence of olfactory and gustatory dysfunction was 56% and 44%, respectively.

Conclusion: It can be concluded that there is a significant association between olfactory and gustatory symptoms and COVID-19. Majority of the studies support the use of these symptoms as screening tools for COVID-19.

Keywords: Ageusia, Anosmia, Smell, Taste

INTRODUCTION

The Novel Coronavirus was first identified in Wuhan, China on 31st December 2019. It was named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) [1]. World Health Organisation (WHO) named the disease as Coronavirus Disease-2019 (COVID-19). On 11th March 2020, WHO declared COVID-19 as a pandemic [2]. As of 12th May 2020, there have been 4,013,728 confirmed cases and 278,993 deaths worldwide due to COVID-19 [3]. The SARS-CoV-2 Virus is known to transmit through close contact and respiratory droplets (droplets particles >5-10 microns in diameter) as well as aerosols of smaller size [4]. Till date, airborne transmission of SARS-CoV-2 has not been reported. However, WHO's recent communication has stated that this form of transmission in small, poorly ventilated rooms cannot be ruled out [5]. The transmission is occurring at an exponential rate resulting in steep curves in many countries [6]. There has been significant transmission of virus from asymptomatic and paucisymptomatic individuals [7]. A meta-analysis including 3,600 patients from 43 studies has reported the most common symptoms of COVID-19 to be fever (83.3%), cough (60.3%) and fatigue (38%) [8]. According to a large series of 72,314 cases from the Chinese Center for Disease Control and Prevention (CDC), 80% of the cases presented with mild symptoms. Limited attention has been given to the mild symptoms that may present at the initial stage of infection and often may be the only clinical manifestation of the disease [9].

There is increasing anecdotal evidence that olfactory and gustatory dysfunction may be associated with SARS-CoV-2 and they may potentially be the early symptoms of the disease [10]. Smell and taste dysfunctions have been known to be associated with various other viral infections, such as rhinovirus, Epstein-Barr virus and certain other strains of coronavirus like Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). These viruses cause inflammation of nasal

passages leading to rhinorrhoea, nasal obstruction and olfactory dysfunction [11,12]. Evidence suggests that unlike other viruses, olfactory dysfunction in COVID-19 may not present with co-existing rhinorrhoea and nasal obstruction [6].

Walker A et al., used Google trends to analyse the number of Google searches made, related to smell in multiple countries. They found a strong correlation between smell related searches and onset of COVID-19 infections, hypothesising that smell dysfunction may be an under-recognised symptom of COVID-19 [13]. In view of emerging evidence of smell and taste dysfunctions in COVID-19, the American Association of Otorhinolaryngology and Head and Neck Surgery has proposed to include anosmia, hyposmia and dysgeusia as screening tools for detection of COVID-19 [14].

A number of studies across the world have reported the prevalence of smell and taste dysfunctions such as anosmia, hyposmia, dysgeusia and ageusia in association with COVID-19 [6,15-29]. Few more have also established a strong association between smell and taste dysfunction and COVID-19 [23,30-32]. This systematic review and meta-analysis estimated the association of olfactory and gustatory dysfunctions with COVID-19 and their pooled prevalence across the studies [23]. To author's knowledge, this is the first meta-analysis assessing the association of smell and taste dysfunction with COVID-19.

MATERIALS AND METHODS

Protocol and registration: This systematic review and meta-analysis was done according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) and Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines. The protocol for this systematic review was designed and registered with PROSPERO (Registration Number- CRD42020181841) [33]. The review was conducted in May, 2020 and extended over a study period of two months.

Search strategy: The following databases were searched: PubMed, Embase, EBSCO and Cochrane Central Register of Controlled Trials (CENTRAL) database. The searches were supplemented by screening references of the included studies. Respective authors were also contacted for a few unclear data. The primary search period included all studies published until 1st May 2020, without language restrictions. The following strategy was used to search the MEDLINE database: [{"COVID-19"}[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR [{"Wuhan"}[All Fields] AND [{"coronavirus"}[MeSH Terms] OR "coronavirus"[All Fields]]] AND [2019/12[PDAT] OR 2020[PDAT]]] OR [{"coronavirus"}[MeSH Terms] OR "coronavirus"[All Fields]] OR [{"severe acute respiratory syndrome coronavirus 2"}[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]]] AND [{"olfaction disorders"}[MeSH Terms] OR "olfaction"[All Fields] AND "disorders"[All Fields]] OR "olfaction disorders"[All Fields] OR "anosmia"[All Fields] OR hyposmia[All Fields] OR [{"dysgeusia"}[MeSH Terms] OR "dysgeusia"[All Fields] OR [{"ageusia"}[MeSH Terms] OR "ageusia"[All Fields] OR [{"taste"}[MeSH Terms] OR "taste"[All Fields] OR [{"smell"}[MeSH Terms] OR "smell"[All Fields] OR [{"taste"}[MeSH Terms] OR "taste"[All Fields] OR "gustation"[All Fields]]. The search strategy for CENTRAL, EBSCO and EMBASE were similar to those used in the MEDLINE search.

Selection of studies: Reference management software (Zotero 5.0.85) was used to save all the potentially eligible studies. Two reviewers (KP and SP) independently screened the available searched studies for inclusion by reviewing the title and abstracts. Any disagreements amongst the two reviewers were resolved by involving a third reviewer. In cases where abstracts did not provide adequate or relevant information, full texts of papers were screened for eligibility. Following this, the full text of all included studies was retrieved and reviewed in detail. Excluded studies were stated with the reasons for their exclusion.

Selection criteria: All cross-sectional, cohort and case-control studies evaluating olfactory and gustatory symptoms in patients with COVID-19 were included. Studies published on or before 1st May 2020 were included. Case reports, case-series, narrative reviews and letters to the editor were excluded. Studies with insufficient data regarding olfactory and gustatory symptoms were excluded.

Data collection and synthesis of results: Two reviewers independently extracted relevant information. Tabulation of the following data was done in Microsoft Excel sheet: First author, publication date, study design, country, number of COVID-19 positive patients, mean or median age of patients, gender, total patients with olfactory dysfunction, total patients with gustatory dysfunction, patients with combined olfactory and gustatory dysfunctions (both), patients with olfactory or gustatory dysfunctions as presenting symptoms, patients with anosmia, hyposmia, ageusia, hypogeusia, dysgeusia, smell recovery time and any significant associations between the variables.

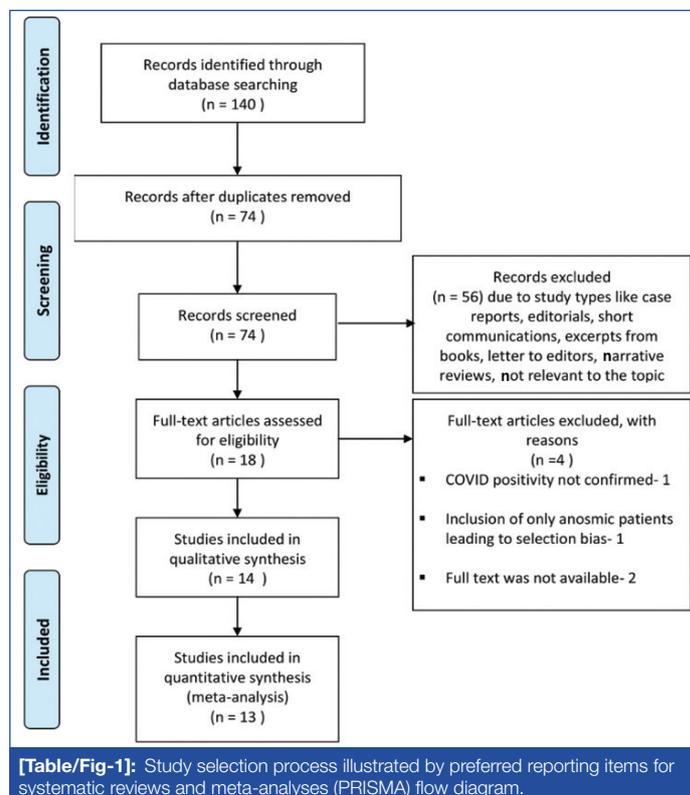
Assessment of study quality: The quality assessment tool by the National Institutes of Health (NIH) for observational studies and case-control was used to assess the quality of included studies [34]. Zero or 1 point was scored for each item according to the criteria and overall quality score was generated by adding the individual scores for each item. Based on the scores, the studies were classified as having good quality (≥ 7), fair quality (5-6) and poor quality (≤ 4). Good quality studies are deemed to have least risk of bias. Studies with fair quality have moderate amount of bias whereas poor quality studies have a significant risk of bias [35].

STATISTICAL ANALYSIS

The data was analysed using STATA 13.0 (StataCorp, College station, TX) and Revman version 5.3. Random effects model was used to calculate a pooled OR to determine the overall association between Olfactory and Taste Disorder (OTD) and COVID-19. Using random effects model, pooled prevalence of olfactory dysfunction, gustatory dysfunction, patients with both olfactory and gustatory dysfunction, and patients with some form of chemosensory dysfunction (taste and/or smell) were assessed. Apart from these, pooled prevalence of different types of smell and taste disturbances such as anosmia, hyposmia, ageusia and dysgeusia were calculated. Heterogeneity of the studies was calculated using I^2 statistics (Higgins JPT et al.) [36].

RESULTS

Study selection: The records identified 140 articles by the application of the search strategy. After removing the duplicate search records, a total of 74 records were identified from the electronic searches [Table/Fig-1].



These search records were screened for title and abstracts. Three articles did not have an English translation of which one was in Danish, one in German and one in Greek. Fifty three records were excluded due to publication types like case reports (2), case series (2), editorials (5), short communications (1), excerpts from books (1), letter to editors (5), narrative reviews (6) and due to irrelevance to the topic (31). For the remaining 18 records, full text articles were searched for eligibility. Of these, four articles were excluded due to the following reasons: COVID-19 positivity was not confirmed in one study, one study included only anosmic patients leading to selection bias and full text was not available for two articles. Thus, 14 [6,16,17,21-23,27,30-32,37-40] studies were included in qualitative synthesis and 13 studies were incorporated in quantitative synthesis. Of these 11 were used to measure the pooled prevalence, and 5 [23,27,30-32] studies were used to establish an overall association by measuring pooled OR.

Study characteristics: Fourteen studies consisting of six cross-sectional surveys [6,16,17,37,39,40], three retrospective observational studies [21,22,38], five case-control studies [23,27,30-32] with a total of 3,125 patients included in the final review [Table/Fig-2] [6,16,17,21-23,27,30-32,37-40].

S. No.	Author	Country	Age (Years) Mean (SD)/ Median	COVID Positive cases	Male	Female	Study design	Patients with olfactory dysfunction (%)	Patients with gustatory dysfunction (%)
1	Giacomelli A et al., [16]	Italy	Median 60	59	40	19	Cross-sectional survey	14 (23.7)	17 (28.8)
2	Lechien JR et al., [6]	Europe	36.9 (11.4)	417	154	263	Cross-sectional survey	357 (85.6)	342 (82.01)
3	Yan CH et al., [38]	USA	18-79	59	29	29	Cross-sectional survey	40 (67.8)	42 (71.2)
4	Klopfenstein T et al., [22]	France	47 (16)	114	Not reported	Not reported	Retrospective observational study	54 (47)	46 (85)
5	Mao L et al., [21]	China	52.7 (15.5)	214	87	127	Retrospective observational study	11 (5.1)	12 (5.6)
6	Moein ST et al., [23]	Iran	46.55 (12.17)	60	40	20	Case-control study	59 (98)	14 (23.3)
7	Benezit F et al., [27]	France	Not reported	68	Not reported	Not reported	Case-control study	31 (45)	42 (62)
8	Vaira LA et al., [39]	Italy	49.2	72	27	45	Cross-sectional	86.1	47.2
9	Spinato G et al., [40]	United Kingdom	Median 56	202	97	105	Cross-sectional survey	Not mentioned	Not mentioned
10	Lechein JR et al., [37]	Europe	39.17 (12.09)	1420	458	962	Cross-sectional	997 (70.2)	770 (54.2)
11	Beltran- Corbellini A et al., [30]	Spain	61.6 (17.4)	79	48	31	Case-control study	25 (80.6)	28 (90.3)
12	Tostmann A et al., [31]	Netherland	Not reported	79	19	71	Case-control study	37 (46.8)	Not mentioned
13	Wee LE et al., [32]	Singapore	Not reported	154	Not reported	Not reported	Case-control study	Not mentioned	Not mentioned
14	Yan CH et al., [17]	USA	53.5: Admitted patients, 43: Ambulatory patients	128	61	67	Retrospective observational study	75 (58.5)	70 (54.6)

[Table/Fig-2]: Table describing the study characteristics of the included studies [6,16,17, 21-23,27,30-32,37-40].

SD: Standard deviation

Assessment of the quality of the studies: The study quality was assessed using National Heart Lung and Blood Institute (NHLBI) quality assessment tool for observational studies by the NIH for the nine observational studies and the NHLBI tool for case-control studies was used for the five included case-control studies. The study qualities were good for nine studies, fair for four studies and poor for one study [Table/Fig-3].

Qualitative synthesis: A total of 14 studies were included in the qualitative synthesis. The key findings, strength and limitations of various studies have been summarised in [Table/Fig-3].

Quantitative synthesis (Meta-analysis): Association between

smell and taste disorders and COVID-19: Five studies compared the smell and taste function of patients with COVID-19 with those who were COVID-19 negative. Smell and taste function was assessed through questionnaires for four of these studies [27,30-32] whereas by objective testing for one study [23]. The pooled OR was 15.59 (95% CI, 6.31-38.55) [Table/Fig-4].

This reflects that smell and taste disorders are strongly associated with COVID-19. The studies had moderate heterogeneity by I^2 test (72%). On the funnel plot, the study by Moein ST et al., appeared

S. No.	Author/Year	Key features	Authors conclusion	Strengths	Limitations	Study quality
1	Giacomelli A et al., [16] March 2020	<ul style="list-style-type: none"> 33.9% had at least one gustatory/olfactory disorder and 18.6% had both. 20.3% presented as initial symptoms. Taste dysfunction was more as an initial symptom (91%) Females had these symptoms more than males (52.6% versus 25%, $p=0.036$). Patients with at least one olfactory/gustatory symptom were younger than those without 	<ul style="list-style-type: none"> Olfactory and gustatory dysfunction are frequent in patients with COVID-19. It may precede the onset of more serious disease. 	<ul style="list-style-type: none"> Patients with memory disorders were excluded 	<ul style="list-style-type: none"> Not used a structured questionnaire Subjective assessment Since the study was done for hospitalised patients, patients with mild symptoms who does not need hospitalisation may be missed Olfactory recovery not assessed 	Fair
2	Lechien JR et al., [6] April 2020	<ul style="list-style-type: none"> Patients with mild-to-moderate disease 85.6% had olfactory dysfunction 88.0% of patients had gustatory dysfunctions. There was a significant association between both dysfunctions ($p<0.001$). Olfactory dysfunction was a presenting symptom in 11.8% cases. Quality of Life (QOL) scores were significantly lower in anosmia Majority olfactory dysfunctions were without nasal obstruction or rhinorrhea. Early olfactory recovery rate was 44.0%. Females were significantly more affected by smell and taste dysfunctions than males ($p=0.001$). 	<ul style="list-style-type: none"> In European COVID-19 patients, olfactory and gustatory dysfunctions were prevalent The sudden anosmia/ageusia should be recognised as a symptom of COVID-19 disease. 	<ul style="list-style-type: none"> Standard questionnaire Included varied ethnicity Mild to moderate cases included. QOL assessed Smell recovery assessed 	<ul style="list-style-type: none"> Subjective assessment Not included severe patients May not be representative as physicians with anosmia voluntarily participated. 	Good
3	Yan CH et al., [38] April 2020	<ul style="list-style-type: none"> Anosmia and ageusia was reported in 68% and 71% patients, respectively ($p<0.001$). Anosmia and ageusia was independently and strongly associated with Covid-19 (anosmia: adjusted Odds Ratio (aOR) 10.9, 95% CI: 5.08-23.5; ageusia: aOR 10.2 95% CI: 4.74-22.1) 74% of anosmia patients recovered in two weeks with overall recovery from illness. 22% reported anosmia as an initial symptom Anosmia and ageusia were 10 times more common in Covid-19-positive patients 	<ul style="list-style-type: none"> Olfactory and gustatory dysfunction was strongly associated with COVID-19. Should be considered as a screening symptom Most of these symptoms recovered with overall recovery from illness 	<ul style="list-style-type: none"> 10 point olfaction score was used. Smell recovery assessed 	<ul style="list-style-type: none"> Subjective assessment Short sampling period Only ambulatory patients with relatively mild COVID-19 infection were included Moderate to severe patients admitted in the hospitals were not included Patients with memory disorders were not excluded 	Good

4	Klopfenstein T et al., [22] April 2020	<ul style="list-style-type: none"> 47% had anosmia. Anosmia was associated with dysgeusia in 85% cases. Patients with anosmia were younger with a female predominance Anosmia started 4.4 {±1.9 (1-8)} days after onset of infection. Mean duration of anosmia - 8.9 {±6.3 (1-21)} days. 80% patients recovered in 14 days & 98% patients recovered within 28 days. 	<ul style="list-style-type: none"> Nearly half of COVID-19 patients had anosmia and it is associated with dysgeusia in 85% cases. Favourable outcome in 28 days. 	<ul style="list-style-type: none"> Smell recovery assessed Patients with memory disorders were excluded 	<ul style="list-style-type: none"> Data was retrospectively collected from the file where mild patients may not be captured Only taken hospitalised patients and ambulatory patients with these symptoms may be missed 	Fair
5	Villalba NL, et al., [24] April 2020	<ul style="list-style-type: none"> Neurologic symptoms was noted in 36.4% patients These were common in patients with severe infection (45.5%) Amongst the peripheral nervous system symptoms, Gustatory dysfunction seen in 5.6% of which 3 had severe infection and 9 had nonsevere infection Olfactory dysfunction was seen in 5.1% patients of which 3 had severe infection and 8 had nonsevere infection 	<ul style="list-style-type: none"> Neurologic symptoms are seen in a sizable proportion of COVID-19 patients. Physicians should suspect COVID-19 as a differential diagnosis, if neurologic manifestations present 	<ul style="list-style-type: none"> Categorised and included both severe and nonsevere infection patients 	<ul style="list-style-type: none"> Data collected retrospectively collected where mild patients may not be captured Included only hospitalised patients Smell recovery not assessed 	Poor
6	Moein ST et al., [23] April 2020	<ul style="list-style-type: none"> 98% patients had some form of olfactory dysfunction which was graded into anosmia, mild, moderate and severe microsmia 35% had either taste or smell loss 12% had only smell loss 7% had only taste loss 17% had combined smell and taste loss Of 83% patients who had anosmia/severe microsmia, only 35% was aware of their smell dysfunction. 	<ul style="list-style-type: none"> Objective assessment shows some degree of olfactory dysfunction and not always anosmia, is a major sign for COVID-19 Objective Olfactory testing may help in screening COVID-19 patients. 	<ul style="list-style-type: none"> This is the only study using objective testing for olfactory function using The University of Pennsylvania Smell Identification Test (UPSIT) Patients were graded based on severity Matched controls used 	<ul style="list-style-type: none"> Quantitative assessment not done for taste dysfunction. Included only hospitalised patients Smell recovery was not assessed 	Fair
7	Bénézit F et al., [27] April 2020	<ul style="list-style-type: none"> 62% had hypogeusia 45% had hyposmia 43% had combined hyposmia and hypogeusia Hyposmia and hypogeusia were strongly associated with COVID-19 diagnosis independently and together 	<ul style="list-style-type: none"> These symptoms can be used for Mass screening and initial diagnosis of COVID-19 	<ul style="list-style-type: none"> Findings compared with COVID negative patients (with Influenza-Like Illness (ILI)) 	<ul style="list-style-type: none"> No objective assessment No standard questionnaire Smell recovery was not assessed. 	Good
8	Vaira LA et al., [39] April 2020	<ul style="list-style-type: none"> Smell: Olfactory threshold and odor discriminative ability assessed Taste: Standardised test to test four primary tastes 73.6% have one or more of olfactory-gustatory disturbance Most patients had mild-moderate olfactory and taste disorders (OTD) Older patients more prone to taste disturbance (p<0.003) 	<ul style="list-style-type: none"> OTD are common clinical findings in COVID-19 OTD occur in early stages of infection If sudden and OTD not associated with rhinitis symptoms, COVID-19 to be suspected 	<ul style="list-style-type: none"> Standardised objective tests used for taste and smell assessment Smell recovery was tested Studies relation of OTD with age and time of onset of clinical symptoms 	<ul style="list-style-type: none"> Evaluation of OTD performed at 19.3 days from the onset of clinical symptoms 	Fair
9	Spinato G et al., [40] April 2020	<ul style="list-style-type: none"> 64.4% reported one or more OTD 11.9% reported it as a presenting symptom 3% reported OTD as an isolated symptom STD more common in women 	<ul style="list-style-type: none"> Testing for COVID-19 and self-isolation to be considered in sudden onset of altered taste or smell 	<ul style="list-style-type: none"> Standard questionnaire- Sino-nasal outcome test 22 (SNOT-22) used Studied grades of OTD 	<ul style="list-style-type: none"> Smell and taste dysfunction not distinguished Objective testing not performed Only mildly symptomatic cases included 	Good
10	Lechein JR et al., [37] April, 20	<ul style="list-style-type: none"> OTD more common in younger patients and in female patients Anosmia-70.2% Dysgeusia-54.2% of 1420 patients Anosmia persisted for 1 week in 37.5% of cured patients 	<ul style="list-style-type: none"> Smell disturbance is a key under estimated symptom of mild to moderated COVID-19 patients 	<ul style="list-style-type: none"> Multi-centre study with large sample size Varied ethnicity Age and sex association with COVID-19 assessed 	<ul style="list-style-type: none"> Only mild-moderate cases Young patients with few comorbidities No objective testing 	Good
11	Yan CH et al., [17] April, 20	<ul style="list-style-type: none"> Investigated association between smell loss and hospitalisation in COVID-19 Smell loss was strongly associated with COVID-19 which does not require hospitalisation (aOR 0.09 95% CI- 0.01-0.74) whereas positive findings on chest imaging was associated with hospitalisation 	<ul style="list-style-type: none"> Anosmia may be related to a mild disease, not requiring hospitalisation 	<ul style="list-style-type: none"> Included both mild and severe cases of COVID-19 	<ul style="list-style-type: none"> No objective testing Grades of smell dysfunction not assessed 	Good
12	Beltrán-Corbellini A et al., [30] April 20	<ul style="list-style-type: none"> Investigate new onset olfactory and taste disorders (OTD) in COVID-19 compared to ILI (controls) 39.2% of cases had OTD compared to 12.5% in controls. Smell dysfunction-80% Taste dysfunction-90.3% Among COVID-19 patients, patients with OTD were younger than those without OTD Mean duration of OTD- 7.5+/- 3.2 days. 40% recovered completely after 1 week. 	<ul style="list-style-type: none"> OTD common in COVID-19 compared to Influenza-Like Illness (ILI) Usually it is a presenting symptom and acute in onset 	<ul style="list-style-type: none"> Case-control study Assessed recovery 	<ul style="list-style-type: none"> No objective testing 	Good
13	Tostmann A et al., [31] April 20	<ul style="list-style-type: none"> Healthcare workers with mild symptoms tested for COVID-19 Anosmia reported in 47% COVID positive and strongly associated with COVID-positivity OR=23.0; 95% confidence interval (CI): 8.2-64.8) Predictive model based on these symptoms showed sensitivity: 91.2%; specificity: 55.6% 	<ul style="list-style-type: none"> Authors propose self-isolation to patients with olfactory symptoms 	<ul style="list-style-type: none"> Predictive model calculated 	<ul style="list-style-type: none"> No objective testing done Study subjects involved only those with mild symptoms 	Good
14	Wee LE et al., [32] April 20	<ul style="list-style-type: none"> COVID testing done for all suspected cases including those with the symptoms of OTD 22.7% patients COVID positive subjects had OTD Odds ratio for OTD was higher for patients with COVID compared to those with other respiratory viruses (odds ratio, OR=10.14, 95% CI 2.37-43.49, p<0.001). 	<ul style="list-style-type: none"> OTD as a self-reported symptom had a high specificity (98.7%) as a screening tool in an Asian cohort 	<ul style="list-style-type: none"> Compared with COVID-negative cases with the same mild symptoms 	<ul style="list-style-type: none"> No objective testing performed 	Fair

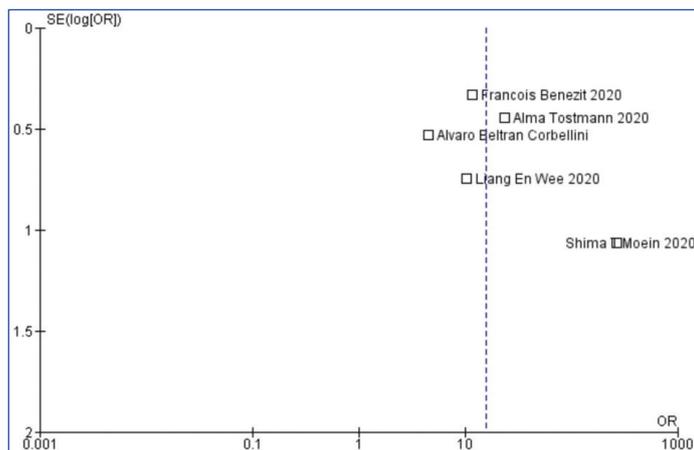
[Table/Fig-3]: Table describing the key findings, strengths and limitations of the studies [6, 16, 17, 22-24, 27, 30-32, 37-40].

Study or Subgroup	COVID		Control		Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total			
Alma Tostmann 2020	37	79	7	190	23.6%	23.03 [9.60, 55.23]	
Alvaro Beltran Corbellini	31	79	5	40	21.6%	4.52 [1.60, 12.79]	
Francois Benezit 2020	44	68	26	189	26.2%	11.49 [6.02, 21.95]	
Liang En Wee 2020	35	154	2	71	17.0%	10.15 [2.37, 43.50]	
Shima T Moein 2020	59	60	11	60	11.6%	262.82 [32.77, 2107.66]	
Total (95% CI)		440		550	100.0%	15.59 [6.31, 38.55]	
Total events		206	51				
Heterogeneity: Tau ² = 0.70; Chi ² = 14.07, df = 4 (P = 0.007); I ² = 72%							
Test for overall effect: Z = 5.95 (P < 0.00001)							

[Table/Fig-4]: Association of olfactory and gustatory symptoms with COVID-19.

to be well away from the central line indicating a publication bias [Table/Fig-5] [23].

Prevalence of Olfactory and gustatory dysfunction: Olfactory dysfunction was reported by 12 studies. The pooled prevalence of olfactory dysfunction was 56% (95% CI 37-75) in the patients with COVID-19 [Table/Fig-6a]. The pooled prevalence for gustatory



[Table/Fig-5]: Funnel plot depicting publication bias.

disturbance as reported by 11 studies was 44% (95% CI 28-62) [Table/Fig-6b]. A 32% of the patients reported both smell and taste disturbance (95% CI, 21-43) [Table/Fig-6c]. Nine studies reported data regarding OTD as presenting symptoms for which the prevalence was 9%. (95% CI, 3-17) [Table/Fig-6d]. Detailed statistical analyses are demonstrated in supplemental tables.

Prevalence of different types of smell and taste dysfunctions:

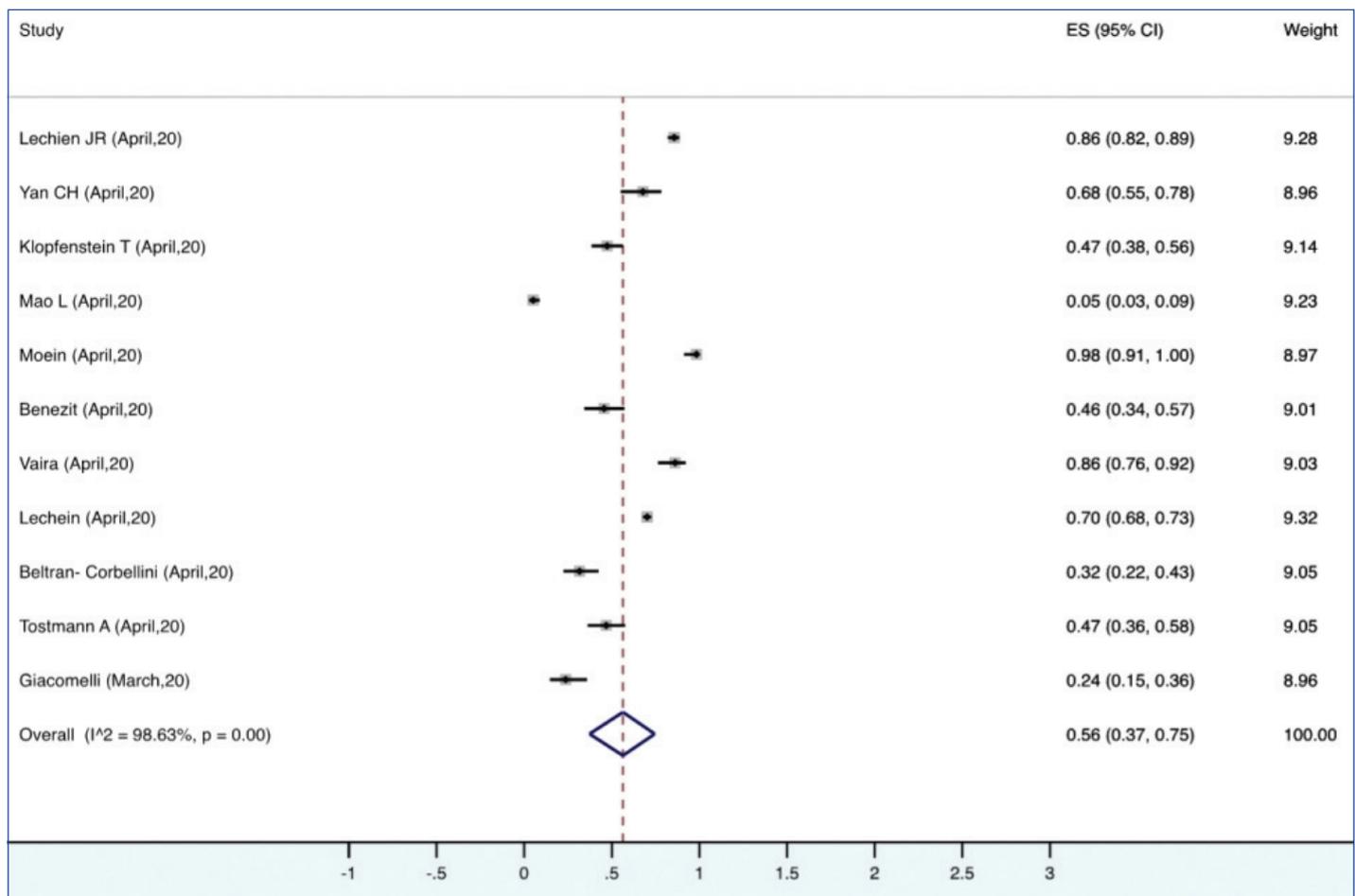
The estimated pooled prevalence of anosmia was 28% (95% CI, 10-50) in the patients with COVID-19. Hyposmia was reported in eight studies, the pooled prevalence for which was 27% (95% CI, 6-54). Eight studies reported ageusia with estimated pooled prevalence of 12% (95% CI, 1-33). Dysgeusia was reported by six studies with pooled prevalence of 8% (95% CI, 0-21) [Table/Fig-7a-d].

Subgroup analysis: A high degree of heterogeneity was found across various studies. Studies were performed in different countries with wide ethnicity. A region-wise subgroup analysis was performed for olfactory and gustatory dysfunction. The prevalence ranged from 5% (China) to 98% (Asia). Pooled prevalence involving only the European countries was 56%, which was similar to the overall pooled prevalence [Table/Fig-8].

DISCUSSION

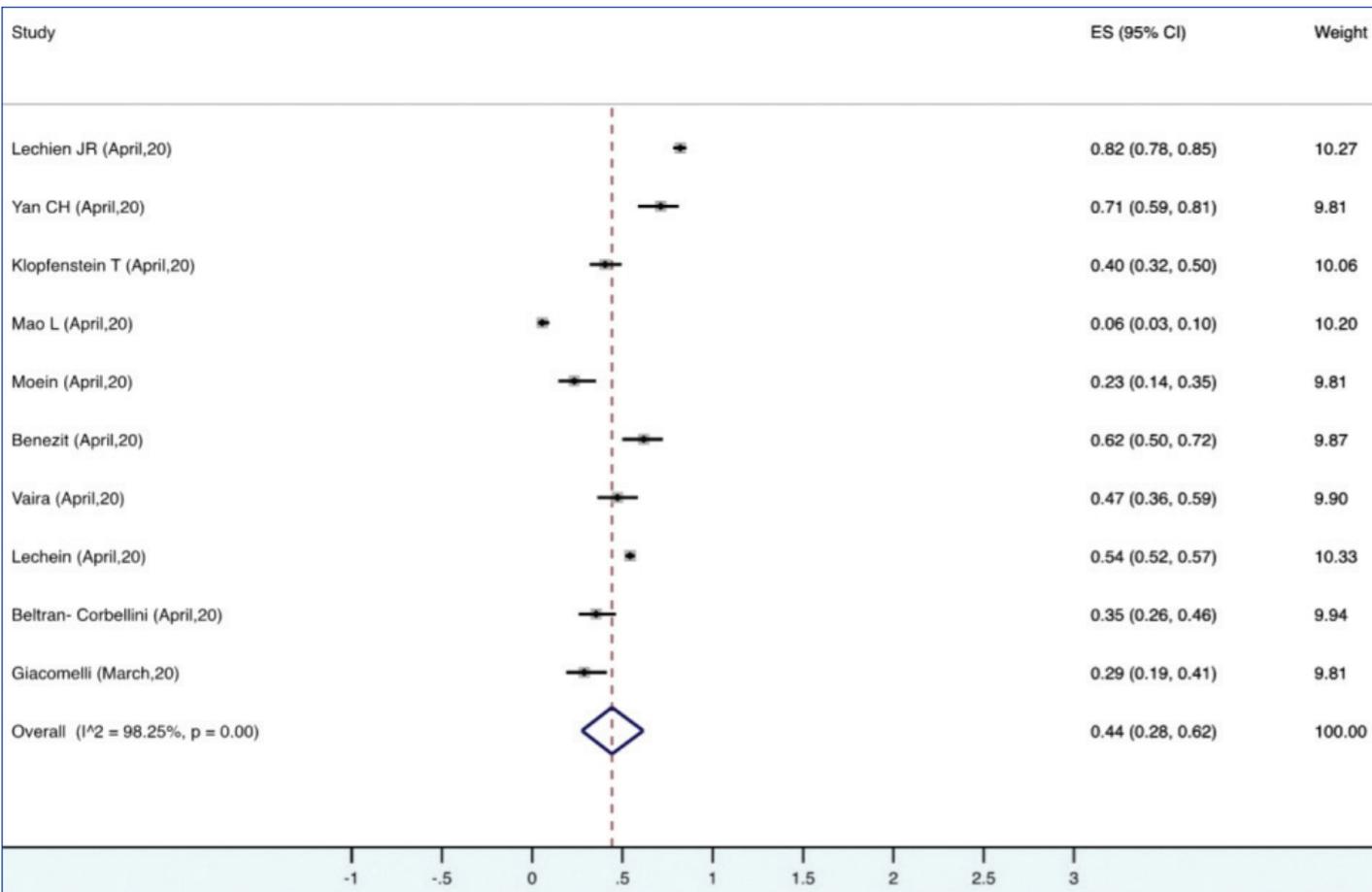
There is growing anecdotal evidence of sudden anosmia or hyposmia with or without other symptoms of COVID-19 infection [10]. This systematic review and meta-analysis involving 13 studies and 3,125 patients demonstrates a significant association between olfactory and gustatory dysfunction and COVID-19. It also demonstrates a high prevalence of these symptoms in patients with COVID-19.

Pooled OR across the five case-control studies was 15.59 showing that OTD were 15 times more common in patients with COVID-19 compared to those without. Lechien JR et al., found



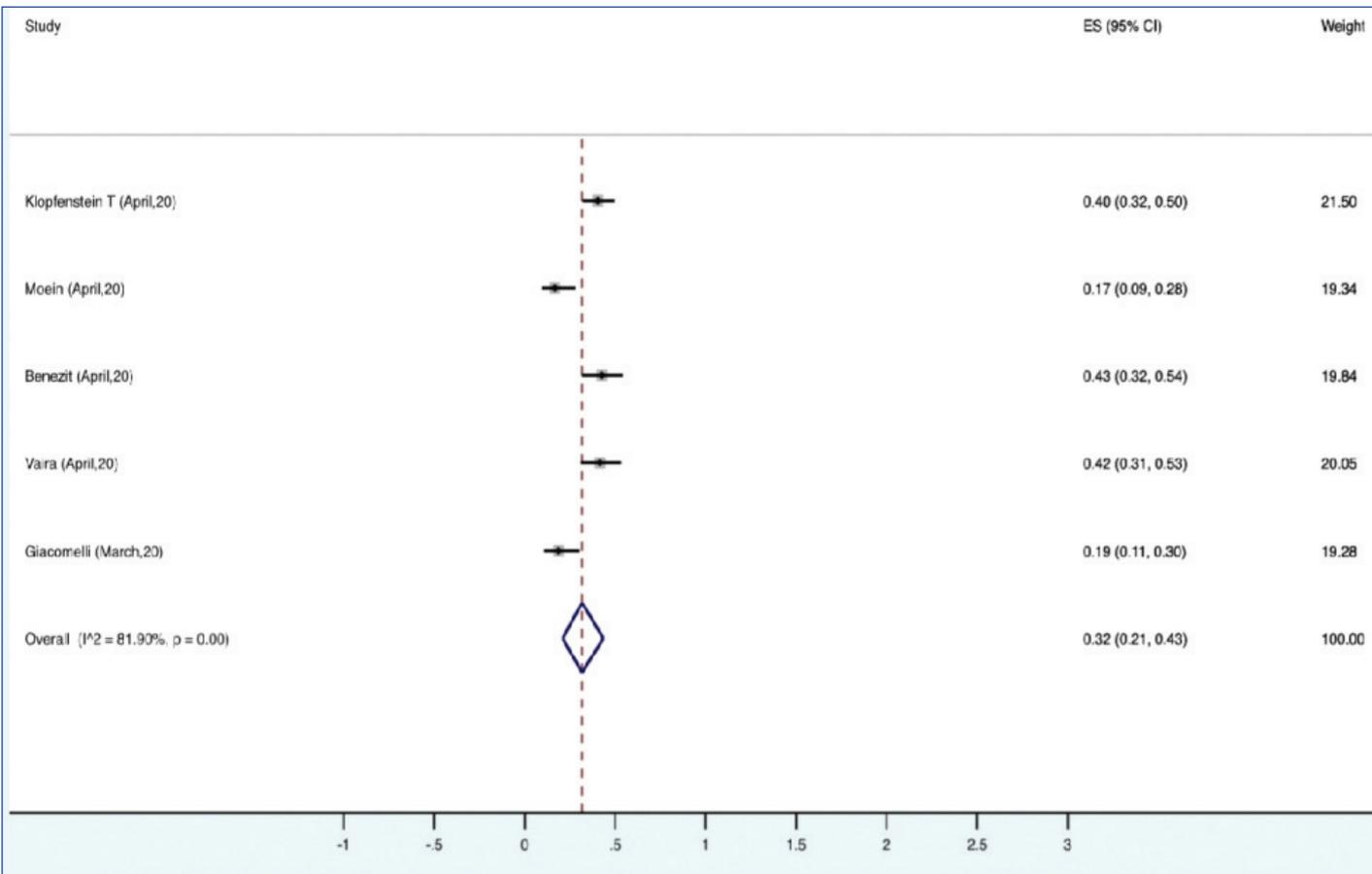
(a)

[Table/Fig-6a]: Forest plot illustrating pooled prevalence of olfactory dysfunction.



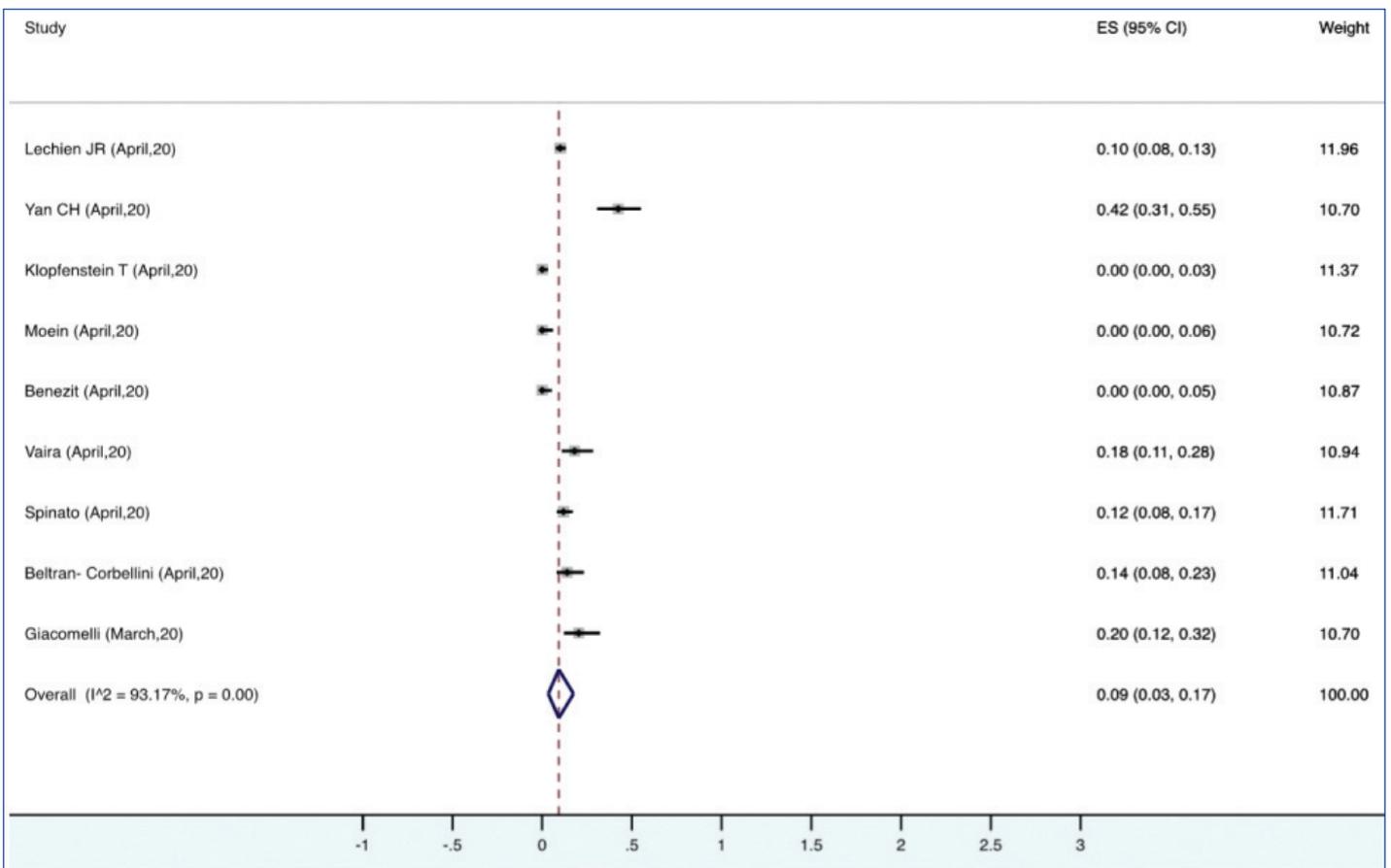
(b)

[Table/Fig-6b]: Forest plot illustrating pooled prevalence of gustatory dysfunction.



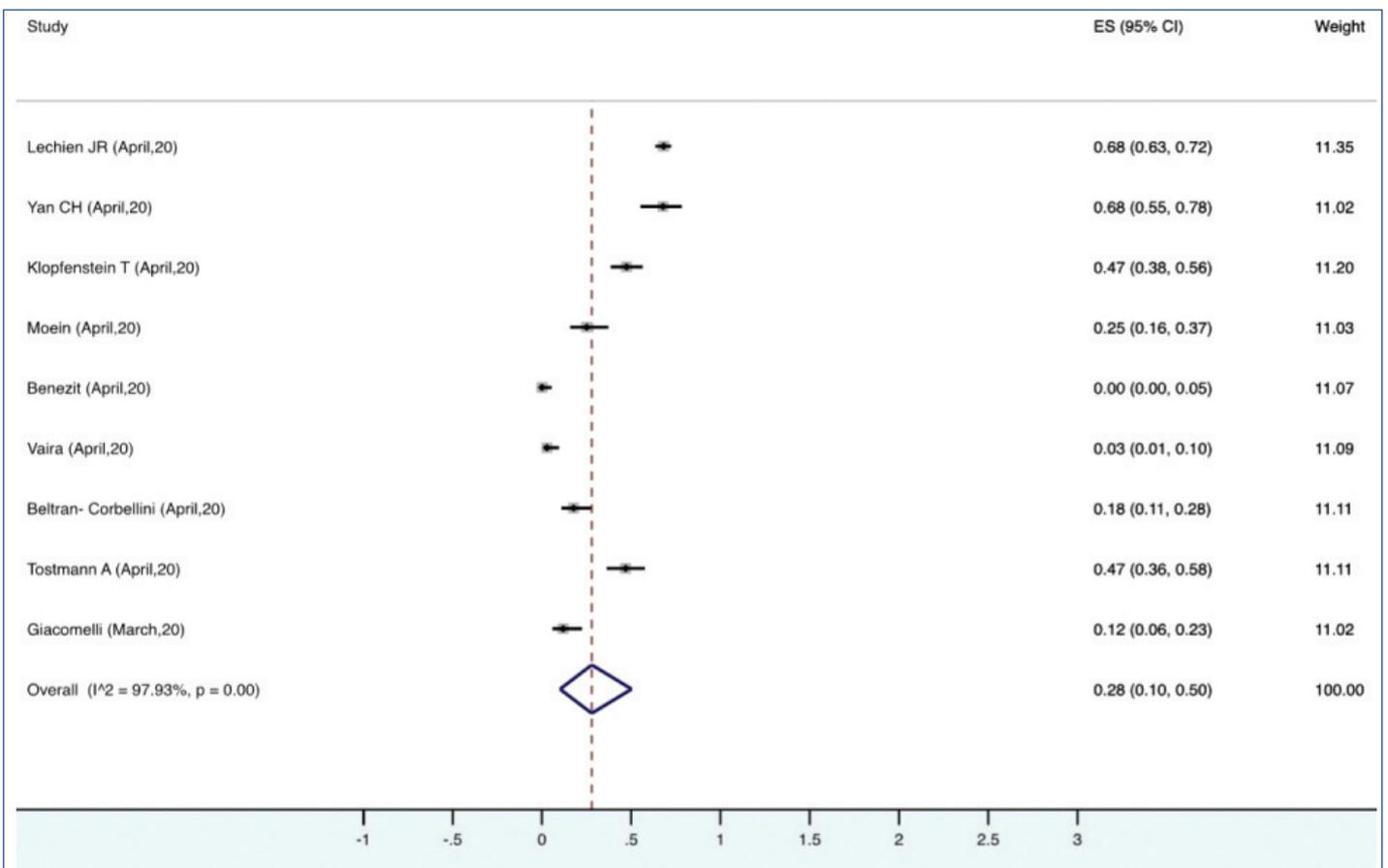
(c)

[Table/Fig-6c]: Forest plot illustrating pooled prevalence of both olfactory and gustatory dysfunction.



(d)

[Table/Fig-6d]: Forest plot illustrating pooled prevalence of olfactory and gustatory dysfunction as presenting symptoms.

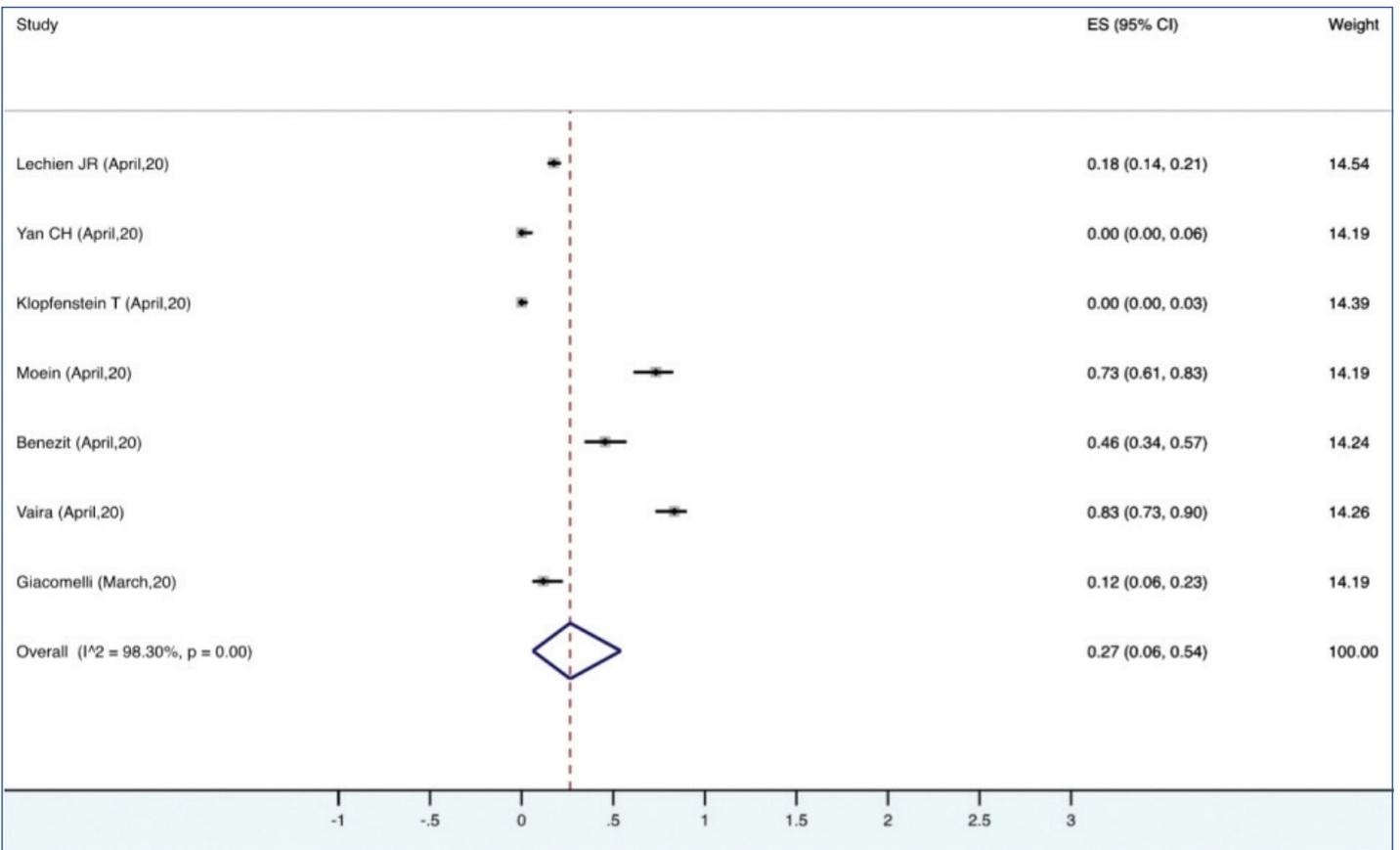


(a)

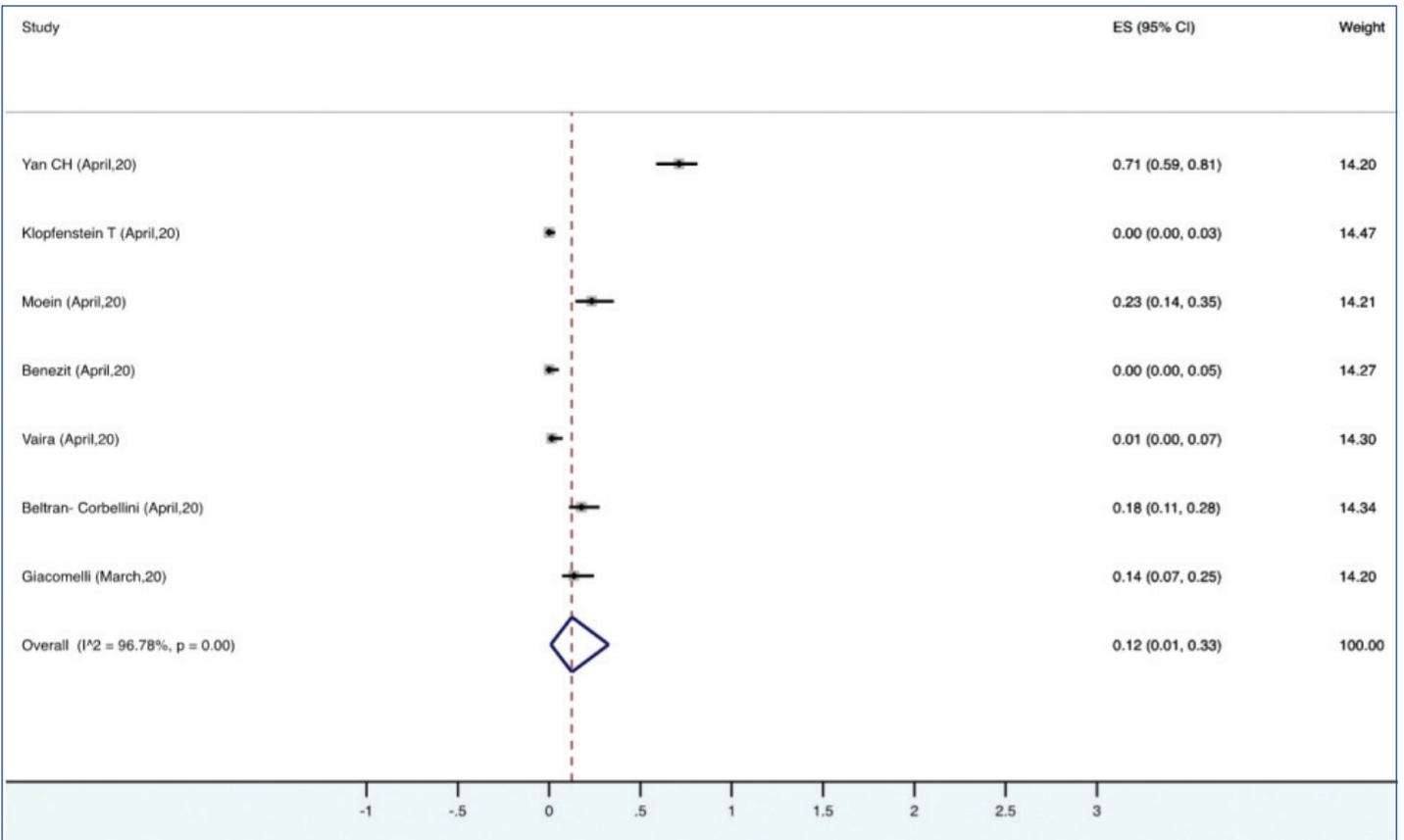
[Table/Fig-7a]: Forest plot depicting pooled prevalence of anosmia.

olfactory and gustatory symptoms show a significant correlation with each other [6]. Yan CH et al., showed that among all

the symptoms, anosmia and ageusia displayed the strongest association with COVID-19 positivity and these symptoms



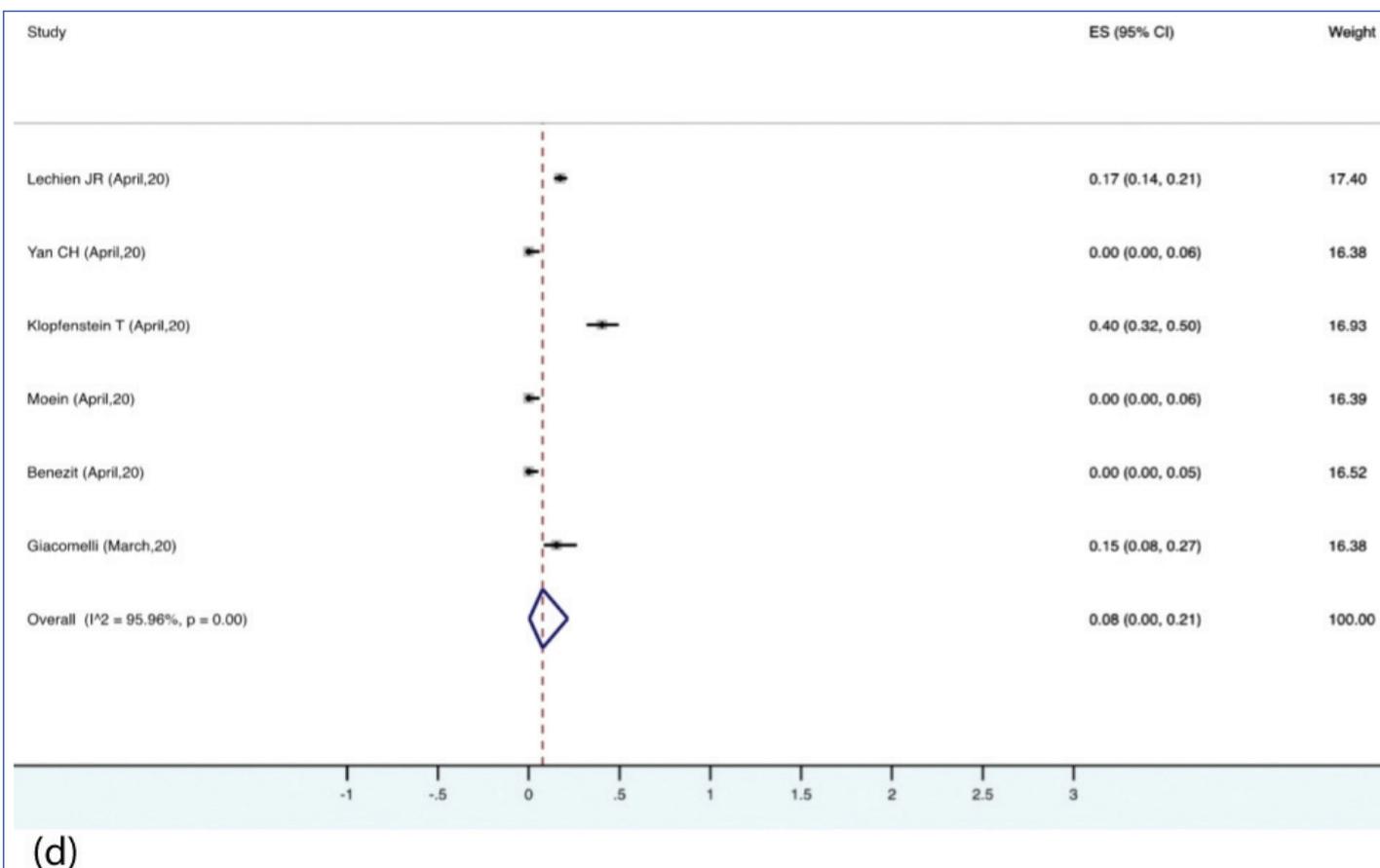
(b) [Table/Fig-7b]: Forest plot depicting pooled prevalence of hyposmia.



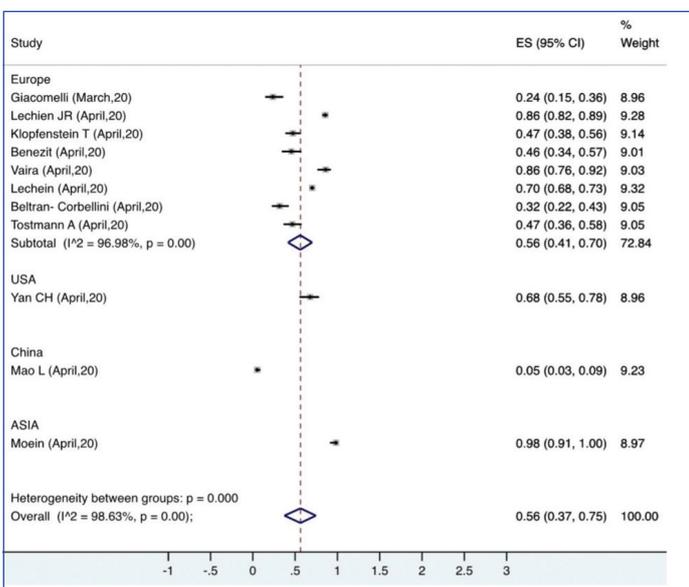
(c) [Table/Fig-7c]: Forest plot depicting pooled prevalence of ageusia.

were 10 times more common than those in COVID-19 negative individuals [17]. This reflects the importance of adding anosmia and ageusia as important components of screening symptoms for COVID-19.

The pooled prevalence of olfactory dysfunction was 56% while that of anosmia and hyposmia was 28% and 27%, respectively [6,16,17,22,27]. It is noteworthy that smell dysfunction in the studies ranged from as low as 5% (Mao L et al.) to 98% (Moein



[Table/Fig-7d]: Forest plot depicting pooled prevalence of dysgeusia.



[Table/Fig-8]: Subgroup analysis for prevalence of olfactory dysfunction based on geographical location.

ST et al.,) with the other authors reporting a smell dysfunction of 23.7%, 85.6%, 67.8%, 47% and 45% [6,16,17,21-23]. Mao L et al., (smell dysfunction-5%) have based their findings on electronic medical records which could have led to under-reporting of minor symptoms such as that related to olfaction [21]. Recent evidence suggests that Angiotensin Converting Enzyme 2 (ACE-2) receptor to which coronavirus binds, might have some diversity across the populations. This may in turn lead to its variable association with SARS-CoV-2. This difference may translate into the difference in symptoms and clinical outcomes of patients that is found among different ethnicities [6,41]. It is noteworthy that in COVID-19 disease, olfactory symptoms were seen without nasal obstruction or rhinorrhoea unlike other viral infections [42]. The aetiology of olfactory and gustatory symptoms in COVID-19 is elusive and

various theories have been proposed for the same [32]. One of the proposed aetiology is the possible neuroinvasive potential of SARS-CoV-2 [43]. Trans-neural penetration of the SARS-CoV virus into the central nervous system through the olfactory bulb has been demonstrated in a mice model [44]. Significant neuronal death has been observed in brain due to rapid spread of SARS-CoV [6]. A similar neuroinvasive potential of the SARS-CoV-2 may have a major role not only in causing OTD but also in causing respiratory failure of patients with COVID-19 [45]. Another proposed mechanism is due to the binding of SARS-CoV-2 to Angiotensin converting enzyme 2 (ACE-2) receptors. Since the taste buds and olfactory epithelium also express ACE-2, SARS-CoV-2 may have a cytopathic effect resulting in these symptoms.

This meta-analysis found gustatory disturbance of 44% in COVID-19 patients. Some studies also reported the type of taste dysfunction as ageusia and dysgeusia, the pooled prevalence of which were 12% and 8%, respectively. In the systematic review, most of the studies reported gustatory dysfunction either in combination with smell dysfunction or in isolation [6,16,17,21-23,30,37,39]. Except for the basic taste types of sour, sweet, salty, umami and bitter, the rest of the gustatory flavours are attributed to the olfactory system. Thus in many cases, taste loss may be attributed to a loss of smell rather than an actual damage to the taste buds [23,46,47].

OTD was reported as presenting symptom with an estimated pooled prevalence of 9% across nine studies [6,16,17,22,23,27,30,39,40]. Since these symptoms have not been identified as screening symptoms by major health organisations, they may often get missed leading to underdiagnosis of COVID-19. Giacomelli A et al., noted taste alteration as an initial symptom before hospitalisation in 91% of the patients [16]. Moreover, a few studies also reported sudden onset anosmia with or without dysgeusia as an isolated symptom of COVID-19 in otherwise asymptomatic patients [19,24,48].

Olfactory disturbances showed a gender predilection towards females across a number of studies [6,16,17]. with the values being statistically significant in the study done by Lechien JR et al., and

Giacomelli A et al., [6,16]. Lechien JR et al., have suggested that this could be due to a possible heightened inflammatory response in females compared to males, warranting further studies to investigate the gender susceptibility to anosmia [6,35].

Many studies assessed smell recovery within a time frame of one week to four weeks. Most studies reported that the smell loss was transient, with a variable recovery after two weeks [6,17,22]. Lechien JR et al., pointed out that smell recovery takes a longer time compared to the recovery of other symptoms [6]. The authors observed a wide amount of heterogeneity in the meta-analysis which is a common finding in most of the studies pertaining to COVID-19 [49]. A subgroup analysis was done based on the prevalence of these symptoms across different countries.

Limitation(s)

This systematic review has various limitations considering the paucity of data available related to olfactory and taste disturbances in COVID-19. Most of the studies included were cross-sectional studies, where the data was collected either retrospectively from medical records or through a survey, without a standard follow-up [16,21,22,27]. The data was mostly collected in the form of a questionnaire except for two studies by Moein ST et al., and Vaira LA et al., which involved an objective testing method [23,39]. Of the studies involving questionnaires, only Lechien JR et al., and Spinato G et al., used standard validated questionnaires [6,40]. Most of the data was collected through internet and phone calls, questioning its reliability. Moein ST et al., reported that of the 85% patients that reported anosmia or severe microsmia, only 35% were aware of their smell dysfunction [23]. From this, it can be inferred that a sizeable population may be unaware of their olfactory disturbances leading to a recall bias in questionnaire-based studies.

CONCLUSION(S)

Since most of the studies were based on self-reported symptoms, more studies with validated objective testing of olfactory and gustatory disturbances in larger sample size are required. It can be concluded that there is a significant association between olfactory and gustatory symptoms and COVID-19 disease. Majority of the studies support the use of these symptoms as screening tools for COVID-19. This could help in early diagnosis and to contain disease transmission, especially from otherwise asymptomatic cases. Considering the ongoing exponential spread of SARS-CoV-2, limited diagnostic tests and scarce health resources worldwide, the authors emphasise the use of olfactory and taste disturbance as early markers of the disease.

REFERENCES

- Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-42.
- WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020 [cited 2020 Apr 27]. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020>.
- WHO COVID-19 Dashboard. World Health Organization c202. [cited 2020 Apr 27]. Available from: <https://covid19.who.int/>.
- Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-207.
- Transmission of SARS-CoV-2: implications for infection prevention precautions. World Health Organization c2021. [cited: 9 July 2020]. Available from: <https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>.
- Lechien JR, Chiesa-Estomba CM, De Siaty 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;277(8):2251-61.
- Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. 2020; 323(14):1406-07.
- Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect*. 2020;80(6):656-65.
- Lovato A, de Filippis C, Marioni G. Upper airway symptoms in coronavirus disease 2019 (COVID-19). *Am J Otolaryngol*. 2020;41(3):102474.
- kaye_covid-19_anosmia_reporting_tool_initial_findings.pdf . [cited 2020 Apr 27]. Available from: https://www.entnet.org/sites/default/files/uploads/kaye_covid-19_anosmia_reporting_tool_initial_findings.pdf.
- Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, et al. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope*. 2007;117(2):272-77.
- Van RD, Verdijk R, Kuiken T. The olfactory nerve: A shortcut for influenza and other viral diseases into the central nervous system. *J Pathol*. 2015;235(2):277-87.
- Walker A, Hopkins C, Surda P. Use of Google Trends to investigate loss-of-smell-related searches during the COVID-19 outbreak. *Int Forum Allergy Rhinol*. 2020;10(7):839-47. doi:10.1002/alr.22580.
- AAO-HNS: Anosmia, hyposmia and dysgeusia symptoms of coronavirus disease. <https://www.entnet.org/content/aaohns-anosmia-hyposmia-and-dysgeusia-symptoms-coronavirus-disease>.
- Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common findings in COVID-19 patients. *The Laryngoscope*. 2020;130(7):1787.
- Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: A cross-sectional study. *Clin Infect Dis*. 2020;71(15):889-90.
- Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*. 2020;10(7):806-13.
- 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? *Ecanermedscience*. 2020;3:14:ed98.
- Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology*. 2020;58(3):299-301.
- Gautier J-F, Ravussin Y. A New symptom of COVID-19: Loss of taste and smell. *Obes Silver Spring Md*. 2020;28(5):848.
- 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;77(6):683-90.
- 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;50(5):436-39.
- 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;10(8):944-50.
- Villalba NL, Mao LY, Ortiz MBA, Sosa ZC, Chahbazian JB, Syrovatkova A, et al. Anosmia and dysgeusia in the absence of other respiratory diseases: Should COVID-19 infection be considered? *Eur J Case Rep Intern Med*. 2020;7(4):001641.
- Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. *Rhinology*. 2020;58(3):295-98.
- Xydakis MS, Dehgani-Mobaraki P, Holbrook EH, Geisthoff UW, Bauer C, Hautefort C, et al. Smell and taste dysfunction in patients with COVID-19. *Lancet Infect Dis*. 2020;20(9):1015-16.
- Bénézit F, Le Turnier P, Declercq C, Paillé C, Revest M, Dubée V, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. *Lancet Infect Dis*. 2020;20(9):1014-15.
- Ollarves-Carrero MF, Rodriguez-Morales AG, Bonilla-Aldana DK, Rodriguez-Morales AJ. Anosmia in a healthcare worker with COVID-19 in Madrid, Spain. *Travel Med Infect Dis*. 2020;35:101666.
- Jang Y, Son H-J, 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;41(9).
- Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-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;27(9):1738-41.
- Tostmann A, Bradley J, Bousema T, Yiek W-K, 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. *Eurosurveillance* 2020;25(16):2000508.
- Wee LE, Chan YFZ, Teo NWW, Chergn 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;277:2389-90. Available from: <https://doi.org/10.1007/s00405-020-05999-5>.
- Pradeep S, Pandya K, Nagappan N, Vidhyadharan S, Hedne N. A systematic review and meta-analysis on olfactory and gustatory symptoms of coronavirus disease (COVID-19). PROSPERO International prospective register of systematic reviews. National Institute of Health Research. 24 April 2020. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181841.
- Study Quality Assessment Tools. National Heart, Lung, and Blood Institute (NHLBI) [Internet]. Available from: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools> [cited 2020 Apr 29].
- Background: Development and Use of Study Quality Assessment Tools. National Heart, Lung, and Blood Institute (NHLBI) [Internet]. Available from: <https://www.nhlbi.nih.gov/node/80102> [cited 2020 May 12].
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
- Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al. Clinical and epidemiological characteristics of 1,420 European patients with mild-to-moderate coronavirus disease 2019. *Journal of Internal Medicine*. 2020;288:335-44.

- [38] Yan CH, Faraji F, Prajapati DP, Ostrand BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. *Int Forum Allergy Rhinol.* 2020;10(7):821-31.
- [39] 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 and Neck-Journal of the Sciences and Specialties of Head and Neck.* 2020;42(6):1252-58.
- [40] 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 [Internet].* 2020 ;323(20):2089-90.
- [41] Li W, Zhang C, Sui J, Kuhn JH, Moore MJ, Luo S, et al. Receptor and viral determinants of SARS-coronavirus adaptation to human ACE2. *EMBO J.* 2005;24(8):1634-43.
- [42] Vukkadala N, Qian ZJ, Holsinger FC, Patel ZM, Rosenthal E. COVID-19 and the otolaryngologist: Preliminary evidence-based review. *The Laryngoscope.* 2020 Mar 26. doi: 10.1002/lary.28672.
- [43] Finsterer J, Stollberger C. Causes of hypogeusia/hyposmia in SARS-CoV2 infected patients. *J Med Virol.* 2020;92(10):1793-94.
- [44] 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(15):7264-75.
- [45] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* 2020;92(6):552-55.
- [46] Deems DA, Doty RL, Settle RG, Moore-Gillon V, Shaman P, Mester AF, et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania smell and taste center. *Arch Otolaryngol Head Neck Surg.* 1991;117(5):519-28.
- [47] Burdach KJ, Doty RL. The effects of mouth movements, swallowing, and spitting on retronasal odor perception. *Physiol Behav.* 1987;41(4):353-56.
- [48] Eliezer M, Hautefort C, Hamel AL, Verillaud B, Herman P, Houdart E, et al. Sudden and complete olfactory loss of function as a possible symptom of COVID-19. *JAMA Otolaryngol Head Neck Surg.* 2020;146(7):674-75.
- [49] Etoom M, Alwardat S, Alwardat M. Issues for conducting meta-analyses in COVID-19. Commentary on "Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis". *J Clin Virol Off Publ Pan Am Soc Clin Virol.* 2020;128:104389.

PARTICULARS OF CONTRIBUTORS:

1. Junior Consultant, Department of Head and Neck Surgical Oncology, Apollo Proton Cancer Center, Chennai, Tamil Nadu, India.
2. Senior Lecturer, Department of Oral and Maxillofacial Surgery, Sri Ramachandra Dental College, Chennai, Tamil Nadu, India.
3. Lecturer, Department of Public Health Dentistry, Goa Dental College, Goa, India.
4. Consultant, Department of Head and Neck Surgical Oncology, Apollo Proton Cancer Center, Chennai, Tamil Nadu, India.
5. Senior Consultant, Department of Head and Neck Surgical Oncology, Apollo Proton Cancer Center, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Kalpa Pandya,
82/1, Second Street, F Block, Anna Nagar East, Chennai, Tamil Nadu, India.
E-mail: kalpa.pandya@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Jul 08, 2020
- Manual Googling: Nov 11, 2020
- iThenticate Software: Dec 28, 2020 (23%)

ETYMOLOGY: Author Origin**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval Obtained for this study? NA
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 07, 2020**Date of Peer Review: **Sep 17, 2020**Date of Acceptance: **Dec 14, 2020**Date of Publishing: **Feb 01, 2021**