Review Article

Olfactory and Gustatory Dysfunction in 2019 Novel Coronavirus: An Updated Systematic Review and Meta-analysis

Marzieh Esmaeili, Fatemeh Abdi[1], Gita Shafiee[2], Hamid Asayesh[3], Zahra Esmaeili Abdar[4], Fereshteh Baygi[5], Mostafa Qorbani[6,7]

Department of Health Information Management, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran, [1]Social Determinants of Health Research Center, Alborz University of Medical Sciences, Karaj, Iran, [2]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran, [3]Department of Medical Emergencies, Qom University of Medical Sciences, Qom, Iran, [4]Dietary Supplements and Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran, [5]Center of Maritime Health and Society, Department of Public Health, University of Southern Denmark, Esbjerg,

Abstract

Background: Evidence showed that partial or complete loss of smell and taste might be a possible primary symptom of the 2019 novel coronavirus (COVID-19). This study aimed to systematically review and pool all available evidence on the olfactory and gustatory dysfunction in COVID-19 patients. **Methods:** In this systematic review, a comprehensive search was carried out systematically through e-databases including PubMed, EMBASE, Scopus, and Web of Science (WoS); that was limited to English-language studies published from 2019 up to 6th May 2020. Afterward, all studies reported the taste and smell dysfunction in the COVID-19 patients were included. The quality of the studies was assessed by the Mixed Methods Appraisal Tool (MMAT). The pooled prevalence of olfactory and gustatory dysfunction was estimated using the random effects meta-analysis method. **Results:** Among 28 eligible included studies in this systematic review, finally, 22 studies met the eligibility criteria and were included in the meta-analysis. According to the random effect meta-analysis, the global pooled prevalence (95% confidence interval) of any olfactory dysfunction, anosmia, and hyposmia was 55% (40%-70%), 40% (22%-57%), and 40% (20%-61%) respectively. The pooled estimated prevalence of any gustatory dysfunction, ageusia, and dysgeusia was 41% (23%-59%), 31% (3%-59%), and 34% (19%-48%) respectively. **Conclusions:** Olfactory and gustatory dysfunction is prevalent among COVID-19 patients. Therefore, olfactory and gustatory dysfunction seems to be part of important symptoms and notify for the diagnosis of COVID-19, especially in the early phase of the infection.

Keywords: *Ageusia, anosmia, COVID-19, sensation disorder, taste, and smell impairment*

Background

In 2019, a new viral pandemic disease began from East Asia and rapidly spread to the world.[1] The World Health Organization (WHO) named this disease COVID-19, determined by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[2] There were 3,855,788 confirmed cases of COVID-19 and 265,862 deaths globally at the time of the writing of this article.[3]

Due to the newly known COVID-19, it is expected that different aspects of the disease will be described daily.[4] The common symptoms of this disease are fever (98%), dry cough (76%), dyspnea (55%), and fatigue/myalgia (44%). Also, lab findings and lung CT abnormalities can help to identify COVID-19.[5-7] In the moderate to severe infection, several organs and systems can be affected, included respiratory, cardiovascular, hematologic, immune systems, kidney, liver, and even skin.[8-10] However, recent reports showed an association between COVID-19 and various neurologic manifestations that involved central and peripheral nervous system (CNS & PNS). A study in China reported that 36.4% of patients with severe infection had neurologic signs.[11] Olfactory and gustatory dysfunction as peripheral nervous system manifestations has been reported in previous studies.[12,13] However, the main pathogenesis is unclear; it seems that epithelial impairment and CNS involvement after the respiratory tract infection with coronaviruses have been presented.[14] Numerous reports from Germany, Iran, Italy, and the US have been shown that anosmia occurs in 34% to 68% of COVID-19 positive patients.[15-19] Evidence showed that partial or complete loss of smell and taste might be a possible primary symptom of the infection even in mild cases would not meet the criteria for testing and therefore they are carriers.[1] The current systematic review and meta-analysis[20] with limited studies showed that olfactory and gustatory dysfunction is

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Denmark, [6]Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran, [7]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence: *Dr. Mostafa Qorbani,*
Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran.
E-mail: mqorbani1379@yahoo.com

common symptom in patients with COVID-19. Therefore, the smell and taste impairment may be an important symptom of infection and a significant factor of COVID-19 carriers.

The primary aim of this systematic review was to evaluate the all available evidences on the olfactory and gustatory dysfunction in COVID-19 patients. The secondary aim of this review was to perform an update meta-analysis to pool the prevalence of olfactory and taste dysfunction in COVID-19 patients.

Methods

This study is outlined based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21,22]

Eligibility criteria

The inclusion criteria were considered for selection of studies with respect to the review's purposes; they are as follows:

- Published in the English language
- Full-text available
- Reported the prevalence of olfactory and taste disorders related to the positive COVID-19 patients.

Information sources and Search strategy

To acquire the relevant studies, four e-databases including PubMed, EMBASE, Scopus, and Web of Science (WoS) were systematically searched. The search strategy comprising of two concepts, the 2019 novel coronavirus disease and the sense of smell and taste, was designed by two authors (M.E. & M.Q.). Moreover, the results were limited to the English-language research articles published from 2019 up to 6th May 2020. The building process of the search query in PubMed with the keywords and their synonyms are represented in Table 1. A similar search query was taken for other databases based on their facilities.

Study selection

The EndNote reference management software was applied to manage the acquired articles. At first, removing duplicate articles was done through the software and also checked manually. Then, in the screening phase, the title and abstract of the studies were examined with respect to the including criteria. Afterward, if needed the full texts were screened in details. The selection process was done independently by two authors (M.E. & M.Q.). They came to an agreement about the conflicting results.

Quality assessment

The methodological quality of the included studies in this review was conducted by the Mixed Methods Appraisal Tool (MMAT).[23,24] The quality assessment was conducted independently by two authors (M.E. & M.Q.). The MMAT was developed to appraise different empirical studies that categorized in five categories including qualitative, randomized controlled trial, nonrandomized, quantitative descriptive and mixed methods studies. This tool consists of 5 items for each category - each of which could be marked as Yes, No, or Can't tell. Based on the scoring system, the score 1 assigns to Yes and the score 0 to all other answers. In other words, the total score would be the percentage of affirmative responses. To evaluate the final scores qualitatively, scores above half (more than 50%) are considered as high quality.

Statistical analysis

Qualitative synthesis (meta-analysis) was performed to pool the prevalence of olfactory and gustatory dysfunction in patients with COVID-19. Cochrane Q test and I square statistics were used to assess the heterogeneity of reported prevalence among the studies. A value of $P < 0.1$ was regarded as statistically significant for heterogeneity assessment. Due to severe heterogeneity among studies regarding reported prevalence, the pooled prevalence was estimated using a random-effect meta-analysis

Table 1: PubMed search query

Search	Strategy
1.	"covid 19" [Title/Abstract] OR "covid-19" [Title/Abstract] OR "*covid-19*" [Title/Abstract] OR "*covid*"[Title/Abstract] OR "*SARS-CoV-2*"[Title/Abstract] OR "*2019-nCoV*"[Title/Abstract] OR "*novel coronavirus*"[Title/Abstract] OR "*new coronavirus*"[Title/Abstract] OR "*coronavirus*"[Title/Abstract]
2.	"smell*"[Title/Abstract] OR "olfact*"[Title/Abstract] OR "anosmia*"[Title/Abstract] OR "hyposmia*"[Title/Abstract] OR "taste*"[Title/Abstract] OR "ageusia*"[Title/Abstract]) OR "dysgeusia*"[Title/Abstract] OR "hypogeusia*" [Title/Abstract] OR "gustative*"[Title/Abstract] OR "OTD"[Title/Abstract] OR "sensation disorder*"[Title/Abstract] OR "chemosensory disorder*"[Title/Abstract] OR "chemical sense*"[Title/Abstract] OR "upper airway symptom*"[Title/Abstract] OR "cacosmia*" [Title/Abstract] OR "dysosmia*" [Title/Abstract]
3.	#1 AND #2
Filters	English; Publication date from 2019 up to 6th May 2020

proposed by Der-Simonian and Laird method. Subgroup meta-analysis was performed according to study design (case-control/cross-sectional) and measurement method of olfactory and/or gustatory dysfunction (questionnaire, medical records, and test). Meta-regression analysis was used to assess the effect of study covariates, including the quality score, measurement tool. To assess the effect of each study on over-all prevalence, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis. Statistical analysis was performed using STATA software, V.11.1 (StataCorp LP, College Station, Texas, USA).

Results

Search results

The systematic search resulted in 160 potentially relevant articles. They were obtained from four e-databases including PubMed (65), EMBASE (41), Scopus (43), and WoS (11). After leaving out 84 duplicated studies, the titles and abstracts of the rest were examined, if needed their full texts were also checked. Hence, during the screening process, 56 studies did not meet the eligibility criteria and one study was excluded due to inaccessibility to the full text. Afterward, the reference list of related studies was examined for finding the other studies. Finally, 28 articles were included in qualitative review; then in quantitative review six studies were excluded due to reporting the olfactory and gustatory dysfunction in COVID-19 patients with sudden loss of smell (SLS) (5 studies) or individuals with olfactory and gustatory dysfunction without known COVID-19 status. The searching and selecting process is shown in the PRISMA diagram, Figure 1. Characteristics of the 28 selected studies including study characteristics, outcome characteristics, findings, and quality score are shown in Table 2.

Quality assessment

The included studies consist of a variety of study designs - cross-sectional (n = 22);[11,12,16-19,25-40] case-control (n = 3);[41-43] case-report and case series (n = 3) studies.[44-46] Two categories of the MMAT were employed based on the study design to examine the methodological quality of these studies; quantitative non-randomized category for cross-sectional and case-control studies and quantitative descriptive category for case-report and case series ones.

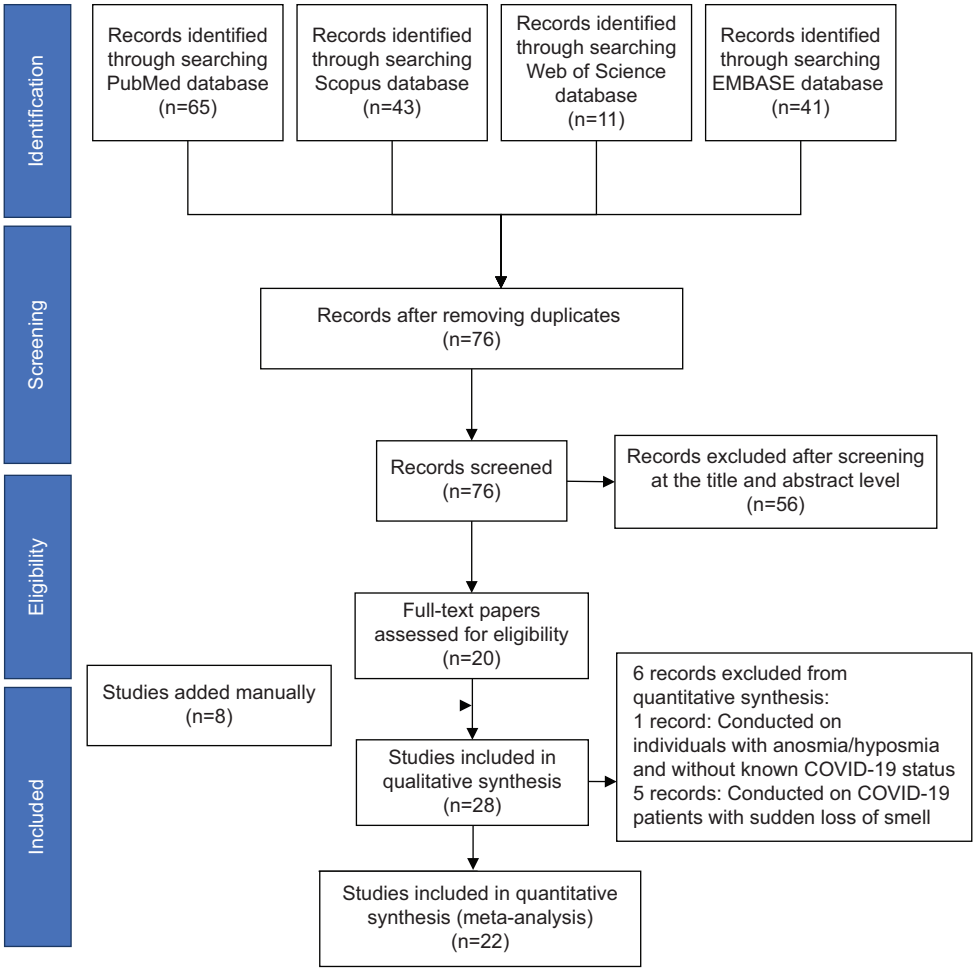

Figure 1: PRISMA diagram for searching resources

Table 2: Characteristics of the included studies

ID	Study characteristics				Outcome characteristics	
	Author [ref]	Country/Study time	Study type	Population/sample size	Reported outcomes	Measurements tool (range of score)
1	Yan *et al.*[19]	USA, California March 31 - April 3, 2020	Cross-sectional	Confirmed Covid-19 patients: 59	Olfactory impairment Anosmia Gustatory impairment Ageusia	Online questionnaire (0-270)
2	Giacomelli *et al.*[18]	Italy, Milan 19 March 2020	Cross-sectional	Covid-19- Positive hospitalized: 59	Olfactory disorder Hyposmia Anosmia Taste disorder Dysgeusia Ageusia Olfactory and Taste disorders (OTDs)	Questionnaire
3	Klopfenstein *et al.*[33]	France 1-17 March, 2020	Cross-sectional	Covid-19- Positive: 114	Anosmia Dysgeusia	Extracted from medical records
4	Mao *et al.*[11]	China January 16 - February 19, 2020	Cross-sectional	Covid-19- Positive hospitalized: T: 214 Severe: 88 Nonsevere: 126	Taste impairment Smell impairment	Extracted from medical records
5	Lechien *et al.*[12]	Some European countries (Belgium, France, Spain, Italy)[a] NR	Cross-sectional	Mild-to-moderate COVID-19 patients: 417 From 12 European hospitals	Olfactory dysfunction Anosmia Hyposmia Gustatory dysfunction Reduced/discontinued taste ability Distorted taste ability	Online questionnaire[b]
6	Moein *et al.*[43]	Iran, Tehran 21-23 March, or March 31 - April 5, 2020	Case-control	Covid-19- Positive: 60	Olfactory dysfunction Anosmia Hyopsomia Smell Gustatory dysfunction Taste loss	Odorant test- UPSIT (0-40) Self-report
7	Bénézit *et al.*[30]	France 15-18 March, 2020	Cross-sectional	Covid-19- Positive: 68	Olfactory disorder Hyposmia Taste disorder Hypogeusia	Online questionnaire

Contd...

Table 2: Contd...

ID	Study characteristics				Outcome characteristics	
	Author [ref]	**Country/Study time**	**Study type**	**Population/sample size**	**Reported outcomes**	**Measurements tool (range of score)**
8	Lechien *et al*.[34]	Some European countries a March 22 - April 10, 2020	Multicenter, Cross-sectional	Covid-19- Positive: 1420 From 18 European hospitals	Loss of smell Gustatory dysfunction	Online questionnaire[b]
9	Beltran-Corbellini *et al*.[42]	Spain, Madrid 23-25 March, 2020	Case-control	Covid-19- Positive hospitalized: 79	Smell disorder: Anosmia Hyposmia Dysosmia Taste disorder: Ageusia Hypogeusia Dysgeusia Capable of distinguish sweetness/ saltiness/bitterness	Questionnaire
10	Spinato *et al*.[36]	Italy, Treviso and Belluno provinces 19-22 March, 2020	Cross-sectional	Covid-19- Positive: 202	Alteration of sense of smell or taste	SNOT-22: None (0) very mild (1) mild or slight (2) moderate (3) Severe (4) As bad as it can be (5)
11	Aggarwal *et al*.[29]	USA March 1 - April 4, 2020	Cross-sectional	Covid-19- Positive: 16	Loss of smell Anosmia Loss of taste Dysgeusia	Extracted from EMR
12	Kaye *et al*.[31]	USA, Mexico, Italy, UK, Other March 25 - April 3, 2020	Cross-sectional	Covid-19- patient: 237	Anosmia	Extracted from the COVID-19 Anosmia Reporting Tool
13	Vaira *et al*.[38]	Italy March 31 - April 6, 2020	Cross-sectional	Covid-19- Positive: 72	Olfactory disorder Hyposmia Anosmia Gustatory disorder Dysgeusia Ageusia	Olfaction test- CCCRC (0-100) gustatory test (0-4)

Contd...

Table 2: Contd...

ID	Study characteristics				Outcome characteristics	
	Author [ref]	Country/Study time	Study type	Population/sample size	Reported outcomes	Measurements tool (range of score)
14	Luers *et al.*[35]	Germany 22-28 March, 2020	Cross-sectional	Covid-19- Positive:72	Olfactory disorder Hyposmia Anosmia Gustatory disorder Dysgeusia Ageusia	Questionnaire
15	Yan *et al.*[40]	USA, California March 3 - April 8, 2020	Cross-sectional	Covid-19- Positive: 128	Olfactory impairment Anosmia/hyposmia Gustatory impairment Dysgeusia	Extracted from EMR or by email/call
16	Tostmann *et al.*[37]	The Netherlands 10-29 March, 2020	Cross-sectional	Covid-19- Positive (Healthcare workers): 79	Anosmia	Online questionnaire
17	Wee *et al.*[39]	Singapore March 26 - April 10, 2020	Cross-sectional	Covid-19- Positive: 154	Olfactory or taste disorders	Questionnaire
18	Bagheri *et al.*[17]*	Iran, All provinces 12-17 March, 2020	Cross-sectional	Volunteer cases with self-reported anosmia/hyposmia in the last month: 10069	Olfactory dysfunction Anosmia Hyposmia	Online checklist
19	Kim *et al.*[32]*	South Korea	Cross-sectional	Covid-19 Positive: 172	Hyposmia Hypogeusia	Questionnaire
20	Menni *et al.*[16]*	UK 24-29 March, 2020	Cross-sectional	Covid-19- Positive: 579	Loss of taste and smell	The COVID RADAR Symptom Tracker app[d]
21	Lechien *et al.*[26]*	Some European countries a	Cross-sectional	All cases with SLS: 78 psychophysical olfactory evaluation in SLS patients: 46	Dysgeusia: Smelling dysfunction Anosmia Hyposmia	Sniffin Sticks test (0-12)
22	Hornuss *et al.*[41]*	Germany April 2020	Case-control	Hospitalized COVID-19 patients: 45	Smelling dysfunction Anosmia Hyposmia	Sniffin Sticks test (0-12)
23	Levinson *et al.*[28]*	Israel 10-23 March, 2020	Cross-sectional	Hospitalized mild COVID-19 patients: 42	Anosmia Dysgeusia	Extracted from EMR
24	Haehner *et al.*[25]*	Germany April 2020	Cross-sectional	Covid-19 Positive: 34	Sudden smell and/or taste loss	Questionnaire with visual analogue scale (0-10)
25	Lechien *et al.*[27]*	Belgium NR	Cross-sectional	Patients with SLS and COVID-19 Positive: 28	Olfactory dysfunction: Aroma disorder Cacosmia	Self-report by an online questionnaire[b] Sniffin stick test (0-12) SNOT-22

Contd...

Table 2: Contd...

ID	Study characteristics				Outcome characteristics	
	Author [ref]	Country/Study time	Study type	Population/sample size	Reported outcomes	Measurements tool (range of score)
					Phantosmia Anosmia Hyposmia Gustatory Dysfunction: Dysgeusia	
26	Gilani *et al.*[45]	Iran March 11 - April 1, 2020	Case series	Patients with SLS: T: 8 COVID-19 Positive: 5 SLS unknown COVID-19: 3	Anosmia Ageusia	Self-report
27	Gane *et al.*[44]	UK NR	Case report and Case series	Patients with SLS: T: 11 COVID-19 Positive: 1 Unknown COVID-19: 10	NR	Self-report
28	Marchese-Ragona *et al.*[46]*	Italy NR	Case series	Patients with SLS: 6 SC: 5	Hyposmia Hypogeusia	Supra-threshold six odours smell test

ID	Findings			Other main findings	QS (0-100%)
	Prevalence in confirmed cases				
	Any olfactory dysfunction	Any gustatory dysfunction	Olfactory and/or gustatory dysfunction		
1	Anosmia: 67.7%	Ageusia: 71.1%	NR	NR	80%
2	Overall: 23.7% Hyposmia: 11.8% Anosmia: 11.8%	Overall: 28.8% Dysgeusia: 15.2% Ageusia: 13.5%	Overall: 18.6% Dysgeusia and hyposmia: 3.4% Dysgeusia and anosmia: 3.4% Ageusia and hyposmia: 3.4% Ageusia and anosmia: 8.5%	NR	60%
3	Anosmia 47.3%	NR	Anosmia and dysgeusia: 40.3%	NR	60%
4	Overall: 5.1% Severe: 3.4% Non-severe: 6.3%	Overall: 5.6% Severe: 3.4% Non-severe: 7.1%	NR	NR	60%
5	Overall: 85.6% Anosmia: 68.1% Hyposmia: 17.5% Phantosmia: 12.6% Parosmia: 32.4%	Overall: 88.8% Reduced/discontinued taste ability: 70.1% Distorted taste ability: 18.7	Overall: 80.8% Gustatory dysfunction and anosmia: 64.2% Gustatory dysfunction and hyposmia: 16.5%	NR	60%

Contd...

Table 2: Contd...

ID	Findings			Other main findings	QS (0-100%)
	Prevalence in confirmed cases				
	Any olfactory dysfunction	Any gustatory dysfunction	Olfactory and/or gustatory dysfunction		
6	Overall: 98% Anosmia: 25% Hyopsomia: 73% Self-report Smell loss: 28.3%	Self-report Taste loss: 23.3%	Self-report Smell and taste loss: 16.6%	NR	100%
7	Hyposmia: 45.5%	Hypogeusia: 61.7%	Hypogeusia and Hyposmia: 42.6%	NR	60%
8	Anosmia: 70.2%	Any gustatory dysfunction: 54.2%	NR	NR	60%
9	Overall: 31.6% Anosmia: 17.7% Hyposmia: 11.3% Dysosmia: 2.5%	Overall: 35.4% Ageusia: 17.7% Hypogeusia: 8.8% Dysgeusia: 10.1% Capable of distinguish sweetness/ saltiness/bitterness: 24.0%	39.2%	NR	80%
10	NR	NR	Alteration of sense of smell or taste: 64.3% very mild: 2.4% mild/slight: 11.3% moderate: 13.3% severe: 13.3% as bad as it can be: 23.7%	NR	60%
11	Anosmia: 18.7%	Dysgeusia: 18.7%	18.7%	NR	60%
12	Anosmia: 72.5%		Alteration of sense of smell or taste: 64.3%	NR	60%
13	Overall: 83.2% Anosmia: 2.7% Hyposmia: 80.5%	Overall: 48.6% Ageusia: 1.3% Dysgeusia: 47.2%	41.7%	NR	80%
14	73.6%	69.4%	68.0%	NR	60%
15	58.5%	Dysgeusia: 54.6%	NR	NR	60%
16	Anosmia: 46.8%	NR	NR	NR	60%
17	NR	NR	Olfactory or taste disorders: 22.7%	NR	60%
18	NR	NR	NR	Strong correlation between the number of olfactory disorder and reported COVID-19 patients in all provinces.	60%
19	39.5%	33.7%	NR	NR	60%

Contd...

Table 2: Contd...

ID	Findings			Other main findings	QS (0-100%)
	Prevalence in confirmed cases				
	Any olfactory dysfunction	Any gustatory dysfunction	Olfactory and/or gustatory dysfunction		
20	NR	NR	59.4%	NR	60%
21	Overall: 76% Anosmia: 52% Hyposmia: 24%	Dysgeusia: 67.9	NR	NR	80%
22	Overall: 84.4% Anosmia: 40.0% Hyposmia: 44.4%	NR	NR	NR	80%
23	Anosmia: 35.7%	Dysgeusia: 33.3%	33.3%	NR	60%
24	61.7%	NR	NR	NR	60%
25	Overall: 85.7% Anosmia: 53.6% Hyposmia: 21.4%	Dysgeusia: 60.1%	NR	NR	80%
26	NA	Ageusia: 2 of unknown COVID-19 patients	NR	NR	40%
27	NA	NR	NR	NR	40%
28	NA	Hypogeusia: All cases except one SC	NR	NR	40%

QS=Quality score, OTD=Olfactory or taste disorders, T=Total, aOR=Adjusted odds ratio, OR=Odds ratio, NA=Not applicable, NR=Not reported, UPSIT=The University of Pennsylvania Smell Identification Test, SNOT-22=The Sino-nasal Outcome Test 22, EMR=electronic medical records, CCCRC=Connecticut Chemosensory Clinical Research Center olfactory test, SLS=Sudden loss of smellm SC=Strict contact with lab-positive COVID-19; *Not peer-reviewed. [a]Carried out by the COVID-19. Task Force of YO-IFOS (the Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies). [b]The questionnaire was created with Professional Survey Monkey. [c]The survey was developed by the AAO-HNS (American Academy of Otolaryngology-Head and Neck Surgery) Infectious Disease Committee and Patient Safety and Quality Improvement Committee). [d]Developed by Zoe Global Limited and King's College London

Of the 28 included studies, one[43] had a MMAT score of 100%, six.[19,26,27,38,41,42] scored 80%, three[44-46] scored 40% and the rest[11,12,16-18,25,28-37,39-40] had a MMAT score of 60%, Table 2. The most frequent shortcomings in the quality assessment were an inappropriate or not-reported method for measuring exposures and controlling confounders [Appendix 1 - Tables 1 and 2].

Qualitative synthesis

The characteristics of the eligible studies are summarized in Table 2. All 28 included studies in this review were investigated the olfactory and gustatory dysfunction during the COVID-19 outbreak, from January till April 2020. Most of these studies (about 61%, 17/28)[12,16,18,26,27,30,33-38,41,42,44,46] were carried out in the European countries including Italy (5), Germany (3), UK (2), Belgium (1), France (1), Spain (1), the Netherlands (1), and three joint studies; and also in several Asian countries (about 25%, 7/28)[11,17,28,32,39,43,45] including Iran (3), Singapore (1), China (1), South Korea (1), and Israel (1); and in the USA (about 11%, 3/28);[19,29,40] and one study[31] was conducted in European and American countries jointly.

Olfactory and gustatory dysfunction measurement

Olfactory and gustatory dysfunction was measured using different methods. The most common method was the self-report. Self- report could be done through different ways: an online questionnaire,[12,19,27,30,34,37] non-online questionnaire,[18,32,35,39,42,43] online checklist,[17] the COVID RADAR Symptom Tracker app,[16] visual analogue scale (VAS),[25] archived medical records,[11,40] or verbally.[44,45] Four studies[28,29,31,33] did not report how to measure, just extracted from medical records. In three studies,[26,27,41] the Sniffin' Sticks screening test for smelling disorders was used to perform psychophysical olfactory evaluation. The other methods contain: The SNOT-22 test to grade symptom severity,[27,36] the CCCRC test to assess Olfactory function,[38] and the supra-threshold six odors smell test.[46]

Epidemiological characteristics of included studies

Of the 28 eligible studies, 22 reported the prevalence of the olfactory and/or gustatory dysfunction in the COVID-19 patients, five studies described the olfactory and/or gustatory dysfunction in the COVID-19 patients with SLS[26,27,44-46] and one study ecologically assessed the correlation between the number of subjects with olfactory dysfunction and the number of confirmed COVID-19 patients in all provinces of Iran.[17] They were different in design and settings. Majority study design was cross-sectional (about 79%, 22/28);[11,12,16-19,25-40] then case-control (about 11%, 3/25) [41-43] and three case report and case series (about 11%, 3/28). [44-46] The sample size of them except case report and case series, ranged from 16[29] to 10069.[17]

Regardless of the case report and case series studies: the sample size ranged from 16[29] to 10069;[17] the prevalence of the olfactory dysfunction reported by 88% (22/25); the taste disorder reported by 60% (15/25); the olfactory and gustatory dysfunction reported by 44% (11/25); olfactory or gustatory dysfunction reported by 8% (2/25). The presented olfactory or gustatory dysfunction prevalence in Italy[36] and Singapore[39] were 64.3% and 22.7% respectively; while the presented olfactory and gustatory dysfunction prevalence ranged from 16.6% to 80.8%.

The highest reported prevalence of olfactory dysfunction in European, Asian countries, and the USA were 85.7%,[27] 98%,[43] 67.7%[19] respectively; and also the highest occurred prevalence of gustatory dysfunction in European, Asian countries, and the USA were 88.8%,[12] 33.7%,[32] 71.1%[19] respectively.

Quantitative synthesis

Results of meta-analysis

The results of meta-analysis of the prevalence of olfactory and gustatory dysfunction according to study design, measurement tool and dysfunction type are shown in Table 3. The total sample size of the included studies in meta-analysis was 4322. The eligible studies for estimation of the prevalence of any olfactory dysfunction, anosmia and hyposmia were 19, 13, and 7, respectively. According to the random effect meta-analysis, the global pooled prevalence (95% CI) of any olfactory dysfunction, anosmia and hyposmia was 55% (40%-70%), 40% (22%-57%) and 40% (20%-61%) respectively. Appendix 2 - Figures 1-3 show the forest plot of eligible studies for the estimation of olfactory dysfunction, anosmia and hyposmia prevalence. Prevalence (95% CI) of olfactory dysfunction in the case control studies (prevalence: 97%; 95% CI: 94-100) was significantly higher than the cross-sectional studies (prevalence: 51%; 95% CI: 35-66).

The included studies to estimate the prevalence of any gustatory dysfunction, ageusia and dysgeusia were 14 (n = 2878), 7 (*n* = 762), and 7 (*n* = 845) respectively. The pooled estimated prevalence of any gustatory dysfunction, ageusia and dysgeusia was 41% (95% CI: 23%-59%), 31% (95% CI: 3%-59%) and 34% (95% CI: 19%-48%) respectively. Combination of olfactory and/or gustatory dysfunction prevalence was reported in 13 studies (*n* = 1934) demonstrating 42% (95% CI: 29%-55%) prevalence in patients with COVID-19. Appendix 2 - Figure 4 and 6 show the forest plot of the prevalence of any gustatory dysfunction, ageusia dysgusia in patients with COVID-19.

Sensitivity analysis

Sensitivity analyses were performed to assess the effect of each individual study on pooled prevalence of olfactory

Table 3: Meta-analysis of the prevalence of olfactory and gustatory impairments according to study design, measurement tool and impairment type

Impairment	Study ID	Sample size	Pooled prevalence % (95% CI)	Model	Heterogeneity assessment		
					I^2%	Q test	*P*
Olfactory impairment							
Overall (any impairment)	19	3387	55 (40-70)	Random	99.25	2387	<0.001
By study design							
Cross-sectional	17	3282	51 (35-66)	Random	99.1	1768	<0.001
Case control	2	105	97 (94-100)	Fixed	----	----	----
By measurement tool							
Questionnaire	10	2459	55 (43-67)	Random	97.0	306.8	<0.001
Medical records	6	751	38 (9-68)	Random	99.0	513.1	<0.001
Olfaction test	3	177	96 (93-98)	fixed	----	----	----
By type of dysfunction							
Anosmia	13	2700	40 (22-57)	Random	98.9	1183	<0.001
Hyposmia	7	800	40 (20-61)	Random	97.7	272	0.07
Gustatory impairment							
Overall (any impairment)	14	2878	41 (23-59)	Random	99.3	1983	<0.001
By study design							
Cross-sectional	13	2818	42 (24-61)	Random	99.3	1983	<0.001
Case-control	1	60	23 (14-35)	--------	-------	-------	--------
By measurement tool							
Questionnaire	8	2346	48 (17-79)	Random	99.6	1824	<0.001
Medical records	4	400	28 (2-57)	Random	99.6	1824	<0.001
Test	2	132	35 (27-43)	fixed	----	----	----
By type of dysfunction							
Ageusia	7	762	31 (3-59)	Random	99.2	778	<0.001
Dysgeusia	7	845	34 (19-48)	Random	95.9	145.9	<0.001
Olfactory and/or gustatory	13	1934	42 (29-55)	Random	97.3	453.6	<0.001

and gustatory dysfunction. The results showed that no significant change in the pooled prevalence of olfactory and gustatory dysfunction was found in the included studies ($P > 0.05$).

Meta-regression

Results of meta-regression analysis demonstrated that effect of quality score, study design and measurement tool on reported prevalence of olfactory and gustatory dysfunction was not statistically significant ($P > 0.05$).

Discussion

The presented study systematically reviewed the literature to evaluate all available evidence on the olfactory and gustatory dysfunction in the COVID-19 patients as well as to perform an updated meta-analysis to pool the prevalence of olfactory and gustatory dysfunction in them. Of the 28 included studies, five studies described the olfactory and/or gustatory dysfunction in COVID-19 patients with SLS and one study ecologically assessed the correlation between the number of subjects with olfactory dysfunction and the number of confirmed COVID-19 patients in all provinces of Iran.

In the current updated meta-analysis, the global pooled prevalence (95% confidence interval) of any olfactory dysfunction, anosmia and hyposmia was 55%, 40% and 40% respectively. Also, the pooled estimated prevalence of any gustatory dysfunction, ageusia and dysgeusia was 41%, 31% and 34% respectively. These findings were concordant with previous meta-analysis by Tong *et al*.[20] Previous meta-analysis with ten included studies showed that prevalence of olfactory and gustatory dysfunction was 52.73% (95% CI, 29.64%-75.23%) and 43.93% (95% CI, 20.46%-68.95%) among patients with COVID-19.

As expected from initial observations in the world, COVID-19 patients presented with anosmia and ageusia among other clinical features. This was consistently found in this meta-analysis study. The result of our study suggested that olfactory dysfunction was prevalent in approximately 55% of the patients; and taste dysfunction were present in approximately 40%, of the cases, respectively. In various studies, it has been observed that a relative decrease of sense of smell/taste in the early stages of COVID-19 infection occurs in patients with COVID -19 and it is considered as one of the clinical signs of the noted virus.[19] Since the initial reports from China, international reports on COVID-19 patients have been growing, representing a 5% to 85% range of loss of smell sense.[47] In a study on 59 patients with COVID-19 in Italy, 34% of patients reported impaired sense of smell or taste and 19% of them conveyed an impairment of both senses.[18]

Considering, an increasing number of COVID-19 patients stated sudden loss of smell and taste, therefore it is likely that anosmia and ageusia are associated in patients with COVID-19.[48,49] It has been reported that more than a third of patients with COVID-19 have experienced neurological symptoms such as involvement of the central and peripheral nervous system. The most common complaints in patients with clinical manifestations of problems in the peripheral nervous system were the impairment of taste and smell.[50]

In the qualitative synthesis, the olfactory and gustatory dysfunction prevalence ranged variously from 16.6% to 80.8%. According to a study which has been the outcome of knowledge synthesis of 100 million biomedical documents, it was perceived that cells of keratinocytes of the tongue and olfactory epithelial cells were likely to be less important targets for SARS-CoV-2 infection. This is related to reports of loss of sense of smell and taste as primary indicators of COVID-19 infection in asymptomatic patients. In an animal model in which the immune system was suppressed by the SARS-CoV infection, a slight degeneration of the olfactory epithelium was observed. These observations are associated with the emerging reports of anosmia/hyposmia in asymptomatic COVID-19 patients from South Korea and other countries.[51] The researchers also found in a genetic study on mice and humans that the olfactory neurons in the two main genes involved in SARS-CoV-2 were not represented. As a result, SARS-CoV-2 infection can lead to anosmia and other forms of olfactory dysfunction.[52]

In our results, two studies investigated the prevalence of olfactory dysfunction in the individuals with unknown COVID-19 status.[17,31] It should be noted, dysfunction in the sense of smell and taste can also be a sign of other pulmonary infections. Therefore, more research is needed to find answers to questions as well as doubts. Although, the World Health Organization has not yet situated the two symptoms on Corona's list of symptoms, however, it has presented that a disorder in these two senses, along with other symptoms not independently, could provide useful information for identifying patients with COVID-19.

It should be noted that physicians around the world have reported some patients who suddenly lost their sense of taste and smell. It is noteworthy that the detection of the cause of the loss of these senses is crucial in supporting the diagnosis of this disease. Lee *et al*. (2020) in survey of 3191 patients in Korea showed anosmia or ageusia in 15% patients in the early stage of COVID-19 and in 16% patients with asymptomatic-to-mild disease severity.[53] Also, a recent study reported almost one-fifth of the patients presented the symptoms before the hospital admission.[18] Impairment of mucosal epithelial cells of the oral cavity may define ageusia discovered in the early stage of COVID-19. This evidence may describe the pathogenetic mechanism underlying Olfactory or taste disorders in COVID-19.[54] Since the initial reports from China, international reports on COVID-19 patients have been growing, representing a 5% to 85% range of loss of smell sense.[47] In sum, these findings may influence future diagnosis and prevention of COVID-19. It should consider whether isolated disorders of smell/taste are an ample basis for COVID-19 testing or isolation to restriction spread of the virus.

Conclusion

Olfactory and gustatory dysfunction is prevalent among COVID-19 patients. As a result, olfactory and gustatory dysfunction seems to be part of important symptoms and notify for the diagnosis of COVID-19, especially in the early phase of the infection. It is suggested that assessment of sense of smell and taste is considered in screening suspected individuals referred to health care centers.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1

Table 1: Quality assessment of the cross-sectional and case-control studies

Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Items																									
1. Are the participants representative of the target population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?	N	N	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	N	N	Y
3. Are there complete outcome data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Are the confounders accounted for in the design and analysis?	Y	N	N	N	N	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
5. During the study period, is the intervention administered (or exposure occurred) as intended?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
SUM (Y: Yes; N: NO; C: Can't tell)	4	3	3	3	3	5	3	3	4	3	3	3	4	3	3	3	3	3	3	3	4	4	3	3	4

Table 2: Quality assessment of the cross-report and case-series studies

Study ID	26	27	28
Items			
1. Is the sampling strategy relevant to address the research question?	Y	Y	Y
2. Is the sample representative of the target population?	N	N	N
3. Are the measurements appropriate?	C	C	C
4. Is the risk of nonresponse bias low?	Y	Y	Y
5. Is the statistical analysis appropriate to answer the research question?	N	N	N
SUM (Y: Yes; N: NO; C: Can't tell)	2	2	2

Appendix 2

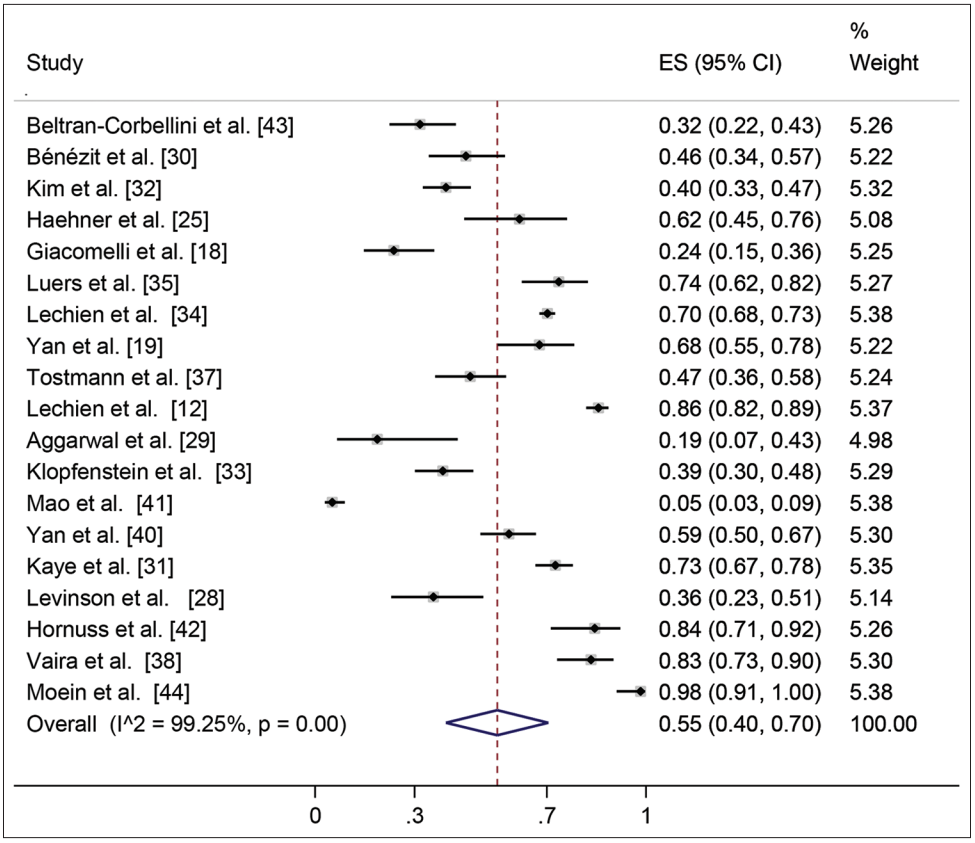

Figure 1: Forest plot of the prevalence of olfactory dysfunction in patients with COVID-19

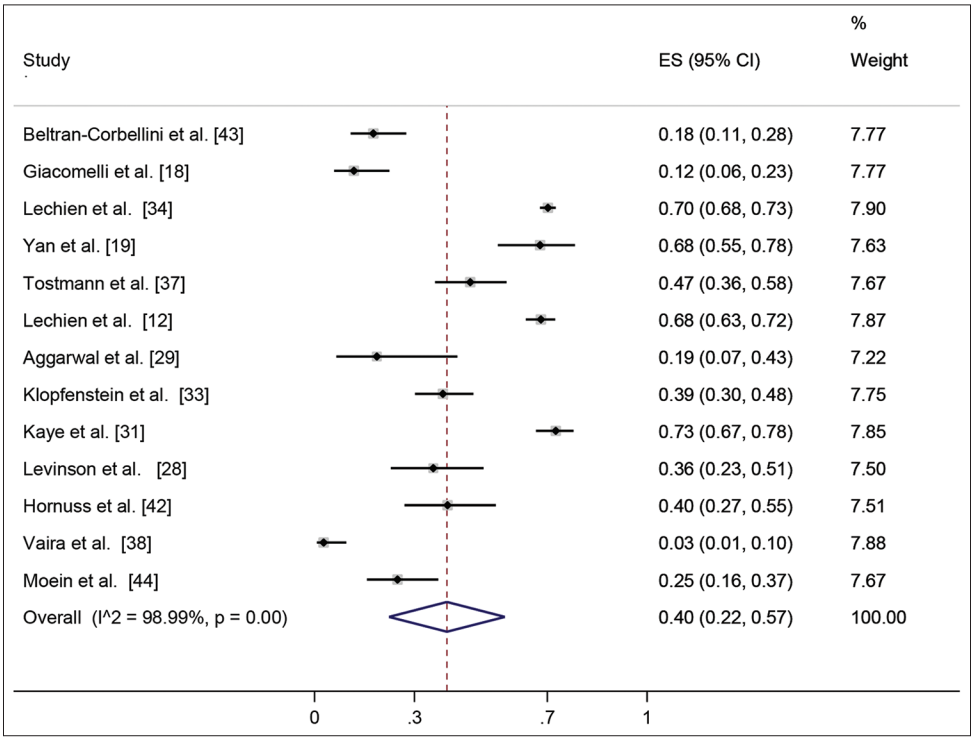

Figure 2: Forest plot of the prevalence of anosmia in patients with COVID-19

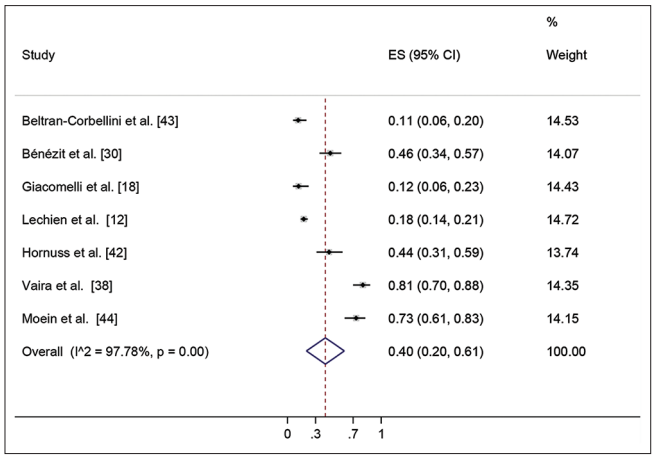

Figure 3: Forest plot of the prevalence of hyposmia in patients with COVID-19

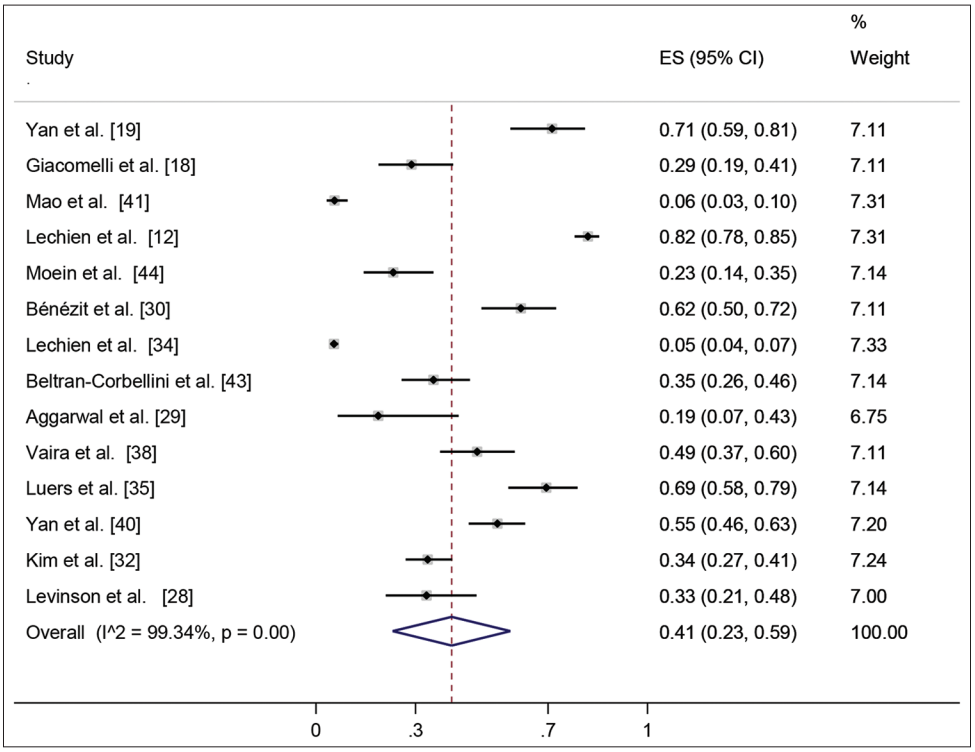

Figure 4: Forest plot of the prevalence of gustatory dysfunction in patients with COVID-19

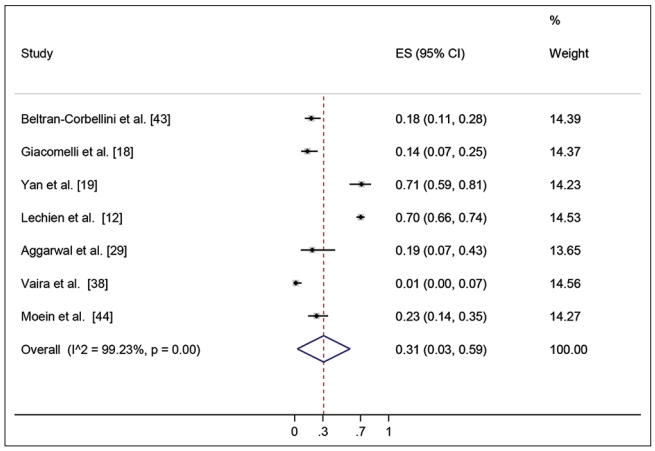

Figure 5: Forest plot of the prevalence of agusia in patients with COVID-19

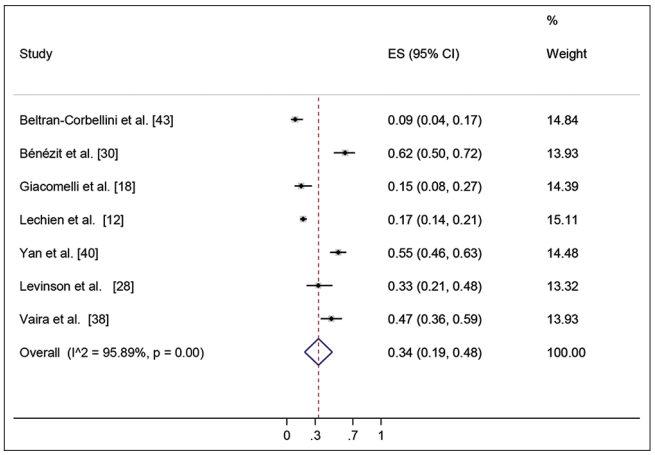

Figure 6: Forest plot of the prevalence of dysgusia in patients with COVID-19