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

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. The World Health Organization (WHO) named this disease COVID-19, determined by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-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. Due to the newly known COVID-19, it is expected that different aspects of the disease will be described daily. 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. In the moderate to severe infection, several organs and systems can be affected, included respiratory, cardiovascular, hematologic, immune systems, kidney, liver, and even skin. 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. Olfactory and gustatory dysfunction as peripheral nervous system manifestations has been reported in previous studies. However, the main pathogenesis is unclear; it seems that epithelial impairment and CNS involvement after the respiratory tract infection with coronaviruses have been presented. Numerous reports from Germany, Iran, Italy, and the US have been shown that anosmia occurs in 34% to 68% of COVID-19 positive patients. 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. The current systematic review and meta-analysis with limited studies showed that olfactory and gustatory dysfunction is
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 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.\textsuperscript{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 6\textsuperscript{th} 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).\textsuperscript{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. Cochran Q test and I\textsuperscript{2} 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.
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
| ID | Author [ref] | Country/Study time | Study type       | Population/sample size             | Reported outcomes                                                                 | Measurements tool (range of score) |
|----|--------------|--------------------|------------------|------------------------------------|----------------------------------------------------------------------------------|------------------------------------|
| 1  | Yan et al.   | USA, California    | Cross-sectional  | Confirmed Covid-19 patients: 59    | Olfactory impairment Anosmia Gustatory impairment Ageusia                         | Online questionnaire (0-270)       |
|    | [19]         | March 31 - April 3, 2020 |                 |                                    |                                                                                 |                                    |
| 2  | Giacomelli et al. | Italy, Milan   | Cross-sectional  | Covid-19- Positive hospitalized: 59 | Olfactory disorder Hyposmia Anosmia Taste disorder Dysgeusia Ageusia Olfactory and Taste disorders (OTDs) | Questionnaire                      |
|    | [18]         | 19 March 2020      |                 |                                    |                                                                                 |                                    |
| 3  | Klopfenstein et al. | France | Cross-sectional  | Covid-19- Positive: 114           | Anosmia Dysgeusia Taste impairment Smell impairment                               | Extracted from medical records    |
|    | [33]         | 1-17 March, 2020   |                 |                                    |                                                                                 |                                    |
| 4  | Mao et al.   | China              | Cross-sectional  | Covid-19- Positive hospitalized: T: 214 | Mild-to-moderate COVID-19 patients: 417                                      | Online questionnaire               |
|    | [11]         | January 16 - February 19, 2020 |                 | Severe: 88 Nonsevere: 126 From 12 European hospitals |                                                                                 |                                    |
| 5  | Lechien et al. | Some European countries | Cross-sectional  | Mild-to-moderate COVID-19 patients: 417 | Olfactory dysfunction Anosmia Hyposmia Gustatory dysfunction Reduced/discontinued taste ability Distorted taste ability | Online questionnaire              |
|    | [30]         | (Belgium, France, Spain, Italy) NR |                 | From 12 European hospitals |                                                                                 |                                    |
| 6  | Moein et al. | Iran, Tehran       | Case-control     | Covid-19- Positive: 60            | Olfactory dysfunction Anosmia Hyposmia Smell Gustatory dysfunction Taste loss     | Odorant test- UPSIT (0-40)         |
|    | [43]         | 21-23 March, or March 31 - April 5, 2020 |                 |                                    |                                                                                 | Self-report                        |
| 7  | Bénézit et al. | France | Cross-sectional  | Covid-19- Positive: 68            | Olfactory disorder Hyposmia Taste disorder Hypogeusia                           | Online questionnaire              |
|    | [30]         | 15-18 March, 2020  |                 |                                    |                                                                                 |                                    |

Contd...
| ID | 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 | Loss of smell | Online questionnaire |
|    |               |                     |            | From 18 European hospitals | Gustatory dysfunction | |
| 9  | Beltran-Corbellini et al.[42] | Spain, Madrid 23-25 March, 2020 | Case-control | Covid-19- Positive hospitalized: 79 | Smell disorder: Anosmia | Questionnaire |
|    |               |                     |            |                          | Hyposmia | |
|    |               |                     |            |                          | Dysosmia | |
|    |               |                     |            |                          | Taste disorder: Ageusia | |
|    |               |                     |            |                          | Hypogeusia | |
|    |               |                     |            |                          | Dysgeusia | |
|    |               |                     |            |                          | Capable of distinguish sweetness/saltiness/bitterness | |
| 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) | very 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 | Extracted from EMR |
|    |               |                     |            |                          | Anosmia | |
|    |               |                     |            |                          | Loss of taste | |
|    |               |                     |            |                          | Dysgeusia | |
| 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 | Olfaction test- CCCRC (0-100) |
|    |               |                     |            |                          | Hyposmia | gustaory test (0-4) |
|    |               |                     |            |                          | Anosmia | |
|    |               |                     |            |                          | Gustatory disorder | |
|    |               |                     |            |                          | Ageusia | |
| ID | 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 | Questionnaire |
| 15 | Yan et al.[40] | USA, California March 3 - April 8, 2020 | Cross-sectional | Covid-19- Positive: 128 | Olfactory impairment | 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 | Gustatory disorder | Online questionnaire |
| 17 | Wee et al.[39] | Singapore March 26 - April 10, 2020 | Cross-sectional | Covid-19- Positive: 154 | Dysgeusia | 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 | Gustatory impairment | Online checklist |
| 19 | Kim et al.[32]* | South Korea | Cross-sectional | Covid-19 Positive: 172 | Anosmia | Questionnaire |
| 20 | Menni et al.[16]* | UK 24-29 March, 2020 | Cross-sectional | Covid-19- Positive: 579 | Hyposmia | The COVID RADAR Symptom Tracker app |
| 21 | Lechien et al.[20]* | Some European countries a | Cross-sectional | All cases with SLS: 78 psychophysical olfactory evaluation in SLS patients: 46 | Dysgeusia: | Sniffin Sticks test (0-12) |
| 22 | Hornuss et al.[41]* | Germany April 2020 | Case-control | Hospitalized COVID-19 patients: 45 | Smelling dysfunction | Sniffin Sticks test (0-12) |
| 23 | Levinson et al.[28]* | Israel 10-23 March, 2020 | Cross-sectional | Hospitalized mild COVID-19 patients: 42 | Anosmia | Extracted from EMR |
| 24 | Haechner et al.[21]* | Germany April 2020 | Cross-sectional | Covid-19 Positive: 34 | Dysgeusia | 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: | Self-report by an online questionnaire |

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### Table 2: Contd...

| ID | Study characteristics | Outcome characteristics |
|----|-----------------------|-------------------------|
|    |                       | Reported outcomes | Measurements tool (range of score) |
|    |                       |                         |                                      |
| 26 | Gilani et al.⁴¹        | Anosmia: 67.7% | Self-report                          |
|    | Iran                  | Ageusia: 71.1% |                          |
|    | March 11 - April 1, 2020 | T: 8 |                          |
|    | Case series           | COVID-19 Positive: 5 |                          |
|    |                       | SLS unknown COVID-19: 3 |                          |
| 27 | Gane et al.⁴⁴         | Hyposmia: 11.8% | Self-report                          |
|    | UK                    | Anosmia: 11.8% |                          |
|    | Case report and       | Overall: 23.7% |                          |
|    | Case series           | Hyposmia: 11.8% |                          |
|    |                       | NR                    |                          |
| 28 | Marchese-Ragona et al.⁴⁶ | Hyposmia: 11.8% | Supra-threshold six odours smell test |
|    | Italy                 | H: 6                  |                          |
|    | Case series           | SC: 5                 |                          |

| ID | Study characteristics | 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% | Overall: 28.8% | Overall: 18.6% | Overall: 18.6% | 60% |
|    |                       | Hyposmia: 11.8% | Dysgeusia: 15.2% | Dysgeusia and hyposmia: 3.4% | Dysgeusia and anosmia: 3.4% | 60% |
|    |                       | Anosmia: 11.8% | Ageusia: 13.5% | Ageusia and hyposmia: 3.4% | Ageusia and anosmia: 8.5% | 60% |
| 3  |                       | Anosmia: 47.3% | NR | Anosmia and dysgeusia: 40.3% | NR | 60% |
| 4  |                       | Overall: 5.1% | Overall: 5.6% | NR | NR | 60% |
|    |                       | Severe: 3.4% | Severe: 3.4% |                         |            |
|    |                       | Non-severe: 6.3% | Non-severe: 7.1% |                         |            |
|    |                       | Overall: 85.6% | Overall: 88.8% | Overall: 80.8% |                         |            |
| 5  |                       | Anosmia: 68.1% | Reduced/discontinued taste ability: 70.1% | Gustatory dysfunction and anosmia: 64.2% | NR | 60% |
|    |                       | Hyposmia: 17.5% | Distorted taste ability: 18.7 | Gustatory dysfunction and hyposmia: 16.5% |            |
|    |                       | Parosmia: 12.6% |                         |                         |            |
|    |                       | Parosmia: 32.4% |                         |                         |            |
| ID | Findings | Other main findings | QS (0-100%) |
|----|----------|---------------------|------------|
| 6  | Overall: 98% | | 100% |
|    | Any olfactory dysfunction | Any gustatory dysfunction | Olfactory and/or gustatory dysfunction |
|    | Anosmia: 25% | Self-report Taste loss: 23.3% | Self-report Smell and taste loss: 16.6% |
|    | Hyopsomia: 73% | | |
|    | Self-report | | |
|    | Smell loss: 28.3% | | |
| 7  | Hyposmia: 45.5% | Hypogeusia: 61.7% | Hypogeusia and Hyposmia: 42.6% |
| 8  | Anosmia: 70.2% | Any gustatory dysfunction: 54.2% | NR |
| 9  | Overall: 31.6% | Overall: 35.4% | 39.2% |
|    | Anosmia: 17.7% | Ageusia: 17.7% | |
|    | Hyposmia: 11.3% | Hyposmia: 8.8% | |
|    | Dysosmia: 2.5% | Dysgeusia: 10.1% | |
|    | | Capable of distinguish sweetness/saltiness/bitterness: 24.0% | |
| 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% |
| 11 | Anosmia: 18.7% | Dysgeusia: 18.7% | 18.7% |
| 12 | Anosmia: 72.5% | Overall: 48.6% | Alteration of sense of smell or taste: 64.3% |
| 13 | Overall: 83.2% | Overall: 48.6% | 41.7% |
|    | Anosmia: 2.7% | Ageusia: 1.3% | |
|    | Hyposmia: 80.5% | Dysgeusia: 47.2% | |
| 14 | 73.6% | 69.4% | 68.0% |
| 15 | 58.5% | Dysgeusia: 54.6% | NR |
| 16 | Anosmia: 46.8% | NR | NR |
| 17 | NR | NR | Olfactory or taste disorders: 22.7% |
| 18 | NR | NR | |
| 19 | 39.5% | 33.7% | NR |

*Strong correlation between the number of olfactory disorder and reported COVID-19 patients in all provinces.*
| 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 |
| 21 | Overall: 76% | | | |
|    | Anosmia: 52% | Dysgeusia: 67.9 | NR |
| 22 | Overall: 84.4% | NR | NR | NR |
|    | Anosmia: 40.0% | | | |
|    | Hyposmia: 44.4% | | | |
| 23 | Anosmia: 35.7% | Dysgeusia: 33.3% | 33.3% | NR |
| 24 | 61.7% | NR | NR | NR |
| 25 | Overall: 85.7% | Dysgeusia: 60.1% | NR | NR |
|    | Anosmia: 53.6% | | | |
|    | Hyposmia: 21.4% | | | |
| 26 | NA | Ageusia: 2 of unknown COVID-19 patients | NR | NR |
| 27 | NA | NR | NR | NR |
| 28 | NA | Hypogeusia: All cases except one SC | NR | NR |

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 ofactory test, SLS=Sudden loss of smell SC=Strict contact with lab-positive COVID-19; *Not peer-reviewed. aCarried out by the COVID-19 Task Force of YO-IFOS (the Young-Otolaryngologists of the International Federation of Otology-laryngological Societies). bThe questionnaire was created with Professional Survey Monkey. cThe 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. dDeveloped by Zoe Global Limited and King’s College London.
Of the 28 included studies, one had a MMAT score of 100%, six scored 90%, three scored 80%, and the rest scored 70% to 60%. 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) 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) including Iran (3), Singapore (1), China (1), South Korea (1), and Israel (1); and in the USA (about 11%, 3/28). One study 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, non-online questionnaire, online checklist, the COVID RADAR Symptom Tracker app, visual analogue scale (VAS), archived medical records, or verbally. Four studies did not report how to measure, just extracted from medical records. In three studies, the Sniffin’ Sticks screening test for smelling disorders was used to perform psychophysical olfactory evaluation. The other studies contain: The SNOT-22 test to grade symptom severity, the CCCRC test to assess Olfactory function, and the supra-threshold six odors smell test.

**Epidemiological characteristics of included studies**

Of the 28 eligible studies, 22 reported the prevalence of the olfactory or gustatory dysfunction in the COVID-19 patients, five studies described the olfactory and/or gustatory dysfunction in the 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. They were different in design and settings. Majority study design was cross-sectional (about 79%, 22/28) then case-control (about 11%, 3/25) and three case report and case series (about 11%, 3/28). The sample size of them except case report and case series, ranged from 16 to 10069.

Regardless of the case report and case series studies: the sample size ranged from 16 to 10069, 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 and Singapore 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%, 98%, 67.7% respectively; and also the highest occurred prevalence of gustatory dysfunction in European, Asian countries, and the USA were 88.8%, 33.7%, 71.1% 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 dysgeusia in patients with COVID-19.

**Sensitivity analysis**

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

| Impairment | Study ID | Sample size | Pooled prevalence % (95% CI) | Model | Heterogeneity assessment |
|------------|----------|-------------|------------------------------|-------|-------------------------|
| Overall | 19 | 3387 | 55 (40-70) | Random | 99.25 | 2387 | <0.001 |
| Cross-sectional | 17 | 3282 | 51 (35-66) | Random | 99.1 | 1768 | <0.001 |
| Case control | 2 | 105 | 97 (94-100) | Fixed | ---- | ---- | ---- |
| 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 | ---- | ---- | ---- |
| Anosmia | 13 | 2700 | 40 (22-57) | Random | 98.9 | 1183 | <0.001 |
| Hyposmia | 7 | 800 | 40 (20-61) | Random | 97.7 | 272 | 0.07 |
| Overall | 14 | 2878 | 41 (23-59) | Random | 99.3 | 1983 | <0.001 |
| Cross-sectional | 13 | 2818 | 42 (24-61) | Random | 99.3 | 1983 | <0.001 |
| Case-control | 1 | 60 | 23 (14-35) | -- | ---- | ---- | ---- |
| 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 | ---- | ---- | ---- |
| 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 |
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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[52]}

In our results, two studies investigated the prevalence of olfactory dysfunction in the individuals with unknown COVID-19 status.\textsuperscript{[17,51]} 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.\textsuperscript{[53]} Also, a recent study reported almost one-fifth of the patients presented the symptoms before the hospital admission.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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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### 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  | Y  | N  | N  | N  | N  | N  | N  | N  | Y  | N  | N  | N  | N  | N  | N  | N  | Y  | N  | N  | Y  | 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  | Y  | N  | N  | N  | 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  |
| 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  | 4  | 3  | 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

| Study                                      | ES (95% CI)     | Weight |
|--------------------------------------------|-----------------|--------|
| Beltran-Corbellini et al. [43]             | 0.32 (0.22, 0.43)| 5.26   |
| Bénézit et al. [30]                       | 0.46 (0.34, 0.57)| 5.22   |
| Kim et al. [32]                            | 0.40 (0.33, 0.47)| 5.32   |
| Haehner et al. [25]                        | 0.62 (0.45, 0.76)| 5.08   |
| Giacomelli et al. [18]                     | 0.24 (0.15, 0.36)| 5.25   |
| Luers et al. [35]                          | 0.74 (0.62, 0.82)| 5.27   |
| Lechien et al. [34]                        | 0.70 (0.68, 0.73)| 5.38   |
| Yan et al. [19]                            | 0.68 (0.55, 0.78)| 5.22   |
| Tostmann et al. [37]                       | 0.47 (0.36, 0.58)| 5.24   |
| Lechien et al. [12]                        | 0.86 (0.82, 0.89)| 5.37   |
| Aggarwal et al. [29]                       | 0.19 (0.07, 0.43)| 4.98   |
| Klopfenstein et al. [33]                   | 0.39 (0.30, 0.48)| 5.29   |
| Mao et al. [41]                            | 0.05 (0.03, 0.09)| 5.38   |
| Yan et al. [40]                            | 0.59 (0.50, 0.67)| 5.30   |
| Kaye et al. [31]                           | 0.73 (0.67, 0.78)| 5.35   |
| Levinson et al. [28]                       | 0.36 (0.23, 0.51)| 5.14   |
| Hornuss et al. [42]                        | 0.84 (0.71, 0.92)| 5.26   |
| Vaira et al. [38]                          | 0.83 (0.73, 0.90)| 5.30   |
| Moein et al. [44]                          | 0.98 (0.91, 1.00)| 5.38   |
| Overall (I² = 99.25%, p = 0.00)            | 0.55 (0.40, 0.70)| 100.00 |

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

| Study                                      | ES (95% CI)     | Weight |
|--------------------------------------------|-----------------|--------|
| Beltran-Corbellini et al. [43]             | 0.18 (0.11, 0.28)| 7.77   |
| Giacomelli et al. [18]                     | 0.12 (0.08, 0.23)| 7.77   |
| Lechien et al. [34]                        | 0.70 (0.68, 0.73)| 7.90   |
| Yan et al. [19]                            | 0.68 (0.55, 0.78)| 7.63   |
| Tostmann et al. [37]                       | 0.47 (0.36, 0.58)| 7.67   |
| Lechien et al. [12]                        | 0.68 (0.63, 0.72)| 7.87   |
| Aggarwal et al. [29]                       | 0.19 (0.07, 0.43)| 7.22   |
| Klopfenstein et al. [33]                   | 0.39 (0.30, 0.48)| 7.75   |
| Kaye et al. [31]                           | 0.73 (0.67, 0.78)| 7.86   |
| Levinson et al. [28]                       | 0.36 (0.23, 0.51)| 7.50   |
| Hornuss et al. [42]                        | 0.40 (0.27, 0.55)| 7.51   |
| Vaira et al. [38]                          | 0.03 (0.01, 0.10)| 7.88   |
| Moein et al. [44]                          | 0.25 (0.16, 0.37)| 7.67   |
| Overall (I² = 98.99%, p = 0.00)            | 0.40 (0.22, 0.57)| 100.00 |

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

| Study                        | ES (95% CI)       | Weight |
|------------------------------|-------------------|--------|
| Beltran-Corbellini et al. [43]| 0.11 (0.06, 0.20) | 14.53  |
| Bénézit et al. [30]          | 0.46 (0.34, 0.57) | 14.97  |
| Giaconelli et al. [18]       | 0.12 (0.06, 0.23) | 14.43  |
| Lechien et al. [12]          | 0.18 (0.14, 0.21) | 14.72  |
| Hornus et al. [42]           | 0.44 (0.31, 0.59) | 13.74  |
| Vaira et al. [38]            | 0.81 (0.70, 0.88) | 14.35  |
| Moein et al. [44]            | 0.73 (0.61, 0.83) | 14.15  |
| Overall (I² = 97.78%, p = 0.00) | 0.40 (0.29, 0.61) | 100.00 |

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

| Study                        | ES (95% CI)       | Weight |
|------------------------------|-------------------|--------|
| Yan et al. [19]              | 0.71 (0.59, 0.81) | 7.11   |
| Giaconelli et al. [18]       | 0.29 (0.19, 0.41) | 7.11   |
| Mao et al. [41]              | 0.06 (0.03, 0.10) | 7.31   |
| Lechien et al. [12]          | 0.82 (0.78, 0.85) | 7.31   |
| Moein et al. [44]            | 0.23 (0.14, 0.35) | 7.14   |
| Bénézit et al. [30]          | 0.62 (0.50, 0.72) | 7.11   |
| Lechien et al. [34]          | 0.05 (0.04, 0.07) | 7.33   |
| Beltran-Corbellini et al. [43]| 0.35 (0.26, 0.46) | 7.14   |
| Aggarwal et al. [29]         | 0.19 (0.07, 0.43) | 6.75   |
| Vaira et al. [38]            | 0.49 (0.37, 0.60) | 7.11   |
| Luers et al. [35]            | 0.69 (0.58, 0.79) | 7.14   |
| Yan et al. [40]              | 0.55 (0.46, 0.63) | 7.20   |
| Kim et al. [32]              | 0.34 (0.27, 0.41) | 7.24   |
| Levinson et al. [28]         | 0.33 (0.21, 0.48) | 7.00   |
| Overall (I² = 99.34%, p = 0.00) | 0.41 (0.23, 0.59) | 100.00 |
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Figure 5: Forest plot of the prevalence of agusia in patients with COVID-19

| Study                          | ES (95% CI) | Weight |
|-------------------------------|-------------|--------|
| Beltran-Corbellini et al. [43]| 0.15 [0.11, 0.29] | 14.39 |
| Giacomelli et al. [18]         | 0.14 [0.07, 0.25] | 14.37 |
| Yan et al. [19]                | 0.19 [0.12, 0.26] | 14.23 |
| Lexichen et al. [12]           | 0.70 [0.66, 0.74] | 14.53 |
| Aggarwal et al. [20]           | 0.19 [0.07, 0.43] | 13.65 |
| Vaira et al. [38]              | 0.01 [0.00, 0.04] | 14.56 |
| Mouin et al. [44]              | 0.23 [0.14, 0.35] | 14.27 |
| Overall (I² = 50.23%, p = 0.00) | 0.31 [0.03, 0.59] | 100.00 |

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

| Study                          | ES (95% CI) | Weight |
|-------------------------------|-------------|--------|
| Beltran-Corbellini et al. [43]| 0.09 [0.04, 0.17] | 14.84 |
| Bembot et al. [30]             | 0.62 [0.56, 0.68] | 13.93 |
| Giacomelli et al. [18]         | 0.15 [0.08, 0.27] | 14.39 |
| Lexichen et al. [12]           | 0.17 [0.14, 0.21] | 15.11 |
| Yan et al. [40]                | 0.55 [0.46, 0.65] | 14.48 |
| Levinson et al. [26]           | 0.33 [0.21, 0.48] | 13.32 |
| Vaira et al. [38]              | 0.47 [0.36, 0.59] | 13.93 |
| Overall (I² = 95.99%, p = 0.00) | 0.34 [0.19, 0.49] | 100.00 |