SYSTEMATIC REVIEW

Anosmia and dysgeusia in SARS-CoV-2 infection: incidence and effects on COVID-19 severity and mortality, and the possible pathobiology mechanisms - a systematic review and meta-analysis [version 1; peer review: 2 approved, 1 approved with reservations]

Endang Mutiawati, Marhami Fahriani, Sukamto S. Mamada, Jonny Karunia Fajar, Andri Frediansyah, Helnida Anggun Maliga, Muhammad Ilmawan, Talha Bin Emran, Youdiil Ophinni, Ichsan Ichsan, Nasrul Musadi, Ali A. Rabaan, Kuldeep Dhama, Syahrul Syahrul, Firzan Nainu, Harapan Harapan

1 Department of Neurology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh, 23111, Indonesia
2 Department of Neurology, Dr. Zainoel Abidin Hospital, Banda Aceh, Aceh, 23111, Indonesia
3 Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh, 23111, Indonesia
4 Faculty of Pharmacy, Hasanuddin University, Makassar, South Sulawesi, 90245, Indonesia
5 Brawijaya Internal Medicine Research Center, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, 65145, East Java, Indonesia
6 Research Division for Natural Product Technology (BPTBA), Indonesian Institute of Sciences (LIPI), Wonosari, 55861, Indonesia
7 Faculty of Medicine, Universitas Brawijaya, Malang, East Java, 65117, Indonesia
8 Department of Pharmacy, BGC Trust University Bangladesh, Chittagong-4381, Bangladesh
9 Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, 02139, USA
10 Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh, 23111, Indonesia
11 Molecular Diagnostic Laboratory, Johns Hopkins Aramco Healthcare, Dhahran, 31311, Saudi Arabia
12 Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, 243122, India
13 Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Aceh, 23111, Indonesia

First published: 21 Jan 2021, 10:40
https://doi.org/10.12688/f1000research.28393.1
Latest published: 21 Jan 2021, 10:40
https://doi.org/10.12688/f1000research.28393.1

Abstract
Background: The present study aimed to determine the global prevalence of anosmia and dysgeusia in coronavirus disease 2019 (COVID-19) patients and to assess their association with severity and mortality of COVID-19. Moreover, this study aimed to discuss the possible pathobiological mechanisms of anosmia and dysgeusia in COVID-19.
Methods: Available articles from PubMed, Scopus, Web of Science, and preprint databases (MedRxiv, BioRxiv, and Researchsquare) were
searched on November 10th, 2020. Data on the characteristics of the study (anosmia, dysgeusia, and COVID-19) were extracted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Newcastle–Ottawa scale was used to assess research quality. Moreover, the pooled prevalence of anosmia and dysgeusia were calculated, and the association between anosmia and dysgeusia in presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was assessed using the Z test.

**Results:** Out of 32,142 COVID-19 patients from 107 studies, anosmia was reported in 12,038 patients with a prevalence of 38.2% (95% CI: 36.5%, 47.2%); whereas, dysgeusia was reported in 11,337 patients out of 30,901 COVID-19 patients from 101 studies, with prevalence of 36.6% (95% CI: 35.2%, 45.2%), worldwide. Furthermore, the prevalence of anosmia was 10.2-fold higher (OR: 10.21; 95% CI: 6.53, 15.96, \( p < 0.001 \)) and that of dysgeusia was 8.6-fold higher (OR: 8.61; 95% CI: 5.26, 14.11, \( p < 0.001 \)) in COVID-19 patients compared to those with other respiratory infections or COVID-19 like illness. To date, no study has assessed the association of anosmia and dysgeusia with severity and mortality of COVID-19.

**Conclusion:** Anosmia and dysgeusia are prevalent in COVID-19 patients compared to those with the other non-COVID-19 respiratory infections. Several possible mechanisms have been hypothesized; however, future studies are warranted to elucidate the definitive mechanisms of anosmia and dysgeusia in COVID-19.

**Protocol registration:** PROSPERO CRD42020223204.

**Keywords**
anosmia, COVID-19, dysgeusia, predictor, SARS-CoV-2

This article is included in the Disease Outbreaks gateway.

This article is included in the Coronavirus collection.
Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was initially identified in late December 2019 in Wuhan, Hubei Province, Republic of China. This viral pandemic rapidly spread worldwide, infecting more than 60 million people, causing more than 1 million deaths, and severely affecting the global healthcare system. Several drugs have been repurposed for treating COVID-19; however, no drug has been recommended or approved by the World Health Organization (WHO). The common symptoms of COVID-19 include dry cough, fever, dyspnea, fatigue, anorexia, diarrhea, chest pain, headache, and muscle ache. In particular, anosmia and dysgeusia have been increasingly identified among asymptomatic people that later tested positive for the presence of SARS-CoV-2: anosmia and dysgeusia. Remarkably, previous studies reported that these olfactory issues were reported in 11.8% of COVID-19 cases before other symptoms occurred.

Anosmia, a severe condition of hyposmia, is a part of olfactory dysfunction where the person is unable to sense smell or detect odor. Dysgeusia is a sensory dysfunction where the individual loses the perception of taste. The British Association of Otorhinolaryngology reported that both dysfunctions varied from 3-20% among COVID-19 patients. A previous study among 42 patients revealed that more than a third presented anosmia and dysgeusia. A higher percentage of anosmia and dysgeusia cases were also reported. Furthermore, another study reported that anosmia in COVID-19 is related to the enlargement of bilateral olfactory bulb edema.

This evidence may be crucial in the present COVID-19 pandemic. As the real-time reverse transcriptase polymerase chain reaction (RT-PCR) test has certain limitations for screening, the manifestation of anosmia and dysgeusia could be used as an early warning for practitioners or clinicians to build a rationale to reach a firm conclusion on patients with SARS-CoV-2 infection. Additionally, a recent study reported that anosmia and dysgeusia are among the earliest symptoms observed in COVID-19 patients; however, in-depth analysis of this dysfunction and its relation to the pathogenesis, severity, and mortality of COVID-19 is missing from the literature. Thus, the present study aimed to summarize the global evidence of anosmia and dysgeusia among COVID-19 patients, in order to assess their association with the severity and mortality of the disease, and provide a comprehensive review related to the possible pathogenesis of anosmia and dysgeusia in SARS-CoV-2 infection.

Methods

Registration and protocol

To comprehensively calculate the cumulative prevalence of anosmia and dysgeusia in SARS-CoV-2 infection worldwide, a systematic review was conducted following guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The protocol of this systematic review has been registered at PROSPERO (CRD42020223204).

Eligibility criteria of studies

All articles reporting anosmia and dysgeusia as the symptom of COVID-19 were included. COVID-19 case was defined by a positive RT-PCR for SARS-CoV-2 from either nasopharyngeal swab, oropharyngeal swab, bronchoalveolar lavage, or cerebrospinal fluid. All cross-sectional, retrospective, and prospective studies that randomly sampled COVID-19 cases from community or hospitals were considered eligible; whereas case reports and case series, including all editorials, reviews, and commentaries, were excluded. Studies targeting specific groups such as pregnant females, children, and other groups, were excluded. Only articles written in English during 2019-2020 were included.

Information sources and search strategy

Three bibliographical databases (PubMed, Scopus, and Web of Science) and three preprint databases (MedRxiv, BioRxiv, and Researchsquare) were used to identify the potential articles (as of November 10th, 2020). The search criteria were as follows. PubMed ([Title] “SARS-CoV-2” OR “COVID-19” OR “Wuhan coronavirus” OR “Wuhan virus” OR “novel coronavirus” OR “nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus disease 2019 virus” OR “2019-nCoV” OR “2019 novel coronavirus” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus” OR “coronaviruses” OR “SARS 2” OR “2019-nCoV acute respiratory disease” OR “novel coronavirus pneumonia” OR “COVID”) AND ([All] “Anosmia” OR “smell loss” OR “smell dysfunction” OR “smell impairment” OR “hyposmia” OR “dysosmia” OR “olfactory dysfunction” OR “olfactory disorder”) AND (“dysgeusia” OR “taste loss” OR “taste dysfunction” OR “taste impairment” OR “gustatory dysfunction” OR “gustatory disorder” OR “hypogeusia” OR “ageusia”). Scopus ([Title] “SARS-CoV-2” OR “COVID-19” OR “Wuhan coronavirus” OR “Wuhan virus” OR “novel coronavirus” OR “nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus disease 2019 virus” OR “2019-nCoV” OR “2019 novel coronavirus” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus” OR “coronaviruses” OR “SARS 2” OR “2019-nCoV acute respiratory disease” OR “novel coronavirus pneumonia” OR “COVID”) AND ([All] “Anosmia” OR “smell loss” OR “smell dysfunction” OR “smell impairment” OR “hyposmia” OR “gustatory dysfunction” OR “gustatory disorder” OR “dysgeusia” OR “ageusia”).
OR “dysosmia” OR “olfactory dysfunction” OR “olfactory disorder”) AND (“dysgeusia” OR “taste loss” OR “taste dysfunction” OR “taste impairment” OR “gustatory dysfunction” OR “gustatory disorder” OR “hypogeusia” OR “ageusia”). Web of Science ([Title] “SARS-CoV-2” OR “COVID-19” OR “Wuhan coronavirus” OR “Wuhan virus” OR “novel coronavirus” OR “nCoV” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus disease 2019 virus” OR “2019-nCoV” OR “2019 novel coronavirus” OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus” OR “coronaviruses” OR “SARS 2” OR “2019-nCoV acute respiratory disease” OR “novel coronavirus pneumonia” OR “COVID”) AND ([All] “Anosmia” OR “smell loss” OR “smell dysfunction” OR “smell impairment” OR “hyposmia” OR “dysosmia” OR “olfactory dysfunction” OR “olfactory disorder”) AND ([All] “dysgeusia” OR “taste loss” OR “taste dysfunction” OR “taste impairment” OR “gustatory dysfunction” OR “gustatory disorder” OR “hypogeusia” OR “ageusia”).

Moreover, we searched the preprint servers MedRxiv, BioRxiv, and Researchsquare for non-peer-reviewed articles. Data were extracted from the articles as well as supplementary materials. Reference lists from the eligible articles were retrieved for further relevant studies.

Study selection and data extraction
The information of identified articles was imported into EndNote X9 (Thompson Reuters, Philadelphia, PA, USA). Duplicates between databases were removed. To identify eligible studies, the retrieved articles were screened based on title and abstract. The potentially eligible studies were then fully reviewed by two authors (MF and JKF). After reviewing the full texts, the eligibility of each study was decided.

Information of study characteristics, study site, study design, number of patients with anosmia, number of patients with dysgeusia, and COVID-19 characteristics such as number of patients, severity, and outcome were collected.

Outcomes
The primary outcomes were: (a) the global incidence of anosmia in COVID-19 patients; (b) the global incidence of dysgeusia in COVID-19 patients; (c) the association of anosmia with the severity of COVID-19; (d) the association of dysgeusia with the severity of COVID-19; (e) the association of anosmia with mortality of COVID-19; and (f) the association of dysgeusia with mortality of COVID-19. Moreover, this review was conducted to provide the possible pathogenesis of anosmia and dysgeusia in SARS-CoV-2 infection.

Data synthesis
The cumulative prevalence rate of anosmia and dysgeusia was calculated for COVID-19 cases by dividing the number of COVID-19 cases with anosmia by the total number of COVID-19 cases with and without anosmia, and was expressed as a percentage (%) with 95% confidence intervals (95% CI). Pooled odds ratios (OR) and 95% CI were calculated to assess the association of anosmia and the occurrence of SARS-CoV-2 compared to non-SARS-CoV-2 respiratory infections. The same method was used for dysgeusia. The pooled OR and 95% CI were presented in a forest plot.

Risk of bias assessment
Critical assessment was conducted for the study setting and diagnosis of SARS-CoV-2 to reduce the bias. The Newcastle-Ottawa scale (NOS)\textsuperscript{26} was used as critical appraisals to assess the quality of eligible studies. Prior to analysis, gathered data from studies were evaluated for heterogeneity and potential publication bias.

Statistical analysis
To assess the association between anosmia or dysgeusia and the presence of SARS-CoV-2, Z test was performed (p < 0.05 was considered statistically significant). Q test was used to evaluate the heterogeneity among studies, and the data with heterogeneity was analyzed using a random effect model. The reporting and publication bias were assessed using Egger’s test and a funnel plot (p < 0.05 was considered having potential for publication bias). The data were analyzed using Review Manager version 5.3\textsuperscript{27}.

Results
Study eligibility results
In total, 691 articles (660 reviewed articles and 31 preprint articles) were identified through the databases; of these, 182 articles were removed as duplicates. An additional 287 articles were excluded following a screening process of the titles and abstracts due to irrelevant studies, leaving 222 references (Figure 1). Full-texts of the remaining 222 references were retrieved and screened for eligibility, and this process excluded an additional 115 references as the inclusion criteria was not met. This exclusion included articles with no access\textsuperscript{28,29}, RT-PCR not clearly stated in the text\textsuperscript{30-45}, case reports\textsuperscript{46-97}, case series\textsuperscript{98-113}, repeated datasets\textsuperscript{114-118}, and studies in specific groups\textsuperscript{119-130}. A complete assessment was conducted for 107 references.
The meta-analysis included 107 studies to calculate the prevalence of anosmia in COVID-19 patients. Additionally, 6 studies were excluded while calculating the prevalence of dysgeusia in COVID-19, thus leaving 101 eligible studies. In total, 20 and 16 studies were included to assess the association of anosmia and dysgeusia with the COVID-19 occurrence, respectively.

### The prevalence of anosmia and dysgeusia in COVID-19

To calculate the prevalence of anosmia in COVID-19 cases, 107 studies were included comprising 32,142 COVID-19 patients, and anosmia was reported in 12,038 patients with a global pooled prevalence of 38.2% (95% CI: 36.5%, 47.2%). The list of the studies and the prevalence of anosmia in each study are presented in Table 1.

In total, 30,901 COVID-19 patients from 101 studies were included to calculate the prevalence of dysgeusia in COVID-19. Dysgeusia was identified in 11,337 out of 30,901 COVID-19 patients resulting in a cumulative prevalence of 36.6% (95% CI: 35.2%, 45.2%). The individual studies and the prevalence of dysgeusia from each study are listed in Table 2.

### Association of anosmia and the occurrence of COVID-19

In total, 20 studies comprising 1,213 COVID-19 cases with anosmia and 2,735 non-COVID-19 patients (mostly COVID-19-like symptoms with negative RT-PCR for SARS-CoV-2) were analyzed to investigate the association between...
### Table 1. The prevalence of anosmia among COVID-19 patients around the globe.

| Study Design     | Country       | Anosmia | Total | Prevalence (%) | 95%CI          | Ref  |
|------------------|---------------|---------|-------|----------------|----------------|------|
| Retrospective    | Singapore     | 53      | 305   | 17.38          | 13.12, 21.63   | 131  |
| Prospective      | Turkey        | 9       | 29    | 31.03          | 14.20, 47.87   | 119  |
| Prospective      | France        | 31      | 225   | 13.78          | 9.27, 18.28    | 132  |
| Case control     | Spain         | 25      | 79    | 31.65          | 21.39, 41.90   | 133  |
| Retrospective    | Taiwan        | 42      | 321   | 13.08          | 9.39, 16.77    | 134  |
| Case control     | Canada        | 69      | 134   | 51.49          | 43.03, 59.95   | 135  |
| Case control     | US            | 60      | 101   | 59.41          | 49.83, 68.98   | 136  |
| Retrospective    | Italy         | 13      | 213   | 6.10           | 2.89, 9.32     | 137  |
| Cross sectional  | US            | 40      | 59    | 67.80          | 55.87, 79.72   | 138  |
| Cross sectional  | Spain         | 138     | 197   | 70.05          | 63.65, 76.45   | 139  |
| Cross sectional  | Brazil        | 539     | 655   | 82.29          | 79.37, 85.21   | 140  |
| Retrospective    | Pakistan      | 4       | 30    | 13.33          | 1.17, 25.50    | 141  |
| Retrospective    | Spain         | 90      | 375   | 24.00          | 19.68, 28.32   | 142  |
| Observational    | Europe        | 997     | 1420  | 70.21          | 67.83, 72.59   | 143  |
| Prospective      | South Korea   | 68      | 172   | 39.53          | 32.23, 46.84   | 144  |
| Prospective      | France        | 62      | 197   | 31.47          | 24.99, 37.96   | 145  |
| Retrospective    | USA           | 45      | 251   | 17.93          | 13.18, 22.67   | 146  |
| Retrospective    | Italy         | 14      | 22    | 63.64          | 43.53, 83.74   | 147  |
| Cross sectional  | India         | 62      | 230   | 26.96          | 21.22, 32.69   | 148  |
| Cross sectional  | US            | 22      | 168   | 13.10          | 7.99, 18.20    | 149  |
| Cross sectional  | Hong Kong     | 39      | 83    | 46.99          | 36.25, 57.73   | 150  |
| Retrospective    | France        | 54      | 114   | 47.37          | 38.20, 56.53   | 151  |
| Retrospective    | Japan         | 19      | 32    | 59.38          | 42.36, 76.39   | 152  |
| Prospective      | Taiwan        | 78      | 217   | 35.94          | 29.56, 42.33   | 153  |
| Prospective      | Turkey        | 18      | 172   | 10.47          | 5.89, 15.04    | 154  |
| Retrospective    | Italy         | 17      | 84    | 20.24          | 11.65, 28.83   | 155  |
| Prospective      | Italy         | 40      | 108   | 37.04          | 27.93, 46.14   | 156  |
| Cross sectional  | Egypt         | 80      | 96    | 83.33          | 75.88, 90.79   | 157  |
| Retrospective    | Kenya         | 279     | 787   | 35.45          | 32.11, 38.79   | 158  |
| Cross sectional  | Germany       | 29      | 73    | 39.73          | 28.50, 50.95   | 159  |
| Prospective      | UK            | 1       | 40    | 2.50           | 0.00, 7.34     | 160  |
| Cross sectional  | India         | 121     | 655   | 18.47          | 15.50, 21.45   | 161  |
| Cross sectional  | France        | 140     | 299   | 46.82          | 41.17, 52.48   | 162  |
| Retrospective    | France        | 54      | 114   | 47.37          | 38.20, 56.53   | 163  |
| Prospective      | Iran          | 22      | 92    | 23.91          | 15.20, 32.63   | 164  |
| Retrospective    | US            | 58      | 509   | 11.39          | 8.63, 14.16    | 165  |
| Cross sectional  | Spain         | 28      | 45    | 62.22          | 48.06, 76.39   | 166  |
| Cross sectional  | Brazil        | 28      | 73    | 38.36          | 27.20, 49.51   | 167  |
| Prospective      | Turkey        | 157     | 262   | 59.92          | 53.99, 65.86   | 168  |
| Retrospective    | France        | 17      | 55    | 30.91          | 18.70, 43.12   | 169  |
| Cross sectional  | UK            | 344     | 579   | 59.41          | 55.41, 63.41   | 170  |
| Study Design     | Country         | COVID-19 | Anosmia | Total | Prevalence (%) | 95%CI     | Ref   |
|------------------|-----------------|----------|---------|-------|----------------|-----------|-------|
| Retrospective    | Somalia         | 24       | 60      | 40.00 | 27.60, 52.40   | 171       |       |
| Prospective      | US              | 18       | 42      | 42.86 | 27.89, 57.82   | 172       |       |
| Prospective      | Turkey          | 33       | 143     | 23.08 | 16.17, 29.98   | 173       |       |
| Retrospective    | China           | 11       | 214     | 5.14  | 2.18, 8.10     | 174       |       |
| Retrospective    | Brazil          | 8        | 1208    | 0.66  | 0.20, 1.12     | 175       |       |
| Retrospective    | US              | 3        | 50      | 6.00  | 0.00, 12.58    | 176       |       |
| Cross sectional  | India           | 26       | 391     | 6.65  | 4.18, 9.12     | 177       |       |
| Retrospective    | China           | 34       | 86      | 39.53 | 29.20, 49.87   | 178       |       |
| Retrospective    | France          | 37       | 70      | 52.86 | 41.16, 64.55   | 179       |       |
| Cross sectional  | Italy           | 34       | 54      | 62.96 | 50.08, 75.84   | 180       |       |
| Retrospective    | UK              | 80       | 141     | 56.74 | 48.56, 64.92   | 181       |       |
| Prospective      | Italy           | 44       | 72      | 61.11 | 49.85, 72.37   | 182       |       |
| Retrospective    | Belgium         | 27       | 47      | 57.45 | 43.31, 71.58   | 183       |       |
| Case control     | Israel          | 3        | 16      | 18.75 | 0.00, 37.88    | 184       |       |
| Case control     | Turkey          | 50       | 81      | 61.73 | 51.14, 72.31   | 185       |       |
| Retrospective    | China, France, Germany | 154     | 394     | 39.09 | 34.27, 43.90   | 186       |       |
| Retrospective    | Malaysia        | 31       | 145     | 21.38 | 14.71, 28.05   | 187       |       |
| Retrospective    | Europe          | 357      | 417     | 85.61 | 82.24, 88.98   | 188       |       |
| Retrospective    | Italy           | 29       | 100     | 29.00 | 20.11, 37.89   | 189       |       |
| Cohort           | Italy           | 126      | 151     | 83.44 | 77.52, 89.37   | 190       |       |
| Cross sectional  | Switzerland     | 63       | 103     | 61.17 | 51.75, 70.58   | 191       |       |
| Case control     | Italy           | 26       | 43      | 60.47 | 45.85, 75.08   | 192       |       |
| Retrospective    | Germany         | 80       | 91      | 87.91 | 81.21, 94.61   | 193       |       |
| Prospective      | Israel          | 78       | 112     | 69.64 | 61.13, 78.16   | 194       |       |
| Cohort           | India           | 29       | 225     | 12.89 | 8.51, 17.27    | 195       |       |
| Case control     | Turkey          | 44       | 116     | 37.93 | 29.10, 46.76   | 196       |       |
| Retrospective    | Turkey          | 55       | 155     | 35.48 | 27.95, 43.02   | 197       |       |
| Retrospective    | France          | 1442     | 3737    | 38.59 | 37.03, 40.15   | 198       |       |
| Retrospective    | South Korea     | 5        | 328     | 1.52  | 0.20, 2.85     | 199       |       |
| Prospective      | US              | 23       | 46      | 50.00 | 35.55, 64.45   | 200       |       |
| Cross sectional  | Spain           | 46       | 58      | 79.31 | 68.89, 89.74   | 201       |       |
| Cross sectional  | Germany         | 22       | 34      | 64.71 | 48.64, 80.77   | 202       |       |
| Cohort           | US              | 145      | 273     | 53.11 | 47.19, 59.03   | 203       |       |
| Retrospective    | Europe          | 3        | 204     | 1.47  | 0.00, 3.12     | 204       |       |
| Cohort           | US              | 32       | 318     | 10.06 | 6.76, 13.37    | 205       |       |
| Prospective      | South Korea     | 389      | 3191    | 12.19 | 11.06, 13.33   | 206       |       |
| Prospective      | France          | 81       | 115     | 70.43 | 62.09, 78.78   | 207       |       |
| Retrospective    | China           | 30       | 196     | 15.31 | 10.27, 20.35   | 208       |       |
| Retrospective    | Iran            | 96       | 100     | 96.00 | 92.16, 99.84   | 209       |       |
| Retrospective    | Qatar           | 19       | 141     | 13.48 | 7.84, 19.11    | 210       |       |
| Cross sectional  |                | 22       | 100     | 22.00 | 13.88, 30.12   | 211       |       |
| Cross sectional  | France          | 129      | 390     | 33.08 | 28.41, 37.75   | 212       |       |
anosmia and the occurrence of COVID-19. Data suggested that anosmia was 10.2-fold more prevalent in patients with COVID-19 compared to those with COVID-19 like illness, OR 10.21 (95% CI: 6.53, 15.96) with $p < 0.001$ (Figure 2).

**Association of dysgeusia and the occurrence of COVID-19**

In total, 16 studies comprising 1,342 COVID-19 cases with dysgeusia and 1,990 patients with other respiratory illness (COVID-19 like illness with negative RT-PCR for SARS-CoV-2) were included to assess the association between dysgeusia and the occurrence of COVID-19. Data suggested that dysgeusia was 8.6-fold more prevalent in patients with COVID-19 compared to those with other respiratory illness, with OR 8.61 (95% CI: 5.26, 14.11) and $p < 0.001$ (Figure 3).

**Association of anosmia and dysgeusia with COVID-19 severity and mortality**

Limited studies have assessed the association between anosmia and dysgeusia and the severity and mortality of COVID-19 cases. One study linked anosmia with a lower fatality rate and a lower ICU admission\textsuperscript{240}.

**Discussion**

**Anosmia and dysgeusia in COVID-19 patients**

The pooled prevalence of anosmia in our systematic review was 38.2% of 32,142 COVID-19 cases. This result was almost thrice the initial prevalence reported from Wuhan, China\textsuperscript{174,208}. This suggests that anosmia is a potential indicator of SARS-CoV-2 infection, and may be useful for screening and early identification of COVID-19 patients, particularly asymptomatic\textsuperscript{241}. Some countries, such as the UK and US have used anosmia as an indicator for preventive measure, wherein COVID-19 patient with anosmia should commence self-isolation\textsuperscript{242-244}. 

**Table 1**

| Study Design | Country     | COVID-19 | Anosmia | Total | Prevalence (%) | 95%CI      | Ref |
|--------------|-------------|----------|---------|-------|----------------|-----------|-----|
| Case control | India       | 11       | 74      | 14.86 | 6.76, 22.97    | 213       |
| Retrospective| Turkey      | 529      | 1197    | 44.19 | 41.38, 47.01   | 214       |
| Case control | Israel      | 76       | 112     | 67.86 | 59.21, 76.51   | 215       |
| Cross sectional | Canada    | 31       | 56      | 55.36 | 42.34, 68.38   | 216       |
| Retrospective | US         | 75       | 169     | 44.38 | 36.89, 51.87   | 217       |
| Retrospective | China      | 134      | 1172    | 11.43 | 9.61, 13.26    | 218       |
| Cohort       | US          | 15       | 177     | 8.47  | 4.37, 12.58    | 219       |
| Cross sectional | Greece    | 29       | 79      | 36.71 | 26.08, 47.34   | 220       |
| Cross sectional | Saudi Arabia | 28       | 128     | 21.88 | 14.71, 29.04   | 221       |
| Cross sectional | Italy     | 283      | 508     | 55.71 | 51.39, 60.03   | 222       |
| Cross sectional | Italy     | 237      | 355     | 66.76 | 61.86, 71.66   | 223       |
| Cross sectional | Spain     | 26       | 31      | 83.87 | 70.92, 96.82   | 224       |
| Cross sectional | Spain     | 454      | 846     | 53.66 | 50.30, 57.02   | 225       |
| Prospective  | Italy       | 84       | 138     | 60.87 | 52.73, 69.01   | 226       |
| Case control | Brazil      | 23       | 57      | 40.35 | 27.61, 53.09   | 227       |
| Case control | Iran        | 59       | 60      | 98.33 | 95.09, 100.00  | 228       |
| Retrospective | US         | 198      | 949     | 20.86 | 18.28, 23.45   | 229       |
| Prospective  | Italy       | 46       | 50      | 92.00 | 84.48, 99.52   | 230       |
| Cross sectional | Turkey    | 71       | 223     | 31.84 | 25.72, 37.95   | 231       |
| Prospective  | Italy       | 44       | 67      | 65.67 | 54.30, 77.04   | 232       |
| Prospective  | India       | 62       | 76      | 81.58 | 72.86, 90.29   | 233       |
| Cross sectional | Brazil    | 159      | 179     | 88.83 | 84.21, 93.44   | 234       |
| Retrospective | Global     | 1324     | 1698    | 77.97 | 76.00, 79.95   | 235       |
| Retrospective | Italy       | 46       | 111     | 41.44 | 32.28, 50.61   | 236       |
Table 2. The prevalence of dysgeusia among COVID-19 patients around the globe.

| Study design | Country       | COVID-19 |     |       |     |
|--------------|---------------|----------|-----|-------|-----|
|              |               | Dysgeusia| Total| Prevalence (%)| 95%CI |
| Retrospective| Singapore     | 53       | 305 | 17.38 | 13.12, 21.63 |
| Prospective  | Turkey        | 6        | 29  | 20.69 | 5.95, 35.43 |
| Case control | Spain         | 29       | 79  | 36.71 | 26.08, 47.34 |
| Retrospective| Taiwan        | 42       | 321 | 13.08 | 9.39, 16.77 |
| Case control | Canada        | 69       | 134 | 51.49 | 43.03, 59.95 |
| Case control | US            | 60       | 101 | 59.41 | 49.83, 68.98 |
| Retrospective| Italy         | 6        | 213 | 2.82  | 0.59, 5.04  |
| Cross sectional | US      | 42       | 59  | 71.19 | 59.63, 82.74 |
| Cross sectional | Spain    | 128      | 197 | 64.97 | 58.31, 71.64 |
| Prospective  | Brazil        | 502      | 655 | 76.64 | 73.40, 79.88 |
| Retrospective| Pakistan      | 4        | 30  | 13.33 | 1.17, 25.50 |
| Retrospective| Spain         | 90       | 375 | 24.00 | 19.68, 28.32 |
| Cross sectional | Europe   | 770      | 1420| 54.23 | 51.63, 56.82 |
| Prospective  | South Korea   | 58       | 172 | 33.72 | 26.66, 40.79 |
| Prospective  | France        | 56       | 197 | 28.43 | 22.13, 34.73 |
| Retrospective| USA           | 41       | 251 | 16.33 | 11.76, 20.91 |
| Retrospective| Italy         | 14       | 22  | 63.64 | 43.53, 83.74 |
| Cross sectional | India    | 25       | 230 | 10.87 | 6.85, 14.89 |
| Cross sectional | US        | 15       | 168 | 8.93  | 4.62, 13.24 |
| Cross sectional | Hongkong  | 36       | 83  | 43.37 | 32.71, 54.04 |
| Retrospective| France        | 54       | 114 | 47.37 | 38.20, 56.53 |
| Retrospective| Japan         | 18       | 32  | 56.25 | 39.06, 73.44 |
| Prospective  | Taiwan        | 78       | 217 | 35.94 | 29.56, 42.33 |
| Prospective  | Turkey        | 11       | 172 | 6.40  | 2.74, 10.05 |
| Retrospective| Italy         | 26       | 84  | 30.95 | 21.07, 40.84 |
| Prospective  | Italy         | 66       | 108 | 61.11 | 51.92, 70.31 |
| Prospective  | Iran          | 66       | 76  | 86.84 | 79.24, 94.44 |
| Retrospective| Kenya         | 279      | 787 | 35.45 | 32.11, 39.79 |
| Cross sectional | Germany  | 29       | 73  | 39.73 | 28.50, 50.95 |
| Cross sectional | France    | 124      | 299 | 41.47 | 35.89, 47.05 |
| Retrospective| France        | 46       | 54  | 85.19 | 75.71, 94.66 |
| Prospective  | Iran          | 15       | 92  | 16.30 | 8.76, 23.85 |
| Retrospective| Illinois       | 81       | 509 | 15.91 | 12.74, 19.09 |
| Cross sectional | Brazil   | 29       | 73  | 39.73 | 28.50, 50.95 |
| Prospective  | Turkey        | 157      | 262 | 59.92 | 53.99, 65.86 |
| Retrospective| France        | 17       | 55  | 30.91 | 18.70, 43.12 |
| Cross sectional | UK         | 344      | 579 | 59.41 | 55.41, 63.41 |
| Retrospective| Somalia       | 17       | 60  | 28.33 | 16.93, 39.74 |
| Prospective  | US            | 24       | 42  | 57.14 | 42.18, 72.11 |
| Prospective  | Turkey        | 51       | 143 | 35.66 | 27.81, 43.52 |
| Retrospective| China         | 12       | 214 | 5.61  | 2.52, 8.69  |
| Study design     | Country                        | Dysgeusia | Total | Prevalence (%) | 95%CI                  | Ref |
|------------------|--------------------------------|-----------|-------|----------------|------------------------|-----|
| Retrospective    | Brazil                         | 3         | 1208  | 0.25           | 0.00, 0.53             | 175 |
| Retrospective    | Illinois                       | 5         | 50    | 10.00          | 1.68, 18.32            | 176 |
| Retrospective    | China                          | 12        | 214   | 5.61           | 2.52, 8.69             | 237 |
| Cross sectional  | India                          | 35        | 391   | 8.95           | 6.12, 11.78            | 177 |
| Retrospective    | China                          | 33        | 86    | 38.37          | 28.09, 48.65           | 178 |
| Retrospective    | France                         | 34        | 70    | 48.57          | 36.86, 60.28           | 179 |
| Cross sectional  | Italy                          | 34        | 54    | 62.96          | 50.08, 75.84           | 115 |
| Retrospective    | UK                             | 89        | 141   | 63.12          | 55.16, 71.08           | 181 |
| Prospective      | Italy                          | 39        | 72    | 54.17          | 42.66, 65.68           | 182 |
| Case control     | Turkey                         | 43        | 52    | 82.69          | 72.41, 92.97           | 125 |
| Prospective      | Belgium                        | 37        | 86    | 43.02          | 32.56, 53.49           | 238 |
| Retrospective    | Belgium                        | 6         | 47    | 12.77          | 3.23, 22.31            | 183 |
| Case control     | Israel                         | 3         | 16    | 18.75          | 0.00, 37.88            | 184 |
| Case control     | Turkey                         | 22        | 81    | 27.16          | 17.47, 36.85           | 185 |
| Retrospective    | China, France, Germany         | 100       | 394   | 25.38          | 21.08, 29.68           | 186 |
| Retrospective    | Malaysia                       | 34        | 145   | 23.45          | 16.55, 30.34           | 187 |
| Retrospective    | Europe                         | 342       | 417   | 82.01          | 78.33, 85.70           | 188 |
| Retrospective    | Italy                          | 41        | 100   | 41.00          | 31.36, 50.64           | 189 |
| Cohort           | Italy                          | 135       | 151   | 89.40          | 84.49, 94.31           | 190 |
| Cross sectional  | Switzerland                    | 67        | 103   | 65.05          | 55.84, 74.26           | 191 |
| Prospective      | Israel                         | 82        | 112   | 73.21          | 65.01, 81.42           | 194 |
| Cohort           | India                          | 39        | 225   | 17.33          | 12.39, 22.28           | 195 |
| Case control     | turkey                         | 48        | 116   | 41.38          | 32.42, 50.34           | 196 |
| Retrospective    | turkey                         | 25        | 155   | 16.13          | 10.34, 21.92           | 197 |
| Retrospective    | France                         | 1389      | 3737  | 37.17          | 35.62, 38.72           | 198 |
| Cross sectional  | Iran                           | 37        | 49    | 75.51          | 63.47, 87.55           | 129 |
| Prospective      | NA                             | 476       | 751   | 63.38          | 59.94, 66.83           | 239 |
| Retrospective    | South Korea                    | 3         | 328   | 0.91           | 0.00, 19.94            | 199 |
| Cross sectional  | Spain                          | 51        | 58    | 87.93          | 79.55, 96.31           | 201 |
| Cohort           | US                             | 145       | 273   | 53.11          | 47.19, 59.03           | 203 |
| Retrospective    | Europe                         | 3         | 204   | 1.47           | 0.00, 3.12             | 204 |
| Cohort           | US                             | 24        | 318   | 7.55           | 4.64, 10.45            | 205 |
| Prospective      | South Korea                    | 353       | 3191  | 11.06          | 9.97, 12.15            | 206 |
| Prospective      | France                         | 81        | 115   | 70.43          | 62.09, 78.78           | 207 |
| Retrospective    | China                          | 23        | 196   | 11.73          | 7.23, 16.24            | 208 |
| Retrospective    | Qatar                          | 28        | 141   | 19.86          | 13.27, 26.44           | 210 |
| Cross sectional  | India                          | 40        | 100   | 40.00          | 30.40, 49.60           | 211 |
| Cross sectional  | France                         | 130       | 390   | 33.33          | 28.65, 38.01           | 212 |
| Retrospective    | Turkey                         | 526       | 1197  | 43.94          | 41.13, 46.75           | 214 |
| Case control     | Israel                         | 80        | 112   | 71.43          | 63.06, 79.80           | 215 |
| Cross sectional  | Canada                         | 32        | 56    | 57.14          | 44.18, 70.10           | 216 |
| Retrospective    | US                             | 70        | 169   | 41.42          | 33.99, 48.85           | 217 |
Anosmia is not only present in COVID-19 patients, but also in patients with other respiratory diseases such as influenza, parainfluenza, Epstein Barr virus, picornavirus, and rhinovirus²⁴⁵-²⁴⁸. However, our study demonstrated that the prevalence of anosmia was 10.2-fold higher in COVID-19 patient than that in non-COVID-19 patient. During the previous pandemics, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), anosmia was rarely reported²⁴⁹. Only one study reported persistent anosmia after 2 years of recovery from SARS²⁵⁰.

### Table 2

| Study design     | Country | COVID-19 Dysgeusia | Total | Prevalence (%) | 95% CI | Ref |
|------------------|---------|--------------------|-------|---------------|--------|-----|
| Retrospective    | China   | 242                | 1172  | 20.65         | 18.33, 22.97 | 218 |
| Cohort           | US      | 15                 | 177   | 8.47          | 4.37, 12.58 | 219 |
| Cross sectional  | Greece  | 22                 | 79    | 27.85         | 17.96, 37.73 | 220 |
| Cross sectional  | Saudi Arabia | 28        | 128   | 21.88         | 14.71, 29.04 | 221 |
| Cross sectional  | Italy   | 321                | 508   | 63.19         | 58.99, 67.38 | 222 |
| Cross sectional  | Italy   | 232                | 355   | 65.35         | 60.40, 70.30 | 223 |
| Cross sectional  | Spain   | 28                 | 128   | 21.88         | 14.71, 29.04 | 221 |
| Cross sectional  | Spain   | 442                | 846   | 52.25         | 48.88, 55.61 | 225 |
| Prospective      | Italy   | 56                 | 138   | 40.58         | 32.39, 48.77 | 226 |
| Case control     | Brazil  | 5                  | 57    | 8.77          | 1.43, 16.12 | 227 |
| Case control     | Iran    | 14                 | 60    | 23.33         | 12.63, 34.04 | 228 |
| Prospective      | Italy   | 35                 | 50    | 70.00         | 57.30, 82.70 | 230 |
| Cross sectional  | Turkey  | 77                 | 223   | 34.53         | 28.29, 40.77 | 231 |
| Prospective      | Italy   | 17                 | 67    | 25.37         | 14.95, 35.79 | 232 |
| Prospective      | India   | 64                 | 76    | 84.21         | 76.01, 92.41 | 233 |
| Cross sectional  | Brazil  | 159                | 179   | 88.83         | 84.21, 94.44 | 234 |
| Retrospective    | Global  | 1149               | 1687  | 68.11         | 65.89, 70.33 | 235 |
| Retrospective    | Italy   | 66                 | 111   | 59.46         | 50.33, 68.59 | 236 |

Figure 2. Forest plot of the association between anosmia and the risk of COVID-19 (OR: 10.21; 95%CI: 6.53, 15.96; p<0.001; Egger’s p=0.8340; heterogeneity p=0.001; I-squared 79.33%).
Another study reported that anosmia in COVID-19 patients varied based on ethnicity; anosmia in Caucasian is three times more prevalent than in Asian population.\(^{251}\)

Dysgeusia was initially reported in 11.7% of patients who were discharged from Wuhan hospital, which persisted for at least four weeks. This result was lower than ours (36.6% out of 30,901 COVID-19 cases), which might be attributable to either lower dysgeusia prevalence in China or underestimation of this symptom itself.\(^{208}\) Moreover, the prevalence of dysgeusia in COVID-19 patients was 8.6-fold higher than that in non-COVID-19 like illness. Herpes zoster and HIV have also been linked to gustatory dysfunction.\(^{252,253}\) Furthermore, another study reported that anosmia and dysgeusia have 82.5% predictive value for positive SARS-CoV-2 RT-PCR.\(^{254}\)

**Possible pathogenesis of anosmia in COVID-19**

Several mechanisms have been proposed to explain the emergence of anosmia in COVID-19 patients.

**a. Obstruction in the nasal airway**

As several viral infections in the respiratory system display blockage of nasal airway or nasal congestion, this hypothesis was initially proposed. According to this mechanism, the interaction between the odorants and olfactory receptors is inhibited by certain obstructions, thereby impairing the subsequent smelling processes.\(^{255}\) This condition results in anosmia. The obstruction could be caused by nasal discharge or by inflammation occurring in the nasal cavity; however, this hypothesis can be presumably ruled out. Moreover, several studies reported that anosmia is more prevalent than nasal congestion in COVID-19 patients.\(^{188,256-259}\) Interestingly, the incidence of rhinorhea and nasal obstruction in SARS-CoV-2 infection is lower than other coronaviruses such as SARS-CoV and MERS-CoV.\(^{260}\)

Furthermore, presumably, nasal obstruction is a secondary mechanism by which anosmia is induced in COVID-19 patients as the obstruction in viral infection typically occurs as a subsequent event after damage in the mucociliary system, thereby inhibiting the nasal discharge and leading to nasal obstruction. In certain viral infections, the mucociliary system operated by ciliated cells is impaired. A previous study reported that human coronavirus (HCoV) disrupted the nasal ciliated respiratory epithelium leading to impaired mucociliary escalator system.\(^{261}\)

**b. Damage in olfactory sensory neurons**

Smelling processes commence when the odorants bind to the olfactory sensory neurons (OSNs) in the olfactory epithelium located in the nasal cavity, subsequently transmits this information through their axons to the olfactory bulb in the brain.\(^{262}\) According to this concept, a viral attack on the receptor neurons eventually creates disturbances in the sense of smell; however, this hypothesis remains under debate as several recent studies reported the absence of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS), the key factors for the virus
to enter the cell263, in the OSNs264-267. These findings are supported by another study carried out by Bryche et al., who demonstrated that SARS-CoV-2 was not detected in the OSNs of hamsters266.

Moreover, after comparing the duration between anosmia incidence in COVID-19 patients and the normal cellular regeneration process, this proposed mechanism should be reconsidered. Several studies reported that COVID-19-related anosmia disappeared within 1-2 weeks, whereas regeneration of dead OSNs requires more than 2 week time period188,206,255,262,268. This discrepancy results in a temporary conclusion that COVID-19-related anosmia is not directly associated with the impairment of the OSNs.

c. Olfactory center damage in the brain

The aforementioned dysfunction of OSNs and the mechanism by which SARS-CoV-2 directly affects the olfactory center via axonal transport of the neuron remains unclear, as the OSN lacks ACE2 and TMPRSS2 which hinders viral entry into the cell264-267. Nevertheless, the possibility of olfactory center disruption caused by SARS-CoV-2 should not be overlooked as the cause of anosmia, since a previous study concluded that human ACE2 (hACE2)-transgenic mice suffered from brain infection after intranasal inoculation with SARS-CoV269. The study found that the brain infection commenced from the olfactory bulb, which is the axonal trajectory pathway of the OSNs269. This finding suggests that SARS-CoV-2 might also first utilize another structure in the nasal cavity before it is transported into the OSNs.

d. Olfactory supporting cells dysfunction

As OSN does not express ACE2 and TMPRSS2, the virus should use another pathway to infect the olfactory system. Numerous studies have established the expression of these SARS-CoV-2 entry proteins in several supporting cells in olfactory epithelium, that is, Bowman’s gland cells, horizontal basal cells, olfactory bulb pericytes, mitral cells, sustentacular cells, and microvillar cells264-267. Of these supporting cells, the sustentacular cells have gained immense attention as the initial site of SARS-CoV-2 infection in the olfactory epithelium. In addition to their higher expression of ACE2 and TMPRSS2 than the others, sustentacular cells are located on the surface of the nasal cavity making them vulnerable to exposure to the external environment264,267.

Notably, sustentacular cells act as supporting cells and promote olfactory neuron in the olfactory system. These cells detoxify harmful odorants, promote odorant-receptor binding, and provide nutritional substances to support the action of olfactory receptor neurons255,264. Considerably, it is plausible to suggest that any damage occurring in sustentacular cells will in turn affect the olfactory epithelium and produce anosmia.

The corresponding regeneration time to the recovery of anosmia also supports the notion that sustentacular cell damage relates to anosmia caused by SARS-CoV-2. As the replenishment of dead OSNs does not correspond to the duration of COVID-19-related anosmia within 1-2 weeks, the regeneration of sustentacular cells seems to be in line with that time frame264,266,268.

Furthermore, this hypothesis is supported by a recent study conducted by Bryche et al., who reported that SARS-CoV-2 was accumulated in sustentacular cells but not in the OSNs266. The olfactory epithelial damage and sustentacular cell loss occurred 2 days after instilling SARS-CoV-2 intranasally in golden Syrian hamsters266.

e. Inflammation-related olfactory epithelium dysfunction

It is worth noting that the cytokine storm in COVID-19 is strongly associated with organ dysfunctions, including OSNs232. The dysfunction in this structure can lead to disturbance in the sense of smell270. Torabi et al. suggested that proinflammatory cytokines, particularly tumor necrosis factor α (TNF-α), may lead to COVID-19-induced anosmia271. Another proinflammatory cytokine, interleukin-6 (IL-6), increased in cases presenting with anosmia232,272.

The mechanism used by these cytokines, in particular IL-6, to produce anosmia is not fully understood. Cazzolla et al. suggested that this effect can be caused by either peripheral or central action of the cytokines232. In the periphery, IL-6 may induce apoptosis of ciliary neuronal cells in the olfactory epithelium272, whereas in its central action, the olfactory center in the brain is attacked by the cytokine as a result of virus infection232.

Possible pathogenesis of dysgeusia in COVID-19

Although gustatory impairment is always displayed concomitantly with olfactory dysfunction, this symptom has a relatively different mechanism and is often distantly linked to the latter symptom. Several hypotheses have been proposed to explain the mechanism behind the emergence of dysgeusia in COVID-19 patients.
a. The subsequent effect of cranial nerves dysfunction

Considering the close relationship between the olfactory and gustatory system both peripherally and centrally, smell and taste dysfunction in COVID-19 often occurs concomitantly\(^{256,273}\). This hypothesis describes dysgeusia as a secondary event of olfactory dysfunction\(^{274}\); however, several studies revealed that the percentage of dysgeusia in COVID-19 patients is higher than symptoms related to olfactory dysfunction\(^{188,275}\). Based on this finding, another mechanism may be involved in inducing SARS-CoV-2-related dysgeusia. Furthermore, COVID-19-induced dysgeusia could also occur when there is certain damage in the cranial nerves responsible for gustatory transmission (cranial nerve VII, IX, and X)\(^{276}\). Among these nerves, SARS-CoV-2 exposure to cranial nerve VII has gained immense attention. Based on this hypothesis, the virus initially colonizes the nasopharynx structure, then moves to the Eustachian tube, and eventually reaches the middle ear where the virus gets access to chorda tympani and causes dysgeusia\(^{276}\).

b. Zinc deficiency

Another interesting hypothesis underlying dysgeusia in COVID-19 is related to zinc deficiency\(^{276}\). This hypothesis was developed as zinc is an important mineral in carbonic anhydrase, which is pivotal in maintaining taste sensation\(^{277}\). Interestingly, one study reported that zinc level in patients with SARS-CoV-2 infection was significantly lower compared to that in the healthy control groups\(^{278}\). Alterations in the sense of taste after being treated with certain treatments, such as irradiation in cancer patients\(^{279,280}\), could be prevented by zinc supplementation. Moreover, dengue fever virus and human immunodeficiency virus replication could be inhibited by zinc chelation\(^{281,282}\). Furthermore, pharmacological agents influencing ACE2 activity are associated with taste disturbances\(^{283,284}\). Nevertheless, this effect does not relate to zinc deficiency as these drugs do not influence both serum and salivary zinc concentrations\(^{285}\). Further investigation needs to be carried out to reveal the role of zinc in dysgeusia associated with COVID-19.

c. SARS-CoV-2-bound sialic acid

SARS-CoV-2 may produce dysgeusia via interaction with sialic acid receptors\(^{232,274,285}\). Sialic acid plays a pivotal role in the taste processing pathway as it is a component of the normal salivary composition\(^{286}\). Moreover, reduced amount of sialic acid impairs the ability to taste\(^{287}\). An in silico study revealed that SARS-CoV-2 could interact with the sialic acid receptor through its spike protein\(^{288}\). Previously, MERS-CoV was also reported to interact with this receptor\(^{289}\). Following this occupancy, the gustatory threshold increases, while gustatory particles degrade at a higher rate\(^{274,287}\).

d. Direct attack on several oral sites

A previous study investigated the expression of ACE2 in various tissues in the oral cavity and found that the tongue had higher ACE2 expression in comparison to other tissues, such as buccal and gingival tissues\(^{290}\). This finding raised a hypothesis that SARS-CoV-2 could directly attack the taste buds in the tongue, initiating inflammatory responses, and would eventually alter the sense of taste\(^{276}\). It is proposed that the Toll-like receptor-mediated cascade and apoptosis are the subsequent events that could lead to taste dysfunction\(^{276,291}\).

A previous study investigating SARS-CoV infection in rhesus macaques revealed that, initially, the salivary gland was attacked by the virus\(^{292}\). As the human salivary gland expresses a high level of ACE2\(^{293}\), it is reasonable to pay more attention to the vulnerability of this gland against SARS-CoV-2 exposure. Disruption in the activity of the salivary gland would produce either imbalance in salivary composition or impairment of salivary flow, which could ultimately result in dysgeusia\(^{276}\).

Conclusions

Out of 32,142 and 30,901 COVID-19 cases studied for anosmia and dysgeusia, respectively, the prevalence of anosmia was approximately 38.2%, whereas that of dysgeusia was 36.6%. Both of these symptoms were more common in COVID-19 compared to other respiratory infections (approximately 10 and 9 times, respectively). Several mechanisms have been proposed to explain the emergence of anosmia in COVID-19 patients including nasal airway obstruction, damage in OSNs, olfactory center damage in the brain, dysfunction of olfactory supporting cells, and inflammation-related olfactory epithelium dysfunction. Furthermore, some possible pathogenesis of dysgeusia in SARS-CoV-2 infection has been proposed including cranial nerve dysfunction, zinc deficiency, virion interaction, and direct attack of the virus to several oral sites.
Does COVID-19 cause permanent damage to olfactory exanthem as a specific COVID-19-associated skin Erythematosus. Prior Treatment with Hydroxychloroquine for Systemic Lupus Erythematosus. Am. J. Case Rep. 2020; 21: e297364. PubMed Abstract | Full Text

Maggiolo F, Zoboli F, Arosio M, et al. SARS-CoV-2 infection in persons living with HIV: A single center prospective cohort. J. Med. Virol. 2020. PubMed Abstract | Full Text

Seo MY, Seok H, Hwang SJ, et al. Trend of Olfactory and Gustatory Dysfunction in COVID-19 patients in a Quarantine Facility. J. Korean Med. Sci. 2020; 35(41): e675. PubMed Abstract | Full Text

Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: Multicenter case series of 22 patients. J. Am. Acad. Dermatol. 2020; 83(2): 260–265. PubMed Abstract | Full Text

Vaira LA, Lechien JR, Salzano G, et al. Olfactory and gustatory dysfunction impairing COVID-19 patients: Italian objective multicenter-study. Head Neck 2020 Jul; 42(7): 1560–9. PubMed Abstract | Full Text

Peyrony O, Marbeuf-Gueye C, Truong V, et al. Accuracy of Emergency Department Clinical Findings for Diagnosis of Coronavirus Disease 2019. Ann. Emerg. Med. 2020; 76(4): 405–412. PubMed Abstract | Full Text

Beltrán-Corbellini A, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. Eur. J. Neurology. 2020; 27(9): 1738–1741. PubMed Abstract | Full Text

Li J, Chen TJ, Hwang SJ: Analysis of imported cases of covid-19 in taiwan: A nationwide study. Int. J. Environ. Res. Public Health 2020; 17(9). PubMed Abstract | Full Text

Carignan A, Valiquette L, Grenier C, et al. Anosmia and dysgeusia associated with SARS-CoV-2 infection: an age-matched case-control study. Cmaj 2020 Jun 29; 192(26): E702–e7. Epub 2020/05/29. PubMed Abstract | Full Text

Chen A, Agarwal A, Ravindran N, et al. Are Gastrointestinal Symptoms Specific for Coronavirus 2019 Infection? A Prospective Case-Control Study From the United States. Gastroenterology. 2020; 159(3): 1161–3 e2. PubMed Abstract | Full Text

Luigeti M, Iorio R, Bentivoglio AR, et al. Assessment of neurological manifestations in hospitalized patients with COVID-19. Eur. J. Neurology. 2020; 27(11): 2322–2328. PubMed Abstract | Full Text

Yam CH, Faraji F, Prajapat DP, et al. Association of chemosensor dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int. Forum Allergy Rhinol. 2020; 10(7): 806–813. PubMed Abstract | Full Text

Rojas-Lechuga MJ, Izquierdo-Dominguez A, Chiesa-Estomba C, et al: Chemosensory dysfunction in COVID-19 out-patients. Eur. Arch. Otorhinolaryngol. 2020. PubMed Abstract | Full Text

Neto DB, Fornazieri MA, Dib C, et al. Chemosensory Dysfunction in COVID-19: Prevalences, Recovery Rates, and Clinical Associations on a Large Brazilian Sample. Otolaryngol. Head Neck Surg. WOS:000552605000001. PubMed Abstract | Full Text

Papadopoulos A, Drosos A, Chryssoulakis G, et al. The role of autonomic dysfunction in COVID-19 patients. Auton. Neurosci. 2020. PubMed Abstract | Full Text

Mocci G, Drago F, Longobardi S, et al: Objective olfactory test in patients with COVID-19 patients: italian perspective. Int. J. Environ. Res. Public Health 2020; 17(9). PubMed Abstract | Full Text

Kim GU, Kim MJ, Ra SH, et al: Clinical characteristics and trends of asymptomatic and symptomatic patients with mild COVID-19. Clin. Microbiol. Infect. 2020 Jul; 26(7). WOS:000544277300033. PubMed Abstract | Full Text

F1000Research 2021, 10:40 Last updated: 07 SEP 2021

Page 19 of 28
145. Lapostolle F, Schneider E, Viana L, et al.: Clinical features of 1487 COVID-19 patients with outpatient management in the Greater Paris: the COVID-call study. Intern. Emerg. Med. 2020; 15 (5): 813–817. PubMed Abstract | Publisher Full Text | Free Full Text

146. Corsini Camplò C, Cano Cevallos E, Assi M, et al.: Clinical predictors and timing of cessation of viral RNA shedding in patients with COVID-19. J Clin Virol 2020 Sep; 130: 105477. Epub 2020/08/11. eng. PubMed Abstract | Publisher Full Text | Free Full Text

147. Ferrelli F, Gaioli F, Russo E, et al.: Clinical presentation at the onset of COVID-19 and allergic rhinoconjunctivitis. J Allergy Clin Immunol Pract 2020; 8(10): 3587–3589. PubMed Abstract | Publisher Full Text | Free Full Text

148. Rajkumar J, Anand KH, Revathishree K, et al.: Contemporary Analysis of Olfactory Dysfunction in Mild to Moderate Covid-19 Patients in A Tertiary Health Care Centre. Indian J Otolaryngol Head Neck Surg 2020. PubMed Abstract | Publisher Full Text | Free Full Text

149. Wang T, Zell J, Weiss D, et al.: COVID-19 presenting as anosmia and dysgeusia in New York City emergency departments, March-April, 2020. medRxiv 2020: 2020.07.06.20147751. PubMed Abstract | Publisher Full Text | Free Full Text

150. Cho RW, To ZHW, Yeung ZWC, et al.: COVID-19 Viral Load in the Severity of and Recovery From Olfactory and Gustatory Dysfunction. Laryngoscope 2020; 130(11): 2680–2685. PubMed Abstract | Publisher Full Text | Free Full Text

151. Kadiane-Oussou NJ, Klopfenstein T, Royer PY, et al.: COVID-19: comparative clinical features and outcome in 114 patients with or without pneumonia (Nord Franche-Comte Hospital, France). Microbes Infect. 2020. PubMed Abstract | Publisher Full Text | Free Full Text

152. Nakashima H, Suzuki M, Maeda H, et al.: Differential Diagnosis of COVID-19: Importance of Measuring Blood Lymphocytes, Serum Electrolytes, and Olfactory and Taste Functions. Tokohu J. Exp. Med. 2020; 252(2): 109–119. PubMed Abstract | Publisher Full Text | Free Full Text

153. Sheng WH, Liu WD, Wang JT, et al.: Dysosmia and dysgeusia in patients with COVID-19 in northern Taiwan. J. Formos. Med. Assoc. 2020. PubMed Abstract | Publisher Full Text | Free Full Text

154. Sakati E, Temirbekov D, Bayin E, et al.: Ear nose throat-related symptoms with a focus on loss of smell and/or taste in COVID-19 patients. Am J Otolaryngol Head Neck Med Surg 2020; 41(6). PubMed Abstract | Publisher Full Text | Free Full Text

155. Legi F, Piccica M, Graziani L, et al.: Early experience of an infectious and tropical diseases unit during the coronavirus disease (COVID-19) pandemic, Florence, Italy, February to March 2020. Euro Surveill. 2020; 25(17). PubMed Abstract | Publisher Full Text | Free Full Text

156. Vacchiano V, Riguuzzi P, Volpi L, et al.: Early neurological manifestations of hospitalized COVID-19 patients. Neurosci. Lett. 2020; 740(2029–2031). PubMed Abstract | Publisher Full Text | Free Full Text

157. Amer MA, Elsherif HS, Abdel-Hamid AS, et al.: Early recovery patterns of olfactory disorders in COVID-19 patients: a clinical cohort study. Ann J Otolaryngol Head Neck Med Surg 2020; 41(6). PubMed Abstract | Publisher Full Text | Free Full Text

158. Ombajo LA, Mutono N, Sudi P, et al.: Epidemiological And Clinical Characteristics Of Covid-19 Patients In Kenya. medRxiv 2020: 2020.11.09.20228106. PubMed Abstract | Publisher Full Text | Free Full Text

159. Maechler F, Genter M, Herms J, et al.: Epidemiological and clinical characteristics of SARS-CoV-2 infections at a testing site in Berlin, Germany, March and April 2020—a cross-sectional study. Clin. Microbiol. Infect. 2020. PubMed Abstract | Publisher Full Text | Free Full Text

160. Hussain MH, Mair M, Rea P, et al.: Frequency and outcome of olfactory impairment and anosmia in hospitalized patients with COVID-19. Neuro. Sci. 2020; 41(9): 2381–2388. PubMed Abstract | Publisher Full Text | Free Full Text

161. Liotta EM, Batra A, Clark JR, et al.: Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann. Clin. Transl. Neurol. 2020. PubMed Abstract | Publisher Full Text | Free Full Text

162. Membrilla JA, de Lorenzo I, Sastre M: Headache as a Cardinal Symptom of Coronavirus Disease 2019: A Cross-Sectional Study. Headache. PubMed Abstract | Publisher Full Text | Free Full Text

163. Rocha-Filho PAS, Magalhães JE: Headache associated with COVID-19: Frequency, characteristics and association with anosmia and ageusia. Cephalalgia 2020; 40(13): 1443–1451. PubMed Abstract | Publisher Full Text | Free Full Text

164. Uygun O, Ertas M, Ekizoglu E, et al.: Headache characteristics in COVID-19 pandemic: a survey study. J. Headache Pain 2020; 21(1). WOS:000579589000001. PubMed Abstract | Publisher Full Text | Free Full Text

165. Assaad S, Avrillon V, Fournier ML, et al.: High mortality rate in cancer patients with symptoms of COVID-19 with or without detectable SARS-CoV-2 on RT-PCR. Eur. J. Cancer 2020; 135: 251–259. PubMed Abstract | Publisher Full Text | Free Full Text

166. Mao L, Jin HJ, Wang MD, et al.: Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. medRxiv 2020: 2020.04.05.20048421. Publisher Full Text

167. dahsaw P, Rabold EM, Laws RL, et al.: Loss of Taste and Smell as Distinguishing Symptoms of COVID-19. medRxiv 2020: 2020.05.13.20101066. PubMed Abstract | Publisher Full Text | Free Full Text

168. Canica Utuk A, Budak G, Karabay O, et al.: Main symptoms in patients presenting in the COVID-19 period. Scott. Med. J. 2020; 65(4): 127–132. PubMed Abstract | Publisher Full Text

169. Mao L, Jin HJ, Wang MD, et al.: Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Jun; 77(6): 683–690. WOS: 000542138800006. PubMed Abstract | Publisher Full Text | Free Full Text

170. Student-Neto A, Guedes BF, de Luca Tuma R, et al.: Neurological consultations and diagnoses in a large, dedicated COVID-19 university hospital. Arq. Neuropsiquiatr. 2020; 78(9): 494–500. PubMed Abstract | Publisher Full Text | Free Full Text

171. Pinna P, Grewal P, Hall JP, et al.: Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline. J. Neurol. Sci. 2020; 415. PubMed Abstract | Publisher Full Text | Free Full Text

172. Garg R, Jain R, Sodani A, et al.: Neurological symptoms as initial manifestation of COVID-19: An observational study. Ann. Indian Acad. Neurol. 2020; 23(4): 482–485. PubMed Abstract | Publisher Full Text | Free Full Text

173. Liang YJ, Xu JB, Chu M, et al.: Neurosensory dysfunction: A diagnostic marker of early COVID-19. Int. J. Infect. Dis. 2020 Sep; 98: 547–552. WOS:0006956400020. PubMed Abstract | Publisher Full Text | Free Full Text

174. Klopfenstein T, Zahr C, Kadiane-Oussou NJ, et al.: New loss of smell and taste: Uncommon symptoms in COVID-19 patients in Nord Franche-Comte cluster, France. Int. J Infect Dis 2020; 100: 117–122. PubMed Abstract | Publisher Full Text | Free Full Text

175. Boscolo-Rizzo P, Bonetto D, Spina G, et al.: New onset of loss of smell or taste in household contacts of home-isolated SARS-CoV-2-positive subjects. Eur. Arch. Otorhinolaryngol. 2020; 277(9): 2637–2640. PubMed Abstract | Publisher Full Text | Free Full Text

176. Patel A, Charni E, Aryanayagam D, et al.: New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection. Clin. Microbiol. Infect. 2020; 26(9): 1236–1241. PubMed Abstract | Publisher Full Text | Free Full Text

177. Varia LA, Deiana G, Fois AG, et al.: Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head Neck 2020 Jun; 42(6): 1252–6. WOS:
Metropolitan Region. J. Pediatr. 2020; 223: 199-203.e1.

220. Konstantinidis I, Delides A, Tsakrakoulou E, et al.: Short-term follow-up of self-isolated covid-19 patients with smell and taste dysfunction in Greece: Two phenotypes of recovery. ORL 2020.

221. Alshamy A, Alattas R, Anan H, et al.: Silent disease and loss of taste and smell are common manifestations of SARS-COV-2 infection in a quarantined facility: Saudi Arabia. PLoS One 2020; 15(10): e0241258. Epub 2020/10/31.

222. Paderno A, Schreiber A, Grammatica A, et al.: Smell and taste alterations in COVID-19: a cross-sectional analysis of different cohorts. Int Forum Allergy Rhinol 2020; 10(8): 955-962.

223. Santos-Cordero, Sánchez Casasanta, M. et al.: Alterations in COVID-19: a cross-sectional analysis of different cohorts. Int Forum Allergy Rhinol 2020; 10(8): 955-962.

224. Dell’Era V, Farri F, Garzaro G, et al.: Smell and taste disorders during COVID-19 outbreak: Cross-sectional study on 355 patients. Head Neck 2020; 42(7): 1591-1596.

225. Barin-Sánchez I, Santiago C, Goizuetu-San Martin G, et al.: Smell and taste disorders in Spanish patients with mild COVID-19. Neurologia 2020.

226. Izquierdo-Domínguez A, Rojas-Lechuga MJ, Chiesa-Estomba C, et al.: Smell and taste dysfunction in covid-19 is associated with younger age in ambulatory settings: A multicenter cross-sectional study. J Investig Allergol Immunol. 2020; 30(5): 346-357.

227. Lima MA, Silva MT J, Oliveira RV, et al.: Smell dysfunction in COVID-19 patients: More than a yes-no question. J. Neurosurg. Sci. 2020; 418.

228. Moen ST, Hashemian SM, Mansourafshar B, et al.: Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol 2020; 10(8): 944-950.

229. Foster KJ, Jauregui E, Tajadeen B, et al.: Smell loss is a prognostic factor for lower severity of coronavirus disease 2019. Ann. Allergy Asthma Immunol. 2020; 125(4): 481-483.

230. Freni F, Meduri A, Gaza F, et al.: Symptomatology in head and neck district in coronavirus disease (COVID-19): A possible neuroinvasive action of SARS-CoV-2. Eur. Arch. Otorhinolaryngol. 2020; 277(4): 1157-1163.

231. Salepi E, Turk B, Ozcan SN, et al.: Symptomatology of COVID-19 from the otolaryngology perspective: a survey of 223 SARS-CoV-2 RNA-positive patients. Eur. Arch. Otorhinolaryngol. 2020; 277(4): 1157-1163.

232. Gazzano A, Luzzatti R, Lo Mussolo M, et al.: Taste and Smell Disorders in COVID-19 Patients: Role of Interleukin-6. ACS Chem Neurosci. 2020; 11(17): 2774-81. Epub 2020/08/19.

233. Bidkar V, Mishra M, Selvaprakash K, et al.: Testing Olfactory and Gustatory Dysfunctions among Quarantine COVID-19 Suspects. Indian J Otolaryngol Head Neck Surg 2020.

234. Joffily L, Ungererowicz A, David AG, et al.: The close relationship between sudden loss of smell and COVID-19. Braz. J. Otorhinolaryngol. 2020; 86(5): 632-638.

235. Moro E, Priori A, Beghi E, et al.: The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection. Eur. J. Neurolog. 2020; 27(9): 1723-1732.

236. Fantozzi P, Pampena E, Di Vanna D, et al.: Olfactometry, gustatory and olfactory dysfunctions in patients with COVID-19. Ann J Otolaryngol Head Neck Med Surg 2020; 41(6).

237. Mao L, Wang M, Chen S, et al.: Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study. medRxiv 2020; 2020.02.22.20026500.

238. Cabañeras P, Lechín JR, Saussez S, et al.: Objective Olfactory Evaluation of Self-reported Olfactory Dysfunction in a Case Series of 86 COVID-19 Patients. medRxiv 2020; 2020.05.03.20088529.

239. Chiesa-Estomba CM, Lechín JR, Radulescu T, et al.: Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. Eur. J. Neurol. 2020; 27(11): 2318-2321.

240. Talavera B, Garcia-Aazorin D, Martinez-Piñas E, et al.: Anosmia is associated with lower in-hospital mortality in COVID-19. J. Neurol. Sci. 2020; 419.

241. Giorla A, Ferretti F, Biagini C, et al.: A Literature Systematic Review with Meta-Analysis of Symptoms Prevalence in Covid-19: the Relevance of Olfactory Symptoms in Infection Not Requiring Hospitalization. Curr. Treat. Options Neurol. 2020; 22(10): 36. Epub 2020/08/28.

242. Department of Health and Social Care: Statement from the UK Chief Medical Officers on an update to coronavirus symptoms: 18 May 2020.

243. Ear N Throat Society of the United Kingdom (ENTUK): Loss of sense of smell as marker of COVID-19 infection. 2020.

244. Kaye R, Chang CWD, Kazahaya K, et al.: COVID-19 Anosmia Reporting Tool: Initial Findings. Otolaryngol. Head Neck Surg. 2020; 2020/07/01; 163(1): 132-4.

245. Suzuki M, Saito K, Min W-P, et al.: Identification of Viruses in Patients With Postviral Olfactory Dysfunction. Laryngoscope 2007; 2007/02/01; 117(2): 272-7.

246. Kondo Y, Miyazaki S, Yamashita R, et al.: Coinfection with SARS-CoV-2 and influenza A virus, BMJ Case Rep 2020; 13(7).

247. Langerhans P, Fürstenau M, Grueß H, et al.: COVID-19 complicated by parainfluenza co-infection in a patient with chronic lymphocytic leukemia. Eur. J. Haematol. 2020; 105(4): 508-511.

248. Zayet S, Kadian-Oussou NJ, Lepiller Q, et al.: Clinical features of COVID-2019 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect. 2020; 22(9): 481-488.

249. Alshebri MS, Alshouimi RA, Alhumidi HA, et al.: Neurological Complications of SARS-CoV, MERS-CoV, and COVID-19. JN Comp Clin Med 2020; 2020/11/01; 2(1): 2037-47.

250. Hwang C: Olfactory neuropathy in severe acute respiratory syndrome: report of a case. Acta Neuro. Taiwan. 2006; Mar; 15(1): 26-8. Epub 2006/04/08. eng.

251. von Bartheld CS, Hagen MM, Butow R: Prevalence of Chemosensory Dysfunction in COVID-19 Patients: A Systematic Review and Meta-analysis Reveals Significant Ethnic Differences. ACS Chem. Neurosci. 2020; 2020/10/07; 11(19): 2944-61.

252. Heymans M, Lacrocq J-S, Terzic A, et al.: Gustatory dysfunction after mandibular zoster. Neurol. Sci. 2011; 2011/06/01; 32(2): 461-4.

253. Graham CS, Graham BG, Bartlett JA, et al.: Taste and smell losses in HIV infected patients. Physiol. Behav. 1995 1995/08/01; 58(2): 287-93.

254. Zayet S, Kloepferstein T, Mercier J, et al.: Contribution of anosmia and dysgeusia for diagnostic of COVID-19 in outpatients. Infection 2020; 1-5. eng.

255. Butow R, von Bartheld CS: Anosmia in COVID-19: Underlying Mechanisms and Assessment of an Olfactory Route to Brain Infection. Neuroscientist 2020; 2020/11/01; 17(11): 1173-1184.

256. El-Anwar MW, Elzayat S, Fouda YA: ENT manifestation in COVID-19 patients. Auris Nasus Larynx 2020; 47(4): 559-64. Epub 2020/06/15. eng.

Published Abstract. | PubMed Abstract | Publisher Full Text | Free Full Text
273. Small DM, Prescott J: Odor/taste integration and the perception of COVID-19: A systematic review. Contribution of carbonic anhydrase, a zinc-metalloenzyme, to normal taste sensation. Biofactors 2000; 12(4): 65–70. Epub 2001/02/24. eng. PubMed Abstract | Publisher Full Text | Free Full Text

274. Jothimani D, Kallias E, Danielraj S, et al.: COVID-19: Poor outcomes in patients with zinc deficiency. International Journal of Infectious Diseases 2020; 2020/11/01; 100. 343–9. PubMed Abstract | Publisher Full Text | Free Full Text

275. Najizade N, Hemati S, Gookizade A, et al.: Preventive effects of zinc sulfate on taste alterations in patients under irradiation for head and neck cancers: A randomized placebo-controlled trial. J Res Med Sci 2013 Feb; 18(2): 123-6. Epub 2013/08/06. eng. PubMed Abstract | Free Full Text

276. Lozada-Nur F, Chainani-Wu N, Fortuna G, et al.: Dysgeusia in COVID-19: Possible Mechanisms and Implications. Oral Surg Oral Med Oral Pathol Oral Radiol 2020; 130(3): 344–6. Epub 2020/06/27. eng. PubMed Abstract | Publisher Full Text | Free Full Text
Open Peer Review

Current Peer Review Status: ✗ ✗ ✗

Version 1

Reviewer Report 23 March 2021

https://doi.org/10.5256/f1000research.31412.r80213

© 2021 Gachabayov M. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Mahir Gachabayov
Department of Surgery, New York Medical College, Valhalla, NY, USA

Thank you for an interesting systematic review. This systematic review and meta-analysis aimed at evaluating the rate of anosmia and dysgeusia in patients with confirmed COVID-19 and their association with disease severity and mortality. The research question makes sense and the methodology chosen for statistical analysis is logical. The Introduction is comprehensible and easy to read, it clearly states the gap in the literature and the rationale behind this research question. The aim of the study was stated clearly. The Methods are well-formulated. Reporting of this review is compliant with the PRISMA guidelines. The search strategy is comprehensive, includes major databases as well as preprint servers. The details of the search strategy and the PRISMA flow diagrams were provided. Eligibility criteria and definitions were reported. Statistical analysis was adequate. The Results are well-written and clear. The findings of the statistical analysis were nicely summarized in tables and illustrated in forest plots. The Discussion is comprehensible and easy to read. The authors have provided interpretation of their findings, and clinical and scientific implications thereof. The authors have provided possible etiopathogenesis for anosmia and dysgeusia in COVID-19 patients. The Conclusion was justified by the statistical findings.

In order to improve the manuscript, I have a few suggestions:

1. There is some confusion between the terms incidence and prevalence. In fact, in the Methods under the Outcomes, the authors stated the primary outcomes to be incidence of anosmia and dysgeusia, whereas they described this metrics as prevalence in the rest of the manuscript. I believe neither of the terms fits the context. I would change these terms to rate, eg. anosmia rate (rate of anosmia) and dysgeusia rate (rate of dysgeusia).

2. I would not use Newcastle-Ottawa scale for risk of bias assessment as it does not evaluate for heterogeneity due to the differences in the definitions of outcomes and interventions to measure the outcome. I would rather use ROBINS-I tool.

3. I would address in the Discussion the reasons for substantial heterogeneity in the pooled
rates of anosmia and dysgeusia. I would consider heterogeneity in geographic locations and community types, heterogeneity in the definitions of anosmia and dysgeusia, and heterogeneity in the definitions of disease severity across the included studies.

4. I would add a brief paragraph to the Discussion (last paragraph) and acknowledge the strengths and limitations of this study.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: clinical outcomes and evidence synthesis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 22 March 2021

https://doi.org/10.5256/f1000research.31412.r80214

© 2021 Enitan S. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Seyi Samson Enitan
Department of Medical Laboratory Science, Babcock University, Ilishan-Remo, Nigeria

The present study examined the global prevalence of anosmia and dysgeusia in COVID-19 patients, their association with severity and mortality of COVID-19, as well as the possible pathobiological mechanisms of anosmia and dysgeusia in COVID-19. Authors reported a global prevalence of 38.2% and 36.6% for anosmia and dysgeusia, respectively. Identified potential mechanisms for anosmia include: Obstruction in the nasal airway, damage in olfactory sensory neurons, olfactory center damage in the brain, olfactory supporting cells dysfunction and inflammation-related olfactory epithelium dysfunction. On the other hand, the subsequent effect of cranial nerves dysfunction, Zinc deficiency, SARS-CoV-2-bound sialic acid, Direct attack on several oral sites are opined to be responsible for the dysgeusia.
The work is okay and the findings are worth-sharing with the scientific community. The introduction is considered satisfactory. Authors provided background that puts the manuscript into context and allows readers outside the field to understand the purpose and significance of the study. They also identified the existing gap in knowledge that needs to be filled. The methodology section was clearly presented to allow the reproduction of the study. Discussion and Conclusion were well written. However, the limitation of the study was not clearly stated. And except, the association of anosmia and dysgeusia with severity and mortality is properly discussed in the study, it should be deleted from the objectives.

**Rating of the manuscript:** Use (1 = Excellent) (2 = Very Good) (3 = Average) (4 = Fair) (5 = poor)

- Originality: 2
- Contribution To The Field: 1
- Technical Quality: 2
- Clarity of Presentation: 2
- Depth of Research: 2

**Recommendation:** Minor corrections are needed.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**
Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**
Yes

**Is the statistical analysis and its interpretation appropriate?**
Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Medical Virology and Immunology of Infectious Diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Cissy Kartasasmita  
Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

**Objectives of study**  
"The present study aimed to summarize the global evidence of anosmia and dysgeusia among COVID-19 patients, in order to assess their association with the severity and mortality of the disease, and provide a comprehensive review related to the possible pathogenesis of anosmia and dysgeusia in SARS-CoV-2 infection."

- The analysis on the assessment of the association with the severity and mortality of the disease is very short and needs more data to be reported.

**Association of anosmia and dysgeusia with COVID-19 severity and mortality**  
"Limited studies have assessed the association between anosmia and dysgeusia and the severity and mortality of COVID-19 cases. One study linked anosmia with a lower fatality rate and a lower ICU admission."

- In the conclusion the authors did not include all the objectives of the study.

- No statement on the association anosmia and dysgeusia with severity and mortality as stated in the objectives.

**Conclusions**

- My recommendation would be to add the limitations of this study.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**  
Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**  
Yes

**Is the statistical analysis and its interpretation appropriate?**  
Yes

**Are the conclusions drawn adequately supported by the results presented in the review?**  
Partly

*Competing Interests*: No competing interests were disclosed.

*Reviewer Expertise*: Pediatrics, Epidemiology, Vaccinology, and Respirology

I confirm that I have read this submission and believe that I have an appropriate level of
expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

• Your article is published within days, with no editorial bias
• You can publish traditional articles, null/negative results, case reports, data notes and more
• The peer review process is transparent and collaborative
• Your article is indexed in PubMed after passing peer review
• Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com