The Association of "Loss of Smell" to COVID-19: A Systematic Review and Meta-Analysis.

Muhammad Aziz
Hemant Goyal
Hossein Haghbin
Wade M Lee-Smith
Mahesh Gajendran

See next page for additional authors

Follow this and additional works at: https://researchrepository.parkviewhealth.org/other

Part of the Medicine and Health Sciences Commons

Recommended Citation
Aziz, Muhammad; Goyal, Hemant; Haghbin, Hossein; Lee-Smith, Wade M; Gajendran, Mahesh; and Perisetti, Abhilash MD, "The Association of "Loss of Smell" to COVID-19: A Systematic Review and Meta-Analysis." (2021). Other Specialties. 39.
https://researchrepository.parkviewhealth.org/other/39

This Article is brought to you for free and open access by the Parkview Research Center at Parkview Health Research Repository. It has been accepted for inclusion in Other Specialties by an authorized administrator of Parkview Health Research Repository. For more information, please contact julie.hughbanks@parkview.com.
Authors
Muhammad Aziz, Hemant Goyal, Hossein Haghbin, Wade M Lee-Smith, Mahesh Gajendran, and Abhilash Perisetti MD
The Association of “Loss of Smell” to COVID-19: A Systematic Review and Meta-Analysis

Muhammad Aziz, MD1, Hemant Goyal, MD2, Hossein Haghibin, MD1, Wade M. Lee-Smith, MLS, BS3, Mahesh Gajendran, MD, MPH4 and Abhilash Perisetti, MD5

1 Department of Internal Medicine, University of Toledo, Toledo, Ohio; 2 The Wright Center for Graduate Medical Education, Scranton, Pennsylvania; 3 University of Toledo Libraries, Toledo, Ohio; 4 Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, Texas; 5 Department of Gastroenterology and Hepatology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

ABSTRACT

Background: The presence of olfactory dysfunction or “loss of smell” has been reported as an atypical symptom in patients with coronavirus disease 2019 (COVID-19). We performed a systematic review and meta-analysis of the available literature to evaluate the prevalence of “loss of smell” in COVID-19 as well as its utility for prognosticating the disease severity.

Methods: An exhaustive search of the PubMed/Medline, Embase, Web of Science, Cochrane Library, LitCovid NIH, and WHO COVID-19 database was conducted through August 6th, 2020. All studies reporting the prevalence of “loss of smell” (anosmia and/or hyposmia/microsmia) in laboratory-confirmed COVID-19 patients were included. Pooled prevalence for cases (positive COVID-19 through reverse transcriptase (RT-PCR) and/or serology IgG/IgM) and controls (negative RT-PCR and/or serology) was compared, and the odds ratio (OR), 95% confidence interval (CI) and the p-value were calculated. A p-value of <0.05 was considered statistically significant.

Results: A total of 51 studies with 11074 confirmed COVID-19 patients were included. Of these, 21 studies used a control group with 3425 patients. The symptom of “loss of smell” (OR: 14.7, CI: 8.9–24.3) was significantly higher in the COVID-19 group when compared to the control group. Seven studies comparing severe COVID-19 patients with- and without “loss of smell” demonstrated favorable prognosis for patients with “loss of smell” (OR: 0.36, CI 0.27–0.48).

Conclusions: Olfactory dysfunction or “loss of smell” is a prevalent symptom in COVID-19 patients. Moreover, COVID-19 patients with “loss of smell” appear to have a milder course of the disease.

Keywords: COVID-19; Olfactory dysfunction; Loss of smell; SARS-CoV-2; Coronavirus.

INTRODUCTION

The pandemic coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The pandemic has resulted in significant economic and healthcare burden. Along with the pulmonary symptoms, the disease is also associated with neurological manifestations such as headache, impaired consciousness, altered gait/ataxia, seizures, diarrhea, nausea/vomiting, loss of smell, and altered taste/dysgeusia. The disease severity is associated with laboratory abnormalities such as low albumin, elevated interleukin 6, increased alanine/aspartate aminotransferase, increased total bilirubin, increased procalcitonin, increased C-reactive protein (CRP), etc. The “loss of smell” is an atypical symptom of COVID-19 and has been reported with varying prevalence in literature. Further, it has been observed that loss of smell is usually associated with milder form of disease compared to severe disease. We performed a systematic review and meta-analysis of available studies to evaluate the prevalence of “loss of smell” in COVID-19 and its utility as a prognostic indicator.
2020, was conducted. The author (W.L.S.) created the initial search strategy using the vocabulary for “COVID-19” and “smell,” which was cross-checked by another reviewer (M.A.). We highlight an example search strategy using EMBASE in Supplementary table 1. Two independent reviewers (M.A. and H.H.) performed the initial screening and data extraction from the articles. Any discrepancy in article screening or data extraction was resolved through mutual discussion.

Inclusion and exclusion criteria

Only articles reporting the laboratory confirmed COVID-19 patients and “loss of smell” were included. Articles were excluded if they had <10 cases of interest. Articles with suspected cases of COVID-19 without a definitive laboratory diagnosis were also excluded. An adherence to “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines was observed.

Study Definition

Severe disease is defined as the presence of either respiratory distress (i.e., rate >30/min, PaO2/FiO2 <300, and/or SpO2 <93%), need for hospitalization, and/or death. Given the heterogeneity in defining the “loss of smell” across studies, we included the concepts of “anosmia (complete loss of smell)” and “hyposmia/microsmia (diminished or partial loss of smell)” collectively as “loss of smell”. Positive COVID-19 cases are defined as patients with laboratory confirmed COVID-19 (through reverse transcriptase polymerase chain reaction (RT-PCR) and/or serological evidence of COVID-19 through IgG/IgM). Controls are defined as patients with negative RT-PCR and/or serological testing.

Statistical measures and synthesis of results

The pooled prevalence of cases (COVID-19) and controls (non-COVID-19) were compared using the DerSimonian-Laird/Random-effect meta-analysis, and outcomes were reported using forest plots, proportions with 95% confidence interval (CI), odds ratio (OR) with 95% CI, p-value (<0.05 was considered statistically significant) and $I^2$ heterogeneity (>50% considered substantial heterogeneity). Meta-analysis was conducted using comprehensive meta-analysis (BioStat, Englewood, New Jersey, USA) and Open Meta Analyst (CEBM, University of Oxford, Oxford, United Kingdom).

Risk of bias

Publication bias was assessed using a funnel plot and Egger’s regression analysis. If significant publication bias was suspected, we utilized the “trim-and-fill” method and Fail-Safe N test. The presence of bias in the individual study was assessed using the Quality in Prognostic Studies (QUIPS) tool.²

RESULTS

A total of 51 studies were included based on the search strategy mentioned previously (Fig. 1). Publication bias based on prevalence for “loss of smell” was noted based on visual assessment of the funnel plot and Egger’s regression analysis (p = 0.01). We then used the “trim-and-fill” method to create adjusted funnel plot that did not significantly differ from the original funnel plot (Supplementary Fig. 1). The Fail-Safe N test was 504 with an alpha of 0.05. This signifies that 504 studies with effect size zero will be needed to nullify the effect noted for the current analysis. Using the QUIPS tool, only seven studies were considered low risk. The other remaining studies either did not account for confounders in their statistical analyses or outcome/prognostic factors were not adequately assessed (Table 1).

A total of 11074 COVID-19 patients (mean age 46.7 ± 10.4 years and males 46.9%) were included in the final analysis (Table 2).²,¹³–⁶² The overall prevalence of “loss of smell” in COVID-19 patients was 52.0% (CI: 42.5%-61.6%, $I^2 = 99.4%$) (Fig. 2). A total of 21 studies compared these symptoms in COVID-19 patients (n = 2196) and controls (n = 3425).¹³,¹⁴,¹⁸,¹⁹,²¹,²⁵,²⁷,²⁸,³⁴ “Loss of smell” was associated significantly more in the COVID-19 group compared to non-COVID-19 group (OR: 14.7, CI: 8.9–24.3, p < 0.001, $I^2 = 83.2%$) (Fig. 3). Among COVID-19 patients, the odds of patients with severe disease and “loss of smell” were significantly lower when compared to patients with severe disease and without “loss of smell” (OR: 0.36, CI 0.27–0.48, p < 0.01, $I^2 = 27.4%$) (Fig. 4).²,²¹,³²,³⁷,⁵²,⁵⁴,⁵⁷

DISCUSSION

We summarized the overall prevalence of “loss of smell” for COVID-19 patients and compared with control patients i.e. those without laboratory confirmation of COVID-19 from the same study period. The overall prevalence of “loss of smell” was significantly higher for the COVID-19 group compared to control group. In addition, “loss of smell” had a lower association with severe COVID-19 compared to COVID-19 patients without “loss of smell”.

Olfactory and gustatory changes are one of the most underreported symptoms in COVID-19 and can sometimes be only presenting symptoms in these patients.³ As demonstrated in our study, “loss of smell” was associated with somewhat favorable prognosis of the disease and hence careful screening should be undertaken to identify potential patients with COVID-19. These patients should undergo testing to rule out COVID-19. This will help in preventing the spread of the virus.

We noted significant variations in the reporting of symptoms (i.e., dysosmia/anosmia/hyposmia/microsmia) in the studies. Mao et al. noted “loss of smell” in 5.1% of their cohort, while Moein et al. noted that roughly 98% of patients had “loss of smell”.²,¹⁸ Earlier studies such as by Mao et al. relied on the retrospective data.
collection and questionnaire based survey. As the olfactory symptoms became well-recognized, the newer studies might have assessed these patients specifically for these symptoms, resulting in a higher prevalence of olfactory symptoms. Further, only few studies objectively evaluated the “loss of smell” using validated tools.\textsuperscript{18,20,25,35,42,44,60,61} The objective methods used in literature to assess “loss of smell” included: “Sniffing Sticks test”, “The University of Pennsylvania Smell Identification Test (UPSIT)”, “Quick Smell Identification Test (Q-SIT)”, and “Connecticut Chemosensory Clinical Research Center Test (CCCRC test)”. We feel that the actual prevalence of olfactory symptoms could be much higher than what is reported as we have combined data from relatively older studies as well. Our results should be interpreted as such keeping in mind this important limitation.

Only 7 studies compared the disease severity in patients with “loss of smell” versus those without “loss of smell”. Although our results are limited due to the very small sample size, “loss of smell” was characterized by the less severe disease compared to those without this symptom. This finding is noteworthy and needs to be further explored in more extensive studies. The limitation of our analysis is the observational nature of the studies with significant variations in the reporting of symptoms and follow-up. A temporospatial association of the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{prisma_flow_diagram.png}
\caption{PRISMA flow diagram.}
\end{figure}
Table 1. The Quality in Prognostic Studies (QUIPS) table for risk of bias

| Study, year | Participation (The study sample represents population of interest on key characteristics?) | Attrition (The proportion of study sample providing outcome data is adequate?) | Prognostic factor measurement (Prognostic factor is adequately measured in study subjects?) | Outcome measurement (The outcome of interest is adequately measured in study subjects?) | Study confounders (Potential confounders are accounted for?) | Statistical analysis? (Statistical analysis appropriately designed for the study?) |
|-------------|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| Abalo-Lojo  | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No                                                                             | No                                                                              |
| Aggrawal    | Yes                                                                                      | Partly                                                                         | No                                                                                          | Partly                                                                             | No                                                                             | Yes                                                                              |
| Altin       | Yes                                                                                      | No                                                                             | Yes                                                                                          | No                                                                                 | Yes                                                                            | Yes                                                                              |
| Beltran-Corbellini | Yes                                         | Yes                                                                            | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Brandstetter| Yes                                                                                      | Yes                                                                            | Yes                                                                                          | No                                                                                 | Yes                                                                            | Yes                                                                              |
| Carigan     | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | No                                                                                 | Yes                                                                            | Yes                                                                              |
| Chiesa-Estomba | Yes                                           | Yes                                                                            | No                                                                                          | Yes                                                                                 | No                                                                             | Yes                                                                              |
| Chiesa-Estomba 2 | Yes                                             | Yes                                                                            | No                                                                                          | Yes                                                                                 | No                                                                             | Yes                                                                              |
| D'Ascanio   | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | Yes                                                                              |
| Dawson      | Yes                                                                                      | Yes                                                                            | No                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Dell'Era    | Yes                                                                                      | No                                                                             | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Giacomelli  | Yes                                                                                      | No                                                                             | Yes                                                                                          | No                                                                                 | Yes                                                                            | Yes                                                                              |
| Gorzkowski | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No                                                                             | Yes                                                                              |
| Guner       | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No                                                                             | Yes                                                                              |
| Hashner     | Yes                                                                                      | Partly                                                                         | Yes                                                                                          | No                                                                                 | No                                                                             | No                                                                              |
| Hintschich  | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | No                                                                                 | Yes                                                                            | Yes                                                                              |
| Hornus      | Yes                                                                                      | Yes                                                                            | Partly                                                                         | No                                                                                 | No                                                                             | No                                                                              |
| Izquierdo-Dominguez | Yes                             | Yes                                                                            | Yes                                                                                          | Yes                                                                                 | No                                                                             | Yes                                                                              |
| Jalesi      | Yes                                                                                      | No                                                                             | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Kai Chua    | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | No                                                                                 | Yes                                                                            | No                                                                              |
| Kempler     | Yes                                                                                      | Partly                                                                         | Yes                                                                                          | No                                                                                 | No                                                                             | No                                                                              |
| Kin         | Yes                                                                                      | Partly                                                                         | No                                                                                          | Partly                                                                             | No                                                                             | No                                                                              |
| Klopfenstein| Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No Partly                                                                       | Yes                                                                              |
| Lechien (1) | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No Partly                                                                       | Yes Partly                                                                       |
| Lechien (2) | Yes                                                                                      | Yes                                                                            | Partly                                                                         | No                                                                                 | No Partly                                                                       | Yes Partly                                                                       |
| Lechien (3) | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | Yes                                                                              |
| Lechien (4) | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | Yes                                                                              |
| Lee         | Yes                                                                                      | No                                                                             | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Liang       | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No                                                                             | Yes                                                                              |
| Magnavita   | Yes                                                                                      | Yes                                                                            | No                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Mao         | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Partly                                                                         | Partly                                                                         |
| Martin-Sanz | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | No                                                                                 | Yes                                                                            | Yes                                                                              |
| Mishra      | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No                                                                             | No                                                                              |
| Moein       | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Partly                                                                         |
| Noh         | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No Partly                                                                       | Yes                                                                              |
| Paderno (1) | Yes                                                                                      | No                                                                             | Partly                                                                         | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Paderno (2) | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | Yes                                                                              |
| Parente-Arias | Yes                                           | Yes                                                                            | No                                                                                          | Partly                                                                             | No                                                                             | Yes                                                                              |
| Patel       | Yes                                                                                      | No                                                                             | Partly                                                                         | No                                                                                 | No Partly                                                                       | Yes                                                                              |
| Petrocelli  | Yes                                                                                      | No                                                                             | Partly                                                                         | No                                                                                 | No Partly                                                                       | Yes                                                                              |
| Qu          | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No Partly                                                                       | Yes                                                                              |
| Romero-Sanchez | Yes                                   | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | No                                                                               |
| Sakalli     | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | Yes                                                                              |
| Sayin       | Yes                                                                                      | Partly                                                                         | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Tostmann    | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | Partly                                                                             | Yes Partly                                                                     | Partly                                                                           |
| Tsangoulis  | Yes                                                                                      | Partly                                                                         | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | No                                                                               |
| Vaira (1)   | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No Partly                                                                       | Yes                                                                               |
| Vaira (2)   | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | No Partly                                                                       | Yes                                                                               |
| Yan (1)     | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Yan (2)     | Yes                                                                                      | Yes                                                                            | No                                                                                          | Partly                                                                             | Yes                                                                            | Yes                                                                              |
| Zayet       | Yes                                                                                      | Yes                                                                            | Yes                                                                                          | Yes                                                                                 | Yes                                                                            | Yes                                                                              |
| Study, year      | Country     | Center (single, dual, multi) | Study Period | Type of study | Total Patients, non COVID group, N | Total Patients, COVID group, N | Mean age, COVID group (years) | Male gender, COVID group (%) | "Loss of smell" in COVID group, N (%) | "Loss of smell" in non COVID group, N (%) |
|-----------------|-------------|------------------------------|--------------|---------------|-----------------------------------|-------------------------------|-----------------------------|-------------------------------|---------------------------------|---------------------------------|
| Abalo-Lojo, 2020| Spain       | Single                       | –            | Cohort        | –                                 | 131                           | 50.4                        | 56 (42.6%)                    | 77 (58.8%)                      | –                               |
| Aggrawal, 2020  | USA         | Single                       | Mar 1-Apr 4  | Cohort        | –                                 | 16                            | 65.5                        | 12 (75.0%)                    | 3 (18.8%)                       | –                               |
| Altin, 2020     | Turkey      | Dual                         | Mar 25-Apr 20| Cohort        | 40                                | 81                            | 54.2                        | –                             | 50 (61.7%)                      | 0 (0%)                          |
| Beltran-Corbellini, 2020 | Spain | Dual                     | Mar 23-Mar 25| Case-control  | 40                                | 79                            | –                          | 48 (60.8%)                    | 25 (31.6%)                      | 4 (10.0%)                       |
| Brandstetter, 2020 | Germany | Single                     | –            | Cohort        | 170                               | 31                            | –                          | 30 (14.9%)                    | 16 (51.6%)                      | 4 (2.4%)                        |
| Carigan, 2020   | Canada      | Single                       | Mar 10- Mar 23| Case-control  | 134                               | 134                           | 57.1                        | –                             | 69 (51.5%)                      | 6 (4.5%)                        |
| Chiesa-Estomba (1), 2020 | South America (multiple countries) | Multi               | Cross-sectional | –                     | 542                              | 34                            | 218 (40.2%)                | 444 (819%)                     | –                               |
| Chiesa-Estomba (2), 2020 | Europe (multiple countries) | Multi               | Cross-sectional | –                     | 1231                             | 41                            | –                          | 970 (78.8%)                   | –                               |
| D’Ascanio, 2020 | Italy       | Single                       | Feb 1-Apr 24 | Case-control  | 25                                | 43                            | 58.1                        | –                             | 26 (60.5%)                     | –                               |
| Dawson, 2020    | USA         | Single                       | Mar-Apr      | Cohort        | 48                                | 42                            | –                          | 48 (53.3%)                    | 18 (42.9%)                      | 1 (2.1%)                        |
| Dell’Era, 2020  | Italy       | Single                       | Mar 10- Mar 30| Cross-sectional | –                                 | 355                           | 50                          | 192 (54.1%)                  | 237 (66.8%)                    | –                               |
| Giacomelli, 2020| Italy       | Single                       | –            | Cross-sectional | –                                 | 59                            | 60                          | 40 (67.8%)                    | 14 (23.7%)                     | –                               |
| Gorzkowski, 2020| France      | Single                       | Mar 1- Mar 31| Cross-sectional | –                                 | 229                           | 39.7                        | 82 (35.8%)                    | 140 (61.1%)                    | –                               |
| Guner, 2020     | Turkey      | Single                       | Mar 10-Apr 10| Cohort        | –                                 | 222                           | 50.6                        | 132 (59.6%)                  | 19 (8.6%)                      | –                               |
| Haechner, 2020  | Germany     | Single                       | –            | Cross-sectional | 466                               | 34                            | –                          | 15 (44.1%)                    | 21 (61.7%)                      | 47 (10.1%)                      |
| Hintschich, 2020| Germany     | Single                       | –            | Cohort        | 30                                | 41                            | 37                          | 13 (31.7%)                    | 22 (53.7%)                      | 8 (26.7%)                       |
| Hornus, 2020    | Germany     | Single                       | –            | Cross-sectional | 45                                | 45                            | 56                          | –                             | 38 (84.4%)                      | 12 (26.7%)                      |
| Izquierdo-Dominguez, 2020 | Spain | Multi                    | Mar 21-Apr 18| Cross-sectional | 143                               | 846                           | 56.8                        | –                             | 454 (53.6%)                    | 43 (30.1%)                      |
| Jalessi, 2020   | Iran        | Single                       | Feb-Mar      | Cohort        | –                                 | 92                            | 52.9                        | 62 (67.4%)                    | 22 (23.9%)                     | –                               |
| Kai Chua, 2020  | Singapore   | Single                       | Mar 23-Apr 4 | Cohort        | 686                               | 31                            | –                          | –                             | 7 (22.6%)                      | 22 (3.2%)                       |
| Kempker, 2020   | USA         | Single                       | –            | Cohort        | 232                               | 51                            | –                          | 10 (19.6%)                    | 48 (94.1%)                     | 27 (11.6%)                      |
| Kim, 2020       | Korea       | Single                       | Mar 12-16    | Cross-sectional | –                                 | 172                           | 26                          | 66 (38.4%)                    | 68 (39.5%)                     | –                               |
| Klopfenstein, 2020 | France | Single                    | March 1-Mar 17| Cohort        | –                                 | 114                           | –                          | –                             | 54 (47.4%)                     | –                               |
| Lechien (1), 2020 | 18 European hospitals | Multi               | –            | Cross-sectional | –                                 | 417                           | –                          | 357 (85.6%)                   | –                               |
| Lechien (2), 2020 | Belgium       | Single                      | –            | Cross-sectional | –                                 | 86                            | 41.7                        | 30 (34.9)                     | 53 (61.6%)                     | –                               |
| Lechien (3), 2020 | 12 European hospitals | Multi               | Mar 22-Apr 10| Cross-sectional | –                                 | 1420                          | 39.2                        | –                             | 997 (70.2%)                    | –                               |
| Lechien (4), 2020 | Belgium      | Single                       | Mar 20-Apr 16| Cross-sectional | –                                 | 47                            | 58.8                        | 22 (46.8%)                    | 13 (27.6%)                     | –                               |
| Lee, 2020       | Canada      | Single                       | Mar 16-Apr 15| Cross-sectional | 71                                | 56                            | 38                          | 23 (41.1%)                    | 31 (55.4%)                     | 3 (4.2%)                        |
| Liang, 2020     | China       | Single                       | Mar 16-Apr 12| Cohort        | –                                 | 86                            | 25.5                        | 44 (51.2%)                    | 34 (39.5%)                     | –                               |
| Magnavita, 2020 | Italy       | Multi                       | Mar 27-Apr 30| Cross-sectional | 513                               | 82                            | –                          | –                             | 35 (42.7%)                      | 4 (0.8%)                        |
| Mao, 2020       | China       | Multi                       | Jan 16- Feb 19| Cohort        | –                                 | 214                           | –                          | –                             | 11 (5.1%)                      | –                               |
| Martin-Sanz, 2020 | Spain       | Single                      | Mar 1-Apr7   | Case-control  | 140                               | 215                           | –                          | 44 (20.5%)                    | 138 (64.1%)                    | 30 (24.8%)                      |
| Study, year | Country          | Center (single, dual, multi) | Study Period          | Type of study     | Total Patients, non COVID group, N | Total Patients, COVID group, N | Mean age, COVID group (years) | Male gender, COVID group (%) | “Loss of smell” in COVID group, N (%) | “Loss of smell” in non COVID group, N (%) |
|-------------|------------------|-----------------------------|-----------------------|-------------------|-----------------------------------|--------------------------------|--------------------------------|-------------------------------|---------------------------------|-----------------------------------|
| Mishra, 2020 | India            | Single                      | –                     | Cross-sectional   | 74                                | 74                             | –                              | 43 (58.1%)                    | 11 (14.8%)                      | 1 (1.4%)                          |
| Moein, 2020  | Iran             | Single                      | March 21 - Apr 5      | Case-control      | 60                                | 60                             | 46.6                           | 40 (66.7%)                    | 59 (98.3%)                      | 11 (18.3%)                        |
| Noh, 2020    | Korea            | Single                      | NR                    | Cohort            | –                                 | 199                            | 38                             | 69 (34.7%)                    | 52 (26.1%)                      | –                                 |
| Paderno (1), 2020 | Italy      | Single                      | Mar 27-Apr 1          | Cohort            | –                                 | 151                            | 45                             | 56 (37.1%)                    | 126 (83.4%)                     | –                                 |
| Paderno (2), 2020 | Italy      | Single                      | Mar 27-Apr 1          | Cross-sectional   | –                                 | 508                            | 55                             | 284 (55.9%)                    | 283 (55.7%)                     | –                                 |
| Parente-Arias, 2020 | Spain      | Single                      | Mar 3-Mar 24          | Cohort            | –                                 | 151                            | –                              | 53 (35.1%)                    | 75 (49.7%)                      | –                                 |
| Patel, 2020  | UK               | Single                      | Mar 1-Apr 1           | Cross-sectional   | –                                 | 141                            | 45.6                           | 83 (58.8%)                    | 80 (56.7%)                      | –                                 |
| Pietrocelli, 2020 | Italy      | Single                      | Apr 16-May 2          | Cohort            | –                                 | 300                            | 43.6                           | 75 (25.0%)                    | 184 (61.3%)                     | –                                 |
| Qiu, 2020    | China, France, Germany | Multi                     | Mar 15-Apr 5         | Cohort            | –                                 | 394                            | –                              | –                             | 154 (40.9%)                     | –                                 |
| Romero-Sanchez, 2020 | Spain      | Dual                       | Mar 1-Apr 1           | Cohort            | –                                 | 841                            | 66.4                           | 473 (56.2%)                    | 41 (64.1%)                      | –                                 |
| Sakalli, 2020 | Turkey           | Single                      | –                     | Cross-sectional   | –                                 | 172                            | 37.8                           | 84 (48.8%)                    | 18 (10.4%)                      | –                                 |
| Sayin, 2020  | Turkey           | Single                      | –                     | Cross-sectional   | 64                                | 64                             | 37.8                           | 25 (39.1%)                    | 41 (64.1%)                      | 13 (20.3%)                       |
| Tostmann, 2020 | Netherlands  | Single                      | Mar 10-Mar 29         | Cross-sectional   | 190                               | 79                             | –                              | –                             | 37 (46.8%)                      | 7 (3.7%)                          |
| Tsivgoulis, 2020 | Greece      | Single                      | Mar 19- Apr 8         | Case-control      | 22                                | 22                             | 55                             | 6 (54.5%)                     | 17 (77.3%)                      | 8 (36.4%)                        |
| Vaira (1), 2020 | Italy        | Single                      | Mar 31 - Apr 6        | Cross-sectional   | –                                 | 72                             | –                              | –                             | 60 (83.3%)                      | –                                 |
| Vaira (2), 2020 | Italy        | Multi                       | –                     | Cohort            | –                                 | 345                            | 48.5                           | 146 (42.3%)                    | 241 (69.9%)                     | –                                 |
| Yan (1), 2020 | USA             | Single                      | Mar 3-Mar 29          | Cross-sectional   | 203                               | 59                             | –                              | 29 (49.2%)                    | 40 (67.8%)                      | 33 (16.3%)                       |
| Yan (2), 2020 | USA             | Single                      | Mar 3- Apr 8          | Cohort            | –                                 | 128                            | –                              | –                             | 75 (59.6%)                      | –                                 |
| Zayet, 2020  | France           | Single                      | Feb 26-Mar 14         | Cohort            | 54                                | 70                             | 50.4                           | 29 (41.4%)                    | 37 (54.2%)                      | 9 (16.7%)                        |
disease severity and the symptom was not possible. However, our study is novel as we performed a pooled analysis combining the statistical power and further compared and demonstrated the prevalence in the control group.

In conclusion, we demonstrate here that alteration in smell is prevalent in COVID-19 and should be included as one of the essential symptoms to screen the population. Further larger studies are urgently needed to evaluate the utility of olfactory dysfunction in patients with COVID-19, as demonstrated in our study. Therefore,

FIGURE 2. Forest plot demonstrating overall prevalence of “loss of smell” in COVID-19 patients.
alteration in the sense of smell should be added as a screening question to identify not only the symptomatic disease but also possible healthy (or presumed asymptomatic) carriers of the disease.

AUTHOR CONTRIBUTIONS
Conception and design: Muhammad Aziz, Hemant Goyal, Literature search: Wade M. Lee-Smith, First draft: Muhammad Aziz, Critical revision and editing: All authors, Final approval: All authors.

SUPPLEMENTARY MATERIALS
Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjms.2020.09.017.
19. Aziz M, Fatima R, Assaly R. Elevated interleukin–6 and severe COVID–19: a meta–analysis. J Med Virol. 2020. https://doi.org/10.1002/jmv.25942. [article in press].

18. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID–19: a systematic review and meta-analysis. Crit Care. 2020;24:255.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45:139–145.

28. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Syn Meth. 2010;1:97–111.

27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–560.

26. Dell’Era V, Farri F, Garzaro G, Gatto M, et al. Neurosensory dysfunction: a diagnostic marker of early COVID–19. J Investig Allergol Clin Immunol. 2020;9:1308–1313.

25. Aziz M, Fatima R, Assaly R. Loss of smell and taste as a biomarker for COVID-19. J Environ Res Public Health. 2020;13:104521. https://doi.org/10.3390/ijerph17145218. [article in press].

24. Kempker RR, Kempker JA, Peters M, Rebolledo PA, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Laryngoscope. 2020;130:2251–2261.

23. Yan CH, Faraji F, Prajapati DP, Boone CE, et al. Association of chemosensory dysfunction and COVID–19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol. 2020;10:806–813.

22. Yan CH, Faraji F, Prajapati DP, Ostrand BT, et al. Self-reported olfactory dysfunction associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol. 2020;10:821–831.

21. Abalo–Lojo JM, Pouso–Díaz JM, Gonzalez F. Taste and smell dysfunction in COVID–19 patients. Ann Otol Rhinol Laryngol. 2020;129:1041–1042.

20. Vaira LA, Deiana G, Fois AG, Pirina P, et al. Objective evaluation of anosmia and ageusia in COVID–19 patients: Single-center experience on 72 cases. Head Neck. 2020;42:1252–1258.

19. Tostmann A, Bradley J, Bousesma T, Yiek W, et al. Strong associations and moderate predictive value of early symptoms for SARS-Cov-2 test positivity among healthcare workers, the Netherlands, March 2020. Euro Surveill. 2020;25:200058.

18. Altin F, Cingi C, Uzun T, Bal C. Olfactory and gustatory abnormalities in COVID–19 cases. Eur Arch Otorhinolaryngol. 2020. https://doi.org/10.1007/s00405-020-08155-9. [article in press].

17. Dell’Era V, Farri F, Garzaro G, Gatto M, et al. Smell and taste disorders during COVID–19 outbreak: cross-sectional study on 355 patients. Head Neck. 2020;42:1591–1596.

16. Brandstetter S, Roth S, Harner S, Buntrock-Dopke H, et al. Symptoms and immunoglobulin development in hospital staff exposed to a SARS-CoV-2 outbreak. Pediatr Allergy Immunol. 2020. https://doi.org/10.1111/pai.13278. [article in press].

15. Carignan A, Vaillette L, Grenier C, Musonera JB, et al. Anosmia and dysgeusia with SARS-CoV-2 infection: an age–matched case–control study. CMAJ. 2020;192:E702–E707.

14. Chiesa-Estomba CM, Lechjen JR, Portillo-Mazal P, Martinez F, et al. Olfactory and gustatory dysfunctions in COVID-19. first reports of Latin-American ethnic patients. Am J Otolaryngol. 2020;41:108005.

13. Chiesa-Estomba CM, Lechjen JR, Radulescu T, Michel J, et al. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. Eur J Neurol. 2020. https://doi.org/10.1111/ene.14440. [article in press].

12. Gorkowski V, Bevlacqua S, Charmillon A, Jankowski R, et al. Evolution of olfactory disorders in COVID–19 patients. Laryngoscope. 2020. https://doi.org/10.1002/lary.28967.

11. Aziz M, Fatima R, Assaly R. Self-reported anosmia and dysgesia as key symptoms of coronavirus disease 2019. J Investig Allergol Clin Immunol. 2020. https://doi.org/10.1177/jiaa.109599. [article in press].

10. Yan CH, Faraji F, Prajapati DP, Ostrand BT, et al. Objective olfactory dysfunction associates with outpatient clinical course in COVID–19. J Investig Allergol Clin Immunol. 2020. https://doi.org/10.1177/jiaa.109599. [article in press].

9. Yan CH, Faraji F, Prajapati DP, Ostrand BT, et al. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol. 2020;10:821–831.

8. Lechjen JR, Cabarraux P, Chiesa-Estomba CM, Khalife M, et al. Objective evaluation of self-reported loss of smell in a case series of 86 COVID–19 patients. Head Neck. 2020;42:1583–1590.

7. Lee DJ, Lockwood J, Das P, Wang R, et al. Self-reported anosmia and dysgeusia as key symptoms of coronavirus disease 2019. CJEM. 2020. https://doi.org/10.1017/cjem.2020.420. [article in press].

6. Liang Y, Xu J, Chu M, Mai J, et al. Neurosensory dysfunction: a diagnostic marker of early COVID–19. Int J Infect Dis. 2020;98:347–352.

5. Magnavita N, Tripedi G, Di Prinzo RR. Symptoms in health care workers during the COVID-19 epidemic: a cross-sectional survey. Int J Environ Res Public Health. 2020;17:5218. https://doi.org/10.3390/ijerph17145218.

4. Martin-Sanz E, Riestra J, Yebra L, Larran A, et al. Prospective study in 355 patients with suspected COVID-19 infection. value of cough, subjective hypoxemia, and dysgeusia. Laryngoscope. 2020. https://doi.org/10.1002/lary.28999. [article in press].
49. Mishra P, Gowda V, Dixit S, Kaushik M. Prevalence of new onset anosmia in COVID-19 patients: is the trend different between European and Indian populations? Indian J Otolaryngol Head Neck Surg. 2020. https://doi.org/10.1007/s12070-020-01986-8. [article in press].

50. Noh JY, Yoon JG, Seong H, et al. Asymptomatic infection and atypical manifestations of COVID-19: Comparison of viral shedding duration. J Infect. 2020. https://doi.org/10.1016/j.jinf.2020.05.035. [article in press].

51. Paderno A, Mattavelli D, Rampinelli V, Grammatica A, et al. Olfactory and gustatory outcomes in COVID-19: a prospective evaluation in nonhospitalized subjects. Otolaryngol Head Neck Surg. 2020. https://doi.org/10.1177/0194599820939538. [article in press].

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

53. Parente-Arias P, Barreira-Fernandez P, Quintana-Sanzuas A, Patino-Castineira B. Recovery rate and factors associated with smell and taste disruption in patients with coronavirus disease 2019. Am J Otolaryngol. 2020. https://doi.org/10.1016/j.amjoto.2020.102648. [article in press].

54. Patel A, Charani E, Ariyanayagam D, Abdulal A, et al. New-onset anosmia and ageusia in adult patients diagnosed with SARS-CoV-2 infection. Clin Microbiol Infect. 2020;26:1236–1241.

55. Petrocelli M, Ruggiero F, Baietti AM, Pandolfi P, et al. Remote psychophysical evaluation of olfactory and gustatory functions in early-stage coronavirus disease 2019 patients: the Bologna experience of 300 cases. J Laryngol Otol. 2020. https://doi.org/10.1017/jlt.2020.102645. [article in press].

56. Qiu C, Cui C, Hautefort C, Haehner A, et al. Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: an international multicenter study. Otolaryngol Head Neck Surg. 2020. https://doi.org/10.1177/0194599820934376. [article in press].

57. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, Sanchez-Larsen A, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology. 2020. https://doi.org/10.1212/wnl.0000000000009937. [article in press].

58. Sakalli E, Temirbekov D, Bayr E, Alis EE, et al. Ear nose throat-related symptoms with a focus on loss of smell and/or taste in COVID-19 patients. Am J Otolaryngol. 2020;41:102622.

59. Sayil I, Yasar KK, Yazici ZM. Taste and smell impairment in COVID-19: an AAO-HNS anosmia reporting tool-based comparative study. Otolaryngol Head Neck Surg. 2020. https://doi.org/10.1177/0194599820931820. [article in press].

60. Tsivgoulis G, Fragkou PC, Delides A, Karofylakis E, et al. Quantitative evaluation of olfactory dysfunction in hospitalized patients with Coronavirus (COVID-19). J Neurol. 2020;267:2193–2195.

61. Vaira LA, Hopkins C, Salzano G, Petrocelli M, et al. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter study. Head Neck. 2020;42:1560–1569.

62. Zayet S, Kadiane-Oussou NJ, Lepiller G, Zahra H, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect. 2020. https://doi.org/10.1016/j.micinf.2020.05.016. [article in press].

Submitted May 14, 2020; accepted September 28, 2020.

Conflict of Interest and Ethical statement: The authors have no commercial associations or sources of support that might pose a conflict of interest.

Source of funding: None.

Corresponding author. Hemant Goyal (E-mail: doc.hemant@yahoo.com).