Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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

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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. **[Am J Med Sci 2021;361(2):216–225.]**

INTRODUCTION

The pandemic coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] 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.[2–4] 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.[4–8]

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.[2] 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.

METHODS

Search Strategy

A systematic search of the PubMed/Medline, Embase, Web of Science, Cochrane Library, LitCovid NIH, and WHO COVID-19 databases through August 6th,

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).[9–11] 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.[12]

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).[13,14,18,19,21,25,27,28,34–37,39,40,45,47–49,59,60,62] "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

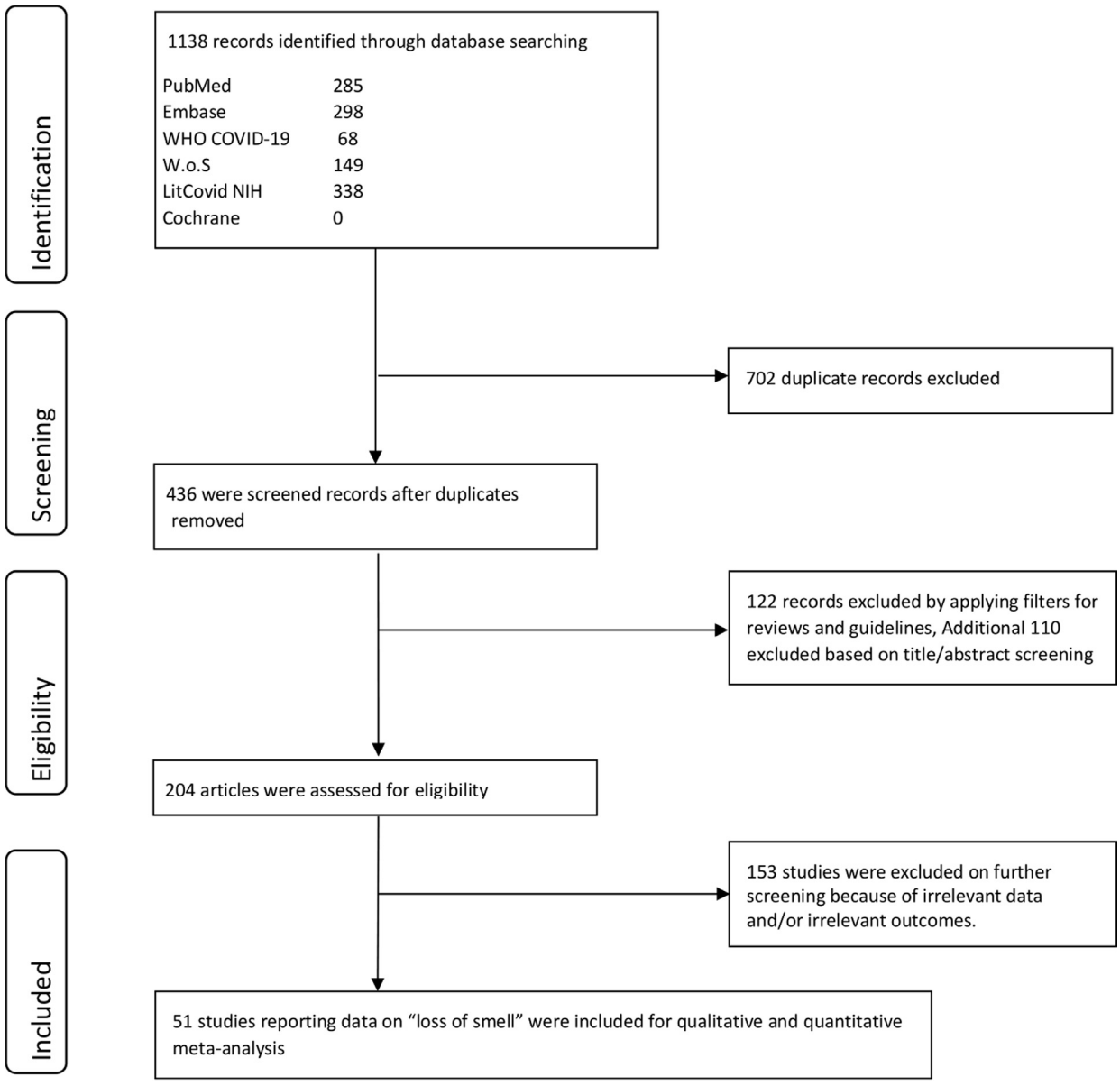

FIGURE 1. PRISMA flow diagram.

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.[18,20,25,35,42,44,60,61] The objective methods used in literature to assess "loss of smell" included: "Sniffin 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

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	Yes	Yes	Yes	No	Yes
Beltran-Corbellini	Yes	Yes	Yes	Yes	Yes	Yes
Brandstetter	Yes	Yes	Yes	Yes	No	Yes
Carigan	Yes	Yes	Yes	Yes	Yes	Yes
Chiesa-Estomba	Yes	Yes	No	Yes	No	No
Chiesa-Estomba 2	Yes	No	No	Yes	No	Yes
D'Ascanio	Yes	Yes	Yes	Partly	Partly	Yes
Dawson	Yes	Yes	Yes	Yes	No	Yes
Dell'Era	Yes	Yes	No	Yes	Yes	Yes
Giacomelli	Yes	Yes	No	Yes	No	No
Gorzkowski	Yes	Yes	No	Partly	No	Yes
Guner	Yes	Yes	No	Partly	No	Yes
Haehner	Yes	Partly	Yes	Yes	No	No
Hintschich	Yes	Partly	Yes	Yes	No	Yes
Hornus	Yes	Yes	Yes	Partly	No	No
Izquierdo-Domínguez	Yes	Yes	Yes	Yes	Yes	Yes
Jalessi	Yes	Yes	No	Yes	Yes	Yes
Kai Chua	Yes	Yes	Yes	Yes	No	No
Kempker	Yes	Partly	Yes	Yes	No	No
Kim	Yes	Partly	No	Partly	No	No
Klopfenstein	Yes	Yes	No	Partly	No	Partly
Lechien (1)	Yes	Yes	No	Partly	Yes	Partly
Lechien (2)	Yes	Yes	Partly	Partly	Yes	Yes
Lechien (3)	Yes	Yes	No	Partly	Yes	Yes
Lechien (4)	Yes	Yes	No	Partly	Partly	Partly
Lee	Yes	No	Yes	Yes	Yes	Yes
Liang	Yes	Yes	No	Partly	No	Yes
Magnavita	Yes	Yes	Yes	Yes	No	Yes
Mao	Yes	Yes	No	Partly	Partly	Partly
Martin-Sanz	Yes	Yes	Yes	Yes	No	Yes
Mishra	Yes	Yes	No	Partly	No	No
Moein	Yes	Yes	Yes	Yes	Yes	Partly
Noh	Yes	Yes	No	Partly	No	Yes
Paderno (1)	Yes	No	No	Partly	Yes	Yes
Paderno (2)	Yes	Yes	No	Partly	Yes	Yes
Parente-Arias	Yes	Yes	No	Partly	No	Yes
Patel	Yes	No	No	Partly	Partly	No
Petrocelli	Yes	No	No	Partly	No	Yes
Qiu	Yes	Yes	No	Partly	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	Yes	Partly	Partly
Tsivgoulis	Yes	Partly	Yes	Yes	Yes	No
Vaira (1)	Yes	Yes	No	Partly	No	Partly
Vaira (2)	Yes	Yes	No	Partly	No	Yes
Yan (1)	Yes	Yes	Yes	Yes	Yes	Yes
Yan (2)	Yes	Yes	No	Partly	Yes	Yes
Zayet	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. Study characteristics, baseline demographics and prevalence of "loss of smell" in COVID and control group (N: No. of patients)

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	–	Cohort	–	1231	41	–	970 (78.8%)	–
D'Ascanio, 2020	Italy	Single	Febr 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 (59.5%)	19 (8.6%)	–
Haehner, 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-Domínguez, 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%)

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Table 2. (*continued*)

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%)	–
Petrocelli, 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	Mutli	–	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%)

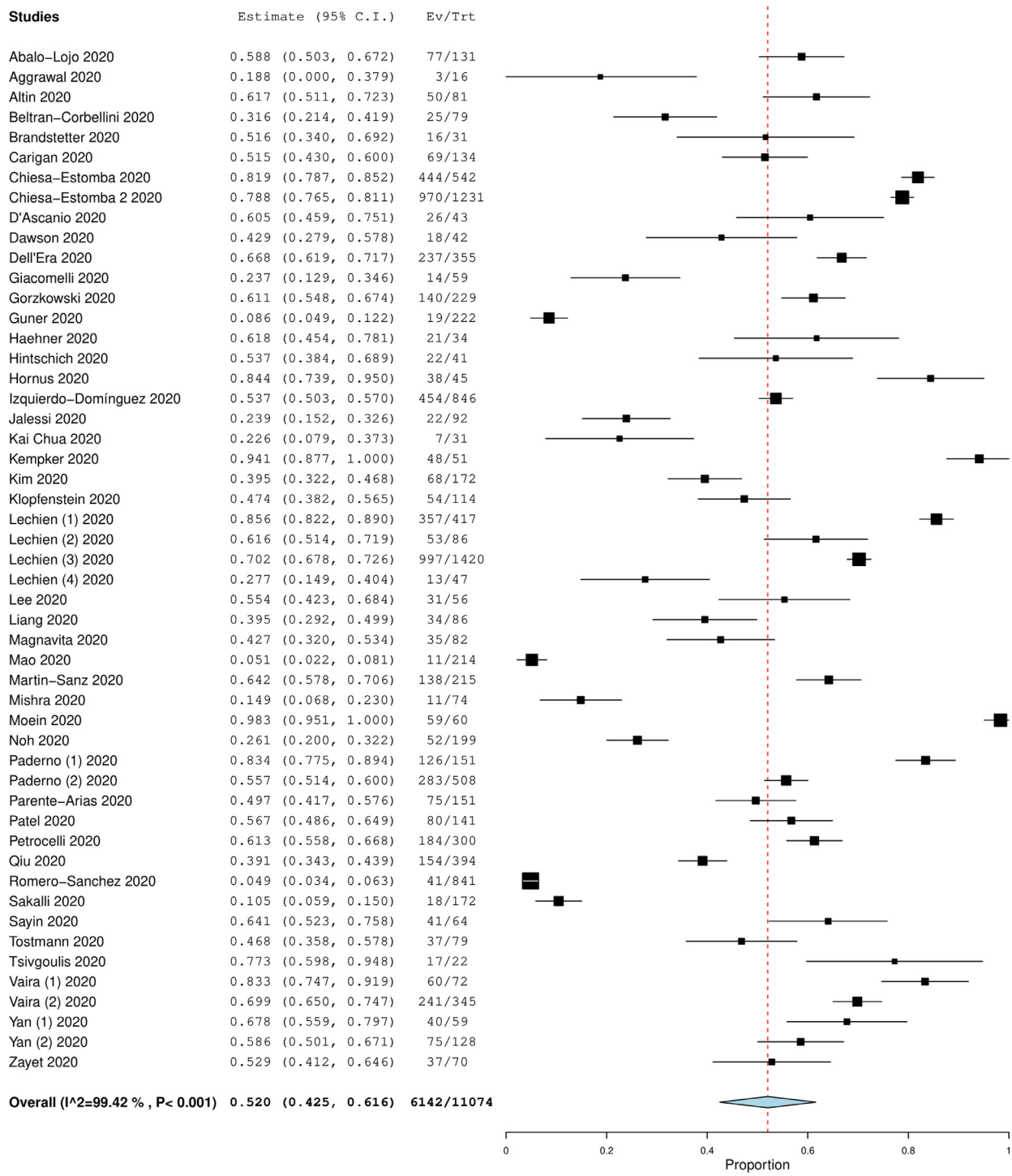

FIGURE 2. Forest plot demonstrating overall prevalence of "loss of smell" in COVID-19 patients.

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,

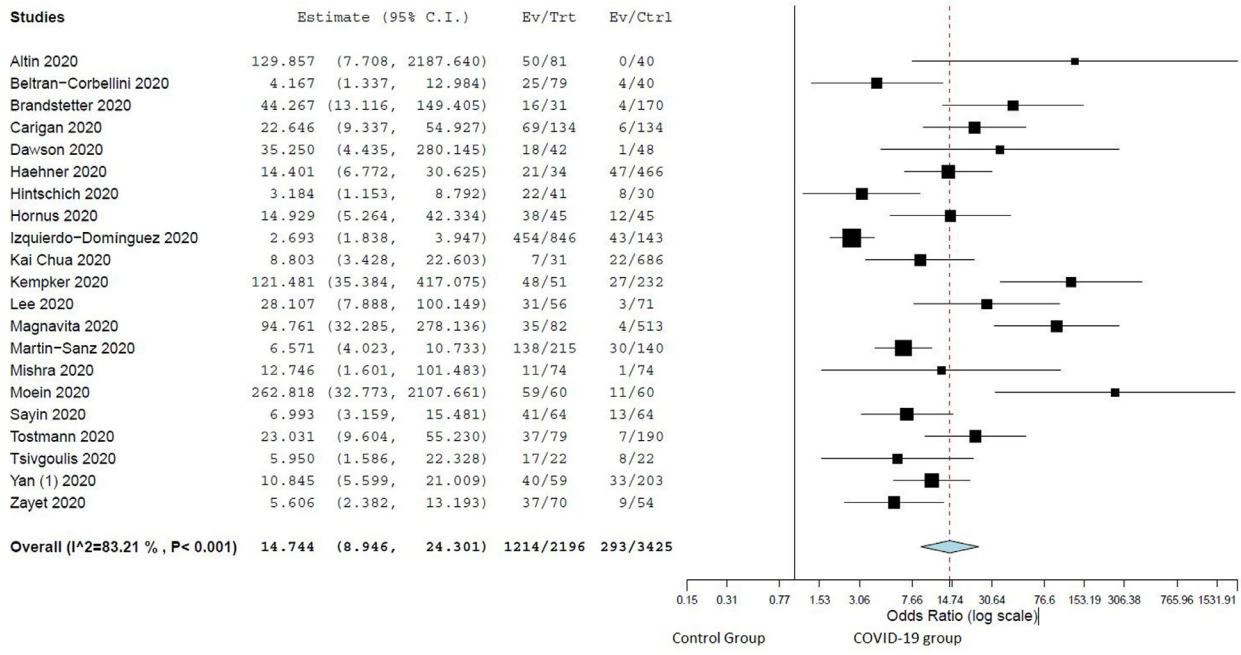

FIGURE 3. Forest plot comparing prevalence in COVID-19 vs control group for "loss of smell".

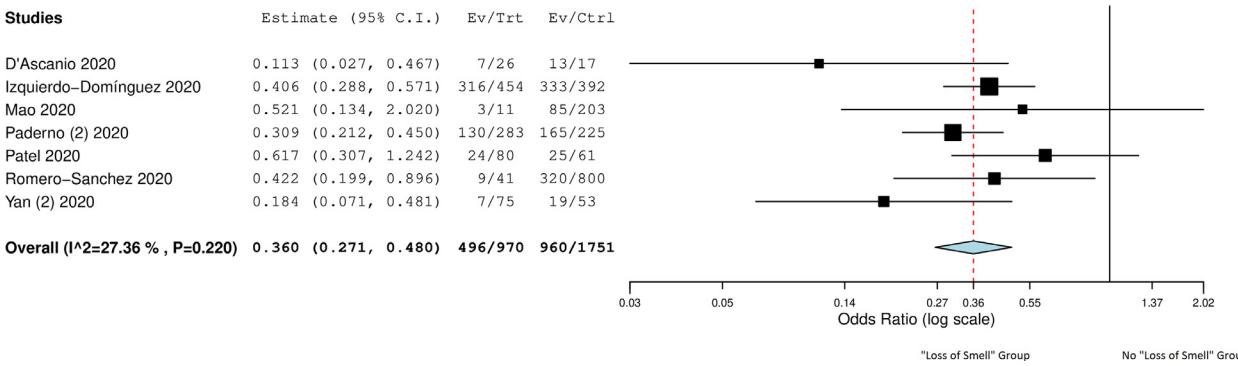

FIGURE 4. Forest plot comparing severe cases in COVID-19 group presenting with "loss of smell" to patients without "loss of smell".

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.

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