The Laryngoscope

Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients

Jeyasakthy Saniasiaya, MD, MMed (ORL-HNS); Md Asiful Islam, PhD; Baharudin Abdullah, MBBS, MMed (ORL-HNS)

Objectives/Hypothesis: Olfactory dysfunction has been observed as one of the clinical manifestations in COVID-19 patients. We aimed to conduct a systematic review and meta-analysis to estimate the overall pooled prevalence of olfactory dysfunction in COVID-19 patients.

Study Design: Systematic review and meta-analyses.

Methods: PubMed, Scopus, Web of Science, Embase, and Google Scholar databases were searched to identify studies published between 1 December 2019 and 23 July 2020. We used random-effects model to estimate the pooled prevalence with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Robustness of the pooled estimates was checked by different subgroup and sensitivity analyses This study is registered with PROSPERO (CRD42020183768).

Results: We identified 1162 studies, of which 83 studies (n = 27492, 61.4% female) were included in the meta-analysis. Overall, the pooled prevalence of olfactory dysfunction in COVID-19 patients was 47.85% [95% CI: 41.20–54.50]. We observed olfactory dysfunction in 54.40% European, 51.11% North American, 31.39% Asian, and 10.71% Australian COVID-19 patients. Anosmia, hyposmia, and dysosmia were observed in 35.39%, 36.15%, and 2.53% of the patients, respectively. There were discrepancies in the results of studies with objective (higher prevalence) versus subjective (lower prevalence) evaluations. The discrepancy might be due to false-negative reporting observed in self-reported health measures.

Conclusions: The prevalence of olfactory dysfunction in COVID-19 patients was found to be 47.85% based on high-quality evidence. Due to the subjective measures of most studies pooled in the analysis, further studies with objective measures are advocated to confirm the finding.

Key Words: Coronavirus, COVID-19, olfactory, smell, meta-analysis.

Level of Evidence: 2

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INTRODUCTION

The world has recently been afflicted by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). China witnessed the first case of pneumonia of unknown origin reported on 8th December 2019 from Wuhan City, Hubei province,[1] and within a very short period, it started to spread globally. World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on 30th January 2020 and a global pandemic disease on 11th March 2020. As of 23rd October 2020, it has become a global pandemic with over 1.1 million deaths and 41.5 million confirmed cases worldwide.[2] As its nature and characteristics are unknown, understanding its presenting symptoms may help in earlier diagnosis. Current accumulated data indicate fever, cough, dyspnea, myalgia, arthralgia, and diarrhea to be the most predominant symptoms of SARS-CoV-2 infection.[1,3]

Initially, a handful of studies reported the observation of olfactory dysfunction in COVID-19 patients.[4–6] Following that the Ear, Nose, and Throat Society of UK and British Rhinological Society came up with an anecdotal report on the association between SARS-CoV-2 infection and olfactory dysfunction, in addition to urging new-onset anosmia to be investigated for SARS-CoV-2 infection while taking precautionary isolation.[7] Similarly, the American Academy of Otolaryngology on 22 March 2020 advocated anosmia, hyposmia, and dysgeusia to be added as symptoms upon screening for COVID-19 with measure such as precautionary isolation advised.[8] With the mounting evidence of olfactory dysfunction as a plausible symptom of COVID-19, the Centers for Disease Control and Prevention has added olfactory dysfunction as part of COVID-19's list of presenting symptoms.[9]

With more cases being reported,[10] it is becoming apparent that the prevalence of olfactory dysfunction in

From the Department of Otorhinolaryngology, Faculty of Medicine (J.S.), University of Malaya, Jalan University, Kuala Lumpur, Malaysia; Department of Haematology (M.A.I.), School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia; and the Department of Otorhinolaryngology-Head and Neck Surgery (B.A.), School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia.

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Jeyasakthy Saniasiaya and Md Asiful Islam should be considered joint first author. Author order was determined alphabetically.

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Send correspondence to Jeyasakthy Saniasiaya, Department of Otorhinolaryngology, Faculty of Medicine, University of Malaya, Jalan Universiti, 50603, Kuala Lumpur, Malaysia. E-mail: shakthy_18@yahoo.com

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COVID-19 patients varies widely across the range. An earlier meta-analysis by Tong et al.[11] revealed the prevalence of olfactory dysfunction in COVID-19 patients was 52.73% based on 10 studies with 1627 patients available at that time. Remarkably, the authors stated that this figure is an underestimation due to the different type of assessment tools, which may be compounded by the smaller number of studies. Hence, another meta-analysis evaluating newer available studies and a larger pool of patients is required to present a more representative figure of the global prevalence of olfactory dysfunction among COVID-19 patients.

MATERIALS AND METHODS

We conducted a systematic review and meta-analysis of the literature in accordance with the PRISMA guideline to identify studies that presented the prevalence of olfactory dysfunction in patients with COVID-19, worldwide.[12] This study is registered with PROSPERO, number CRD42020183768.

Data Sources and Searches

PubMed, Scopus, Web of Science, Embase, and Google Scholar databases were searched to identify studies published between 1 December 2019 and 23 July 2020 without language

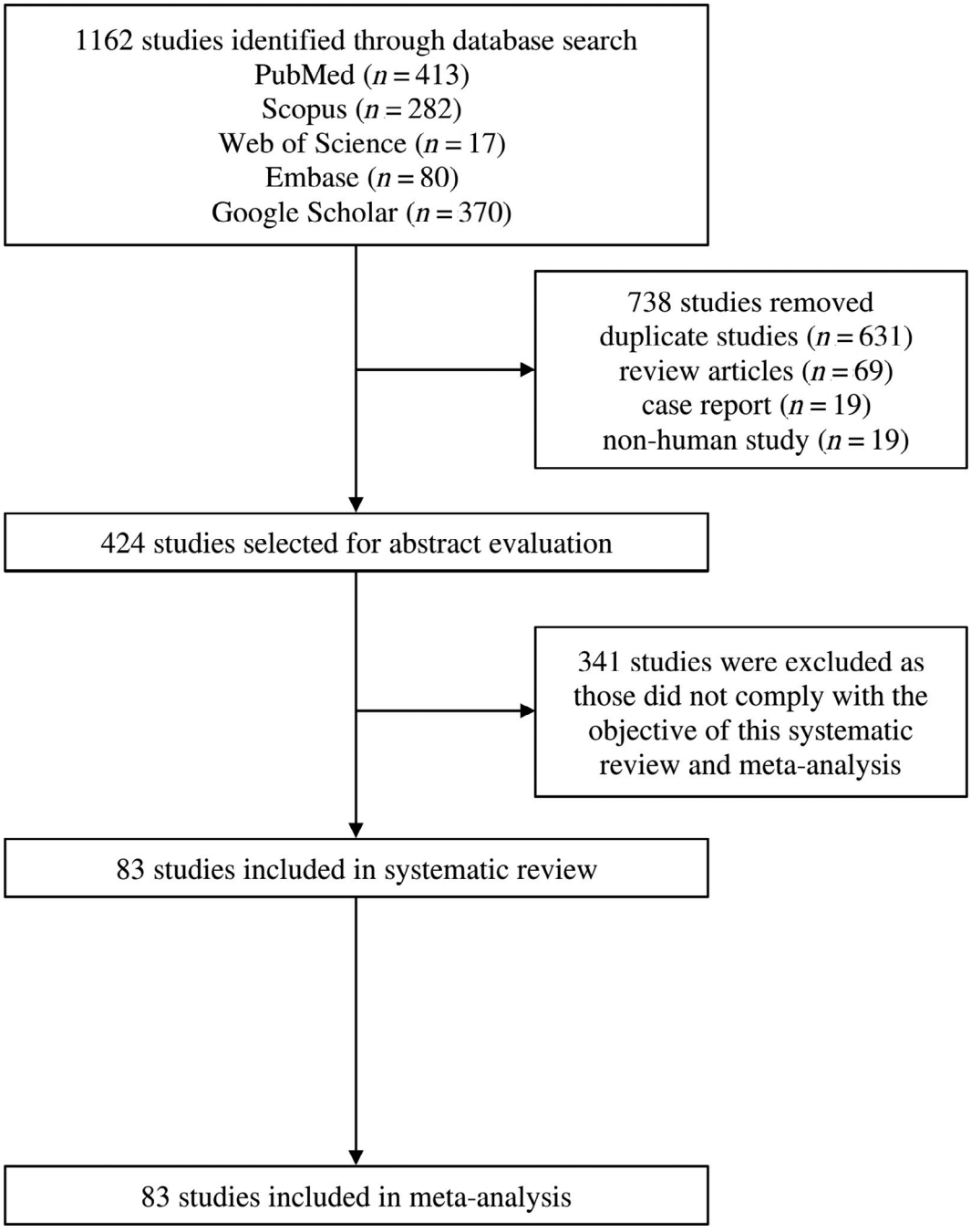

Fig 1. PRISMA flow diagram of study selection.

TABLE I.
Major Characteristics of the Included Studies.

No.	Study ID[Reference]	Study Design	Country	Data Collection Period	Total Number of COVID-19 Patients (Female)	Age (years) (Mean ± SD/ Median (IQR)/Range	COVID-19 Confirmation Procedure	Type of Assessment for Olfactory Dysfunction (Subjective/ Objective)	Method of Assessment for Olfactory Dysfunction
1	Abalo-Lojo 2020[16]	Cross-sectional	Spain	NR	131 (75)	50.4 ± NR	RT-PCR	Subjective	Self-reported
2	Agarwal 2020[17]	Cross-sectional	USA	1 March–4 April 2020	16 (4)	67.0 (38.0–95.0)	RT-PCR	NR	NR
3	Alshami 2020[18]	Cross-sectional	Saudi Arabia	16 March–18 April 2020	128 (69)	39.6 ± 15.5	RT-PCR	Subjective	Telephone questionnaire survey
4	Altin 2020[19]	Case–control	Turkey	25 March–20 April 2020	81 (40)	54.1 ± 16.9	RT-PCR	Objective	Sniffin' Sticks test
5	Beltrán-Corbellini 2020[20]	Case–control	Spain	23–25 March 2020	79 (31)	61.6 ± 17.4	RT-PCR	Subjective	Self-reported questionnaire survey
6	Biadsee 2020[21]	Cross-sectional	Israel	25 March–15 April 2020	128 (70)	36.2 ± NR	RT-PCR	Subjective	Telephone questionnaire survey
7	Brandsetter 2020[22]	Cross-sectional	Germany	NR	31 (26)	18.0–65.0	RT-PCR	Subjective	Self-reported
8	Carignan 2020[23]	Case–control	Canada	10–23 March 2020	134 (81)	57.2 (42.6–64.4)	RT-PCR	Subjective	Telephone interview
9	Cervilla 2020[24]	Cross-sectional	Spain	March–May 2020	51 (44)	43.8 ± 10.7	RT-PCR	Subjective	Telephone questionnaire survey
10	Chary 2020[25]	Cross-sectional	France	25 March–18 April 2020	115 (81)	47.0 (20.0–83.0)	RT-PCR	Subjective	Telephone interview
11	Chiesa-Estomba 2020[26]	Cross-sectional	Spain, Uruguay, Argentina, and Venezuela	NR	542 (324)	34.0 ± 11.0	RT-PCR	Subjective	Online questionnaire survey
12	Chiesa-Estomba 2020a[27]	Cross-sectional	Spain, Belgium, France, Canada, and UK	NR	751 (477)	41.0 ± 13.0	RT-PCR	Subjective	Online questionnaire survey
13	Chua 2020[28]	Cross-sectional	Singapore	23 March–4 April 2020	31 (NR)	NR	RT-PCR	Subjective	Self-reported
14	D'Ascanio 2020[29]	Cross-sectional	Italy	1 February–24 April	43 (14)	58.1 ± 15.7	RT-PCR	Subjective	Self-reported questionnaire survey
15	Dawson 2020[30]	Cross-sectional	USA	March–April 2020	42 (NR)	NR	RT-PCR	Subjective	Self-reported questionnaire survey
16	De Maria 2020[31]	Cross-sectional	Italy	NR	95 (NR)	NR	RT-PCR	Subjective	Self-reported questionnaire survey
17	Dell'Era 2020[32]	Cross-sectional	Italy	10–30 March 2020	355 (163)	50.0 (40.0–59.5)	RT-PCR	Subjective	In person interview or telephone questionnaire survey
18	Durrani 2020[33]	Cross-sectional	Pakistan	20 March–10 April 2020	30 (6)	44.0 (7.0–81.0)	RT-PCR	Subjective	Self-reported
19	Freni 2020[34]	Cross-sectional	Italy	NR	50 (20)	37.7 ± 17.9	RT-PCR	Subjective	Online questionnaire survey
20	Gelardi 2020[35]	Cross-sectional	Italy	NR	72 (33)	49.7 (19.0–70.0)	RT-PCR	Subjective	Self-reported

(Continues)

TABLE I.
Continued

No.	Study ID[Reference]	Study Design	Country	Data Collection Period	Total Number of COVID-19 Patients (Female)	Age (years) (Mean ± SD/ Median (IQR)/Range	COVID-19 Confirmation Procedure	Type of Assessment for Olfactory Dysfunction (Subjective/ Objective)	Method of Assessment for Olfactory Dysfunction
21	Giacomelli 2020[4]	Cross-sectional	Italy	19 March 2020	59 (19)	60.0 (50.0–74.0)	NR	Subjective	Self-reported questionnaire survey
22	Gorzkowski 2020[36]	Cross-sectional	France	1 March–31 March 2020	229 (147)	39.7 ± 13.7	RT-PCR	Subjective	Telephone questionnaire survey
23	Güner 2020[37]	Cross-sectional	Turkey	10 March–10 April 2020	222 (90)	50.6 ± 16.5	RT-PCR	Subjective	Self-reported
24	Haehner 2020[38]	Cross-sectional	Germany	NR	34 (16)	43.2 ± 11.6	RT-PCR	Subjective	Self-reported questionnaire survey
25	Hintschih 2020[39]	Cross-sectional	Germany	NR	41 (28)	37 (NR)	RT-PCR	Subjective	Online questionnaire survey
26	Hornuss 2020[40]	Cross-sectional	Germany	April 2020	45 (20)	56.0 ± 16.9	RT-PCR	Objective	Sniffin' Sticks test
27	Jalessi 2020[41]	Cross-sectional	Iran	February–March 2020	92 (30)	52.9 ± 13.2	RT-PCR	Subjective	Self-reported
28	Karadaş 2020[42]	Cross-sectional	Turkey	April–May 2020	239 (106)	46.4 ± 15.4	RT-PCR	Subjective	Self-reported
29	Kerr 2020[43]	Cross-sectional	Ireland	24 March 2020	46 (27)	36.5 (27.0–48.0)	RT-PCR	Subjective	Self-reported
30	Kim 2020[44]	Cross-sectional	Korea	12–16 March 2020	172 (106)	26.0 (22.0–47.0)	RT-PCR	Subjective	Self-reported questionnaire survey
31	Klopfenstein 2020[45]	Cross-sectional	France	1–17 March 2020	114 (36)	47.0 ± 16.0)	RT-PCR	NR	NR
32	Lapostolle 2020[46]	Cross-sectional	France	24 March–6 April 2020	1487 (752)	44.0 (32.0–57.0)	RT-PCR	Subjective	Telephone interview
33	Lazar 2020[47]	Cross-sectional	Romania	28 March 2020	100 (49)	41.0 (NR)	RT-PCR	Subjective	Medical record review
34	Lechien 2020[48]	Cross-sectional	France, Italy, Spain, Belgium, and Switzerland	22 March–10 April 2020	1420 (962)	39.0 ± 12.0	RT-PCR	Subjective	Self-reported questionnaire survey
35	Lechien 2020a[49]	Cross-sectional	Belgium	NR	86 (56)	41.7 ± 11.8	RT-PCR	Subjective	Self-reported questionnaire survey
36	Lechien 2020b[50]	Cross-sectional	European countries	22 March–3 June 2020	2581 (1624)	44.5 ± 16.4	RT-PCR	Subjective	Self-reported
37	Lechien 2020c[51]	Cross-sectional	Belgium, Italy, France, and Spain	NR	417 (263)	36.9 ± 11.4	RT-PCR	Subjective	Self-reported questionnaire survey
38	Lee 2020[52]	Cross-sectional	Canada	16 March–15 April 2020	56 (33)	38.0 (31.8–47.2)	RT-PCR	Subjective	Telephone questionnaire survey
39	Levinson 2020[53]	Cross-sectional	Israel	10–23 March 2020	42 (19)	34.0 (15.0–82.0)	RT-PCR	Subjective	Telephone questionnaire survey
40	Liang 2020[54]	Cross-sectional	China	16 March–12 April 2020	86 (42)	25.5 (6.0–57.0)	RT-PCR	Subjective	Self-reported questionnaire survey
41	Lombardi 2020[55]	Cross-sectional	Italy	24 February–31 March 2020	139 (82)	NR	RT-PCR	Subjective	Self-reported
42	Luers 2020[56]	Cross-sectional	Germany	22–28 March 2020	72 (31)	38.0 ± 13.0	RT-PCR	Subjective	Self-reported questionnaire survey

43	Luigetti 2020[57]	Cross-sectional	Italy	14 March–20 April 2020	213 (76)	70.2 ± 13.9	RT-PCR	Subjective	Self-reported
44	Magnavita 2020[58]	Cross-sectional	Italy	27 March–30 April 2020	82 (56)	NR	RT-PCR	Subjective	Self-reported questionnaire
45	Mao 2020[59]	Cross-sectional	China	16 January–19 February 2020	214 (127)	52.7 ± 15.5	RT-PCR	NR	NR
46	Martin-Sanz 2020[60]	Case control	Spain	15 March–7 April 2020	215 (171)	42.9 ± 0.6	RT-PCR	Objective	VAS
47	Meini 2020[61]	Cross-sectional	Italy	April 2020	100 (40)	65.0 ± 15.0	RT-PCR	Subjective	Telephone interview
48	Menni 2020[5]	Cross-sectional	UK	24–29 March 2020	579 (400)	40.79 ± 11.84	RT-PCR	Subjective	Smartphone-based App survey
49	Menni 2020a[62]	Cross-sectional	UK	24 March–21 April 2020	6452 (4638)	41.2 ± 12.1	RT-PCR	Subjective	Smartphone-based App survey
			USA		726 (567)	44.6 ± 14.3			
50	Mercante 2020[63]	Cross-sectional	Italy	5–23 March 2020	204 (94)	52.6 ± 14.4	RT-PCR	Subjective	Telephone questionnaire survey
51	Merza 2020[64]	Cross-sectional	Iraq	18 March–7 April 2020	15 (6)	28.0 ± 16.4	RT-PCR	NR	NR
52	Moein 2020[65]	Case–control	Iran	21–23 March 2020	60 (20)	46.5 ± 12.1	RT-PCR	Objective	UPSIT
53	Noh 2020[66]	Cross-sectional	Korea	NR	199 (130)	38.0 ± 13.1	RT-PCR	Subjective	In person interview
54	Otte 2020[67]	Cross-sectional	Germany	NR	50 (NR)	43.2 (23.0–69.0)	RT-PCR	Objective	Sniffin' sticks test
55	Paderno 2020[68]	Cross-sectional	Italy	27 March–1 April 2020	508 (223)	55.0 ± 15.0	RT-PCR	Subjective	Self-reported questionnaire survey
56	Parente-Arias 2020[69]	Cross-sectional	Spain	3–24 March 2020	151 (98)	55.2 (18.0–88.0)	RT-PCR	Subjective	Self-reported questionnaire survey
57	Patel 2020[70]	Cross-sectional	UK	1 March–1 April 2020	141 (58)	45.6 (20.0–93.0)	RT-PCR	Subjective	Telephone interview
58	Petrocelli 2020[71]	Cross-sectional	Italy	16 April–2 May 2020	300 (225)	43.6 ± 12.2	RT-PCR	Objective	Olfactory threshold and identification test
59	Peyrony 2020[72]	Cross-sectional	France	9 March–4 April 2020	225 (150)	62.0 (48.0–71.0)	RT-PCR	Subjective	Self-reported
60	Qiu 2020[73]	Cross-sectional	China, France and Germany	15 March–5 April 2020	394 (NR)	NR	RT-PCR	Subjective	Self-reported questionnaire survey
61	Romero-Sánchez 2020[74]	Cross-sectional	Spain	1 March–1 April 2020	841 (368)	66.4 ± 14.9	RT-PCR	Subjective	Medical record review
62	Sakalli 2020[75]	Cross-sectional	Turkey	NR	172 (88)	37.8 ± 12.5	RT-PCR	Subjective	Self-reported questionnaire survey
63	Sayin 2020[76]	Case–control	Turkey	NR	64 (39)	37.7 ± 11.3	RT-PCR	Subjective	Self-reported questionnaire survey
64	Seo 2020[77]	Cross-sectional	Korea	28 April 2020	62 (NR)	NR	RT-PCR	Objective	CC-SIT
65	Sierpiński 2020[78]	Cross-sectional	Poland	17–18 April 2020	1942 (1169)	50.0 (NR)	RT-PCR	Subjective	Telephone interview
66	Song 2020[79]	Cross-sectional	China	27 January–10 March 2020	1172 (595)	61.0 (48.0–68.0)	RT-PCR	Subjective	Telephone interview
67	Speth 2020[80]	Cross-sectional	Switzerland	3 March–17 April 2020	103 (53)	46.8 ± 15.9	RT-PCR	Subjective	Telephone interview
68	Tomlins 2020[81]	Cross-sectional	UK	10–30 March 2020	95 (35)	75.0 (59.0–82.0)	RT-PCR	NR	NR

(Continues)

TABLE I.
Continued

No.	Study ID[Reference]	Study Design	Country	Data Collection Period	Total Number of COVID-19 Patients (Female)	Age (years) (Mean ± SD/ Median (IQR)/Range	COVID-19 Confirmation Procedure	Type of Assessment for Olfactory Dysfunction (Subjective/ Objective)	Method of Assessment for Olfactory Dysfunction
69	Tostmann 2020[82]	Cross-sectional	Netherlands	10–30 March 2020	79 (NR)	NR	NR	Subjective	Self-reported questionnaire survey
70	Trubiano 2020[83]	Cross-sectional	Australia	1–22 April 2020	28 (14)	55.0 (46.0–63.5)	RT-PCR	Subjective	Medical record review
71	Tudrej 2020[84]	Cross-sectional	Switzerland	24 March–14 April 2020	198 (NR)	NR	RT-PCR	Subjective	Self-reported questionnaire survey
72	Vacchiano 2020[85]	Cross-sectional	Italy	NR	108 (46)	59.0 (18.0–83.0)	RT-PCR	Subjective	Telephone questionnaire survey
73	Vaira 2020[86]	Cross-sectional	Italy	31 March–6 April 2020	72 (45)	49.2 ± 13.7	RT-PCR	Objective	CCCRC
74	Vaira 2020a[87]	Cross-sectional	Italy	9–10 April 2020	33 (22)	47.2 ± 10	RT-PCR	Objective	CCCRC
75	Vaira 2020b[88]	Cross-sectional	Italy	NR	345 (199)	48.5 ± 12.8 (23–88)	RT-PCR	Objective	CCCCRC
76	Wee 2020[89]	Cross-sectional	Singapore	26 March–10 April 2020	154 (NR)	NR	RT-PCR	Subjective	Self-reported questionnaire survey
77	Wi 2020[90]	Cross-sectional	Korea	15 April 2020	111 (57)	41.3 ± 19.0	RT-PCR	Subjective	Medical record review
78	Yan 2020[91]	Cross-sectional	USA	3 March–8 April 2020	128 (67)	53.5 (40.0–65.0)	RT-PCR	Subjective	Self-reported
79	Yan 2020a[92]	Cross-sectional	Germany, USA, Bolivia and Venezuela	NR	59 (29)	18.0–79.0	RT-PCR	Subjective	Online questionnaire survey
80	Yan 2020b[93]	Cross-sectional	USA	9 March–29 April 2020	46 (NR)	NR	RT-PCR	Subjective	Medical record review
81	Zayet 2020[94]	Cross-sectional	France	26 February–14 March 2020	70 (41)	56.7 ± 19.3	RT-PCR	Subjective	Self-reported questionnaire
82	Zayet 2020a[95]	Case–control	France	30 March–3 April 2020	95 (79)	39.8 ± 12.2	RT-PCR	Subjective	Medical record review
83	Zou 2020[96]	Cross-sectional	China	1 February–3 March 2020	81 (43)	58.0 (50.0–68.5)	RT-PCR	Subjective	Medical record review

AAO-HNS = American academy of otolaryngology–head and neck surgery; CC-SIT = cross-cultural smell identification test; CCCRC = Connecticut chemosensory clinical research center orthonasal olfaction test; IQR = interquartile range; NR = not reported; RT-PCR = reverse transcription polymerase chain reaction; SD = standard deviation; UPSIT = University of Pennsylvania smell identification test; VAS = visual analog scale..

restrictions. The following key terms were searched: coronavirus, COVID-19, COVID19, nCoV, SARS-CoV-2, SARS-CoV2, olfaction, olfactory, smell, anosmia, hyposmia, dysosmia, cacosmia, and parosmia. Complete details of the search strategy are in the Supporting Table 1. In addition to the published studies, preprints were also considered if data of interest were reported. Review articles, case reports, opinions, and perspectives were excluded. Data reported by news reports and press releases or data collected from websites or databases were not considered. To ensure a robust search procedure, references of the included studies were also reviewed. Duplicate studies were excluded by using EndNote X8 software.

Study Selection

To identify eligible studies, articles of interest were screened based on the title and abstract, followed by full text by two authors (J.S. and M.A.I.) independently. Disagreements about inclusion were discussed and resolved by consensus.

Data Extraction and Quality Assessment

Data extraction was done independently by two authors (J.S. and M.A.I.). From each eligible study, we extracted the following information into a predefined Excel spreadsheet: first author's last name; study design; country of the participants; data collection period; total number of COVID-19 patients; number of female COVID-19 patients; age; COVID-19 confirmation procedure; confirmatory procedure of olfactory dysfunction; olfactory symptoms after the onset of illness; and number of recovered patients from olfactory dysfunction.

Random-effects model was used to obtain the pooled prevalence and 95% confidence intervals (CIs) of olfactory dysfunction in patients with COVID-19. The quality of included studies was assessed independently by two authors (J.S. and M.A.I.) using the Joanna Briggs Institute (JBI) critical appraisal tools.[13] The studies were classified as low-quality (high-risk of bias) if the overall score was ≤50%.[14] To assess publication bias, a funnel plot presenting prevalence estimate against the standard error was constructed and the asymmetry of the funnel plot was confirmed with Egger's test.

Data Synthesis and Analysis

Heterogeneity between studies was assessed using the I^2 statistic ($I^2 > 75\%$ indicating substantial heterogeneity) in addition to using the Cochran's Q test to identify the significance of heterogeneity. As subgroups, the prevalence of olfactory dysfunction in COVID-19 patients from different geographical regions and in different types, including anosmia, hyposmia, and dysosmia were analyzed. To identify the source of heterogeneity and to check the robustness of the results, sensitivity analyses were performed through the following strategies: i) excluding small studies (n < 100); ii) excluding the low-quality studies (high-risk of bias); iii) excluding studies not reporting COVID-19 confirmation assay; iv) considering only cross-sectional studies, and v) excluding outlier studies. In addition, to identify the outlier studies and the sources of heterogeneity, a Galbraith plot was constructed. All the analyses and plots were generated by using metaprop codes in meta (version 4.11–0) and metafor (version 2.4–0) packages of R (version 3.6.3) in RStudio (version 1.2.5033).[15]

RESULTS

Study Selection

Our search initially identified 1162 studies. After removing 738 studies [duplicate studies (n = 631), review

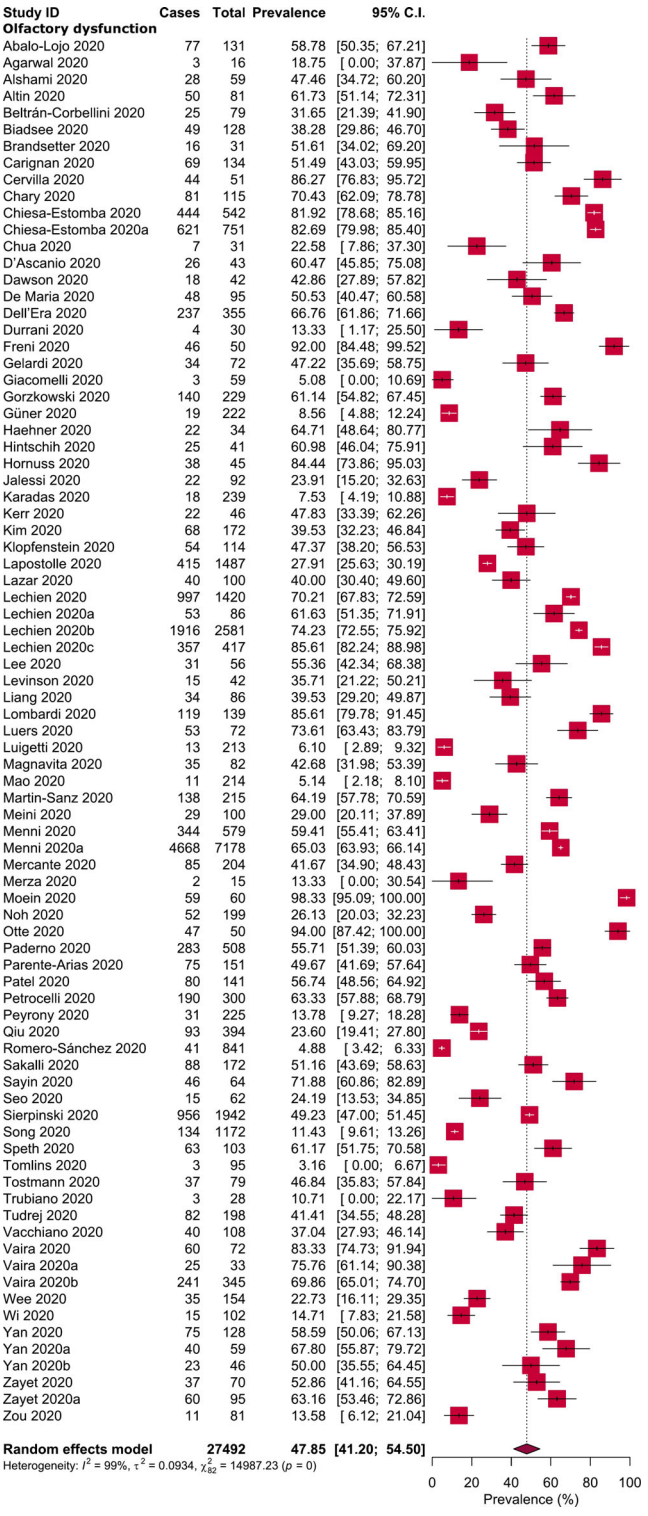

Fig 2. Prevalence of olfactory dysfunction in COVID-19 patients. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE II.
Pooled Prevalence of Olfactory Dysfunction in Different Subgroups of COVID-19 Patients.

Subgroups of COVID-19 Patients	Olfactory Dysfunction Prevalence [95% CIs] (%)	Number of Studies Analyzed	Total Number of COVID-19 Patients	Heterogeneity		Publication Bias, Egger's Test (*P* Value)
				I^2(%)	*P* Value	
Olfactory dysfunction in different regions						
Europe	54.40 [46.19–62.61]	49	20,738	99	<.0001	.19
North America	51.11 [41.10–61.13]	7	1,148	87	<.0001	NA
Asia	31.39 [18.26–44.51]	22	3,477	99	<.0001	.66
Australia	10.71 [0.00–22.17]	1	28	NA	NA	NA
Different types of olfactory dysfunction						
Anosmia	35.39 [27.73–43.04]	43	10,979	99	<.0001	.11
Hyposmia	36.15 [27.65–44.64]	24	5,200	98	<.0001	.003
Dysosmia	2.53 [0.0–6.0]	1	79	NA	NA	NA
Evaluation types of olfactory dysfunction						
Subjective	44.53 [37.59–51.47]	73	26,229	99	<.0001	.60
Objective	72.10 [59.41–84.79]	10	1,263	97	<.0001	.33
Olfactory dysfunction based on clinical severity						
Severe	9.02 [2.67–15.38]	4	687	85	.001	NA
Non-severe	47.48 [21.34–73.62]	8	5,135	100	<.0001	NA

CIs = confidence intervals; NA = not applicable.

articles (n = 69), case reports (n = 19), and non-human studies (n = 19)]; titles and abstracts of 424 studies were screened for eligibility, of which 341 studies were excluded as those did not comply with the objective of this study. Therefore, 83 studies were included in the systematic review and meta-analysis (Fig. 1).

Study Characteristics

Detailed characteristics and references of the included studies are presented in Table I. Overall, this meta-analysis reports data from 27492 COVID-19 patients (61.4% female). Ages of the COVID-19 patients included in this meta-analysis ranged from 28.0 ± 16.4 to 70.2 ± 13.9 years. Studies were from 27 countries, including Spain, Germany, Italy, France, Ireland, Belgium, Romania, Switzerland, UK, Netherlands, Poland, Israel, China, Saudi Arabia, Turkey, Iraq, Iran, Pakistan, Singapore, Korea, Uruguay, Argentina, Bolivia, Venezuela, Australia, Canada, and USA. Among the included studies, 97.5% confirmed COVID-19 patients by using the RT-PCR method, whereas the method was not reported in two of the studies.

Outcomes

Overall, the pooled prevalence of olfactory dysfunction in COVID-19 patients was 47.85% [95% CI: 41.20–54.50] (Fig. 2). From the subgroup analyses, we observed olfactory dysfunction in 54.40% European, 51.11% North American, 31.39% Asian, and 10.71% Australian COVID-19 patients (Table II, Supporting Figure 1). In addition, anosmia, hyposmia, and dysosmia were observed in 35.39%, 36.15%, and 2.53% of the COVID-19 patients, respectively (Table II, Supporting Figure 2). Interestingly, the prevalence of olfactory dysfunction was observed higher in COVID-19 patients on objective rather than subjective evaluations (72.10% vs. 44.53%) (Table II, Supporting Figure 3). Based on the clinical severity, olfactory dysfunction was higher in non-severe patients compared to severe patients with COVID-19 (47.48% vs. 9.02%) (Table II, Supporting Figure 4).

Detailed quality assessment of the included studies is shown in the Supporting information (Supporting Table 2, Supporting Table 3). Briefly, 95.1% of the included studies were of high-quality (low-risk of bias). Overall, very high levels of heterogeneity (ranging from 87% to 99%) were observed during the estimation of olfactory dysfunctions in the main analysis as well as in different subgroup analyses. Visual inspection of the funnel plot and Egger's test results showed that there was no significant publication bias (*P* = .84) (Fig. 3).

Sensitivity analyses on assessing olfactory dysfunction in COVID-19 patients excluding small studies, low-

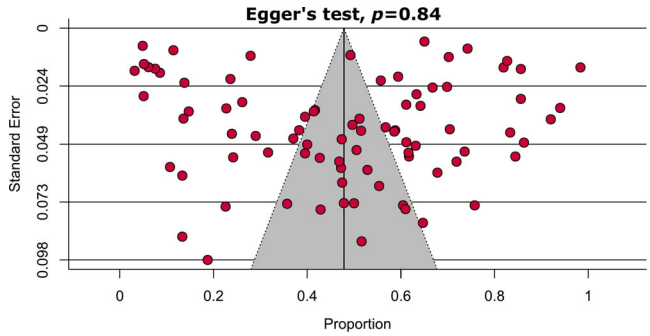

Fig 3. Funnel plot on the prevalence of olfactory dysfunction in COVID-19 patients. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE III.
Sensitivity Analyses.

Strategies of Sensitivity Analyses	Olfactory Dysfunction Prevalence [95% Cis] (%)	Difference of Pooled Prevalence Compared to the Main Result	Number of Studies Analyzed	Total Number of COVID-19 Patients	Heterogeneity	
					I^2(%)	*P* Value
Excluding small studies	46.03 [37.08–54.97]	3.8% lower	43	25,162	100	<.0001
Excluding low-quality studies	49.03 [42.21–55.85]	2.5% higher	79	27,146	99	<.0001
Excluding studies where COVID-19 confirmation test was not reported	48.40 [41.67–55.12]	1.1% higher	81	27,354	99	<.0001
Considering only cross-sectional studies	46.66 [39.87–53.44]	2.5% lower	77	26,979	99	<.0001
Excluding outlier studies	47.28 [40.61–53.95]	1.2% lower	80	27,297	99	<.0001

CIs = confidence intervals.

quality studies, studies where COVID-19 confirmation test was not reported, considering only cross-sectional studies, and excluding outlier studies showed very marginal differences in overall pooled prevalence (Table III, Supporting Figure 5). Overall, our sensitivity analyses indicated that the results of olfactory dysfunction prevalence in COVID-19 patients are robust and reliable. As the source of heterogeneity, from the Galbraith plot, three studies were identified as the source of heterogeneity (Supporting Figure 6).

DISCUSSION

The route of entry of SARS-CoV-2 to the olfactory neuron is via the olfactory epithelium found at the nasal roof.[97] This region is exposed the most to inspired air during inspiration after it passes the nasal valve and moves upwards. The sensory neurons found at the olfactory epithelium are accountable for detecting as well as transmitting information of odors to the brain. It is noteworthy that the unique property of olfactory epithelium is its basal cell, which can regenerate throughout life.[98,99]

The novel SARS-CoV-2 infection was discovered and delineated by Zhou et al.[100] on 3rd February 2020. They described that SARS-CoV-2 enters the cell through angiotensin-converting enzyme 2 (ACE2). It is postulated that SARS-CoV infiltrates cells via the interplay between its spike (S) protein and the ACE2 protein on the target cells.[101,102] Interestingly, the number of ACE2 cells is similar both in nasal and oral tissues, as well as lung and colon tissues,[103] although it is postulated that nasal and oral tissues may be the first site of entry by SARS-CoV-2. The two genes accountable for anosmia following SARS-CoV-2 infection are ACE2 and TMPRSS2.[104] SARS-CoV-2 has been shown to enter the brain via olfactory bulb on transgenic mice causing transneuronal spread and was discovered abundantly in the olfactory bulb following infection.[105] In addition, autopsy samples taken from patients with SARS showed SARS-CoV-2 in the brain samples. The mode of entry into the brain is postulated to be via olfactory bulb.[106,107] Previous experience had led to a revelation that coronaviruses have shown to share a similar structure as well as an infective pathway.[108] Hence, structural changes in the olfactory bulb ought to be assessed.[109] It is noteworthy that, reduction in the volume of olfactory bulb has been reported to result from a prior infection-related olfactory dysfunction.[110] There are several possible mechanisms for olfactory dysfunction following SARS-CoV-2 infection. Among the countless existing theories, the most notable ones include olfactory cleft syndrome and postviral anosmia syndrome.[111] The former theory advocates on mucosal obstruction at the olfactory cleft results in conduction impairment of smell,[112] while the latter proposes on a neural loss mechanism whereby direct injury to the olfactory sensory neurons preceding viral infection.[113]

It is noteworthy that postviral olfactory loss (PVOL) is not a novel phenomenon. Numerous virus has been advocated to enable olfactory dysfunction, including influenza virus, adenovirus, parainfluenza virus, respiratory syncytial virus, coxsackievirus, adenovirus, poliovirus, enterovirus, and herpesvirus.[114–117] Suguira et al.[115] in an earlier study supported parainfluenza virus (PIV) type 3 to be the primary virus responsible for PVOL. Subsequent research revealed a similar finding, whereby PIV-3 was the leading culprit behind PVOL.[116] Tian et al.[117] studied the Sendai virus (SeV), the murine counterpart of the PIV on olfactory function and regenerative ability of the olfactory epithelium. In addition, they found that SeV impairs olfaction and persists in the olfactory epithelium and olfactory body, thus hindering the regenerative ability as well as the normal physiologic function of olfactory sensory neurons.

Suzuki et al.[114] found rhinovirus to be the predominant cause of PVOL followed by PIV-2, Epstein–Barr virus, and coronavirus, which was identified in one patient. PIV-3 was not, however, studied in their sample. Coronavirus was not considered in many studies as the involvement of coronavirus in PVOL was not extensively reported, and it is challenging to isolate coronavirus.[115] In addition, the challenge faced by many researchers in identifying the virus responsible for PVOL is following the delay of patients with the olfactory loss to visiting the clinic, believing the notion that PVOL will resolve spontaneously. A noteworthy study by Potter et al.[118] shed more light on the interaction between virus and host in PVOL related condition. Potter et al. suggested that a seasonal pattern emerged among influenza and non-influenza

related PVOL indicating not only variations of potency and virulence of virus but also on host susceptibility as a factor in determining the progression and manifestation of the infection. Olfactory disorders related to non-influenza virus peaked in warmer months compared to colder months.

In our meta-analysis, all 83 studies revealed a strong association between olfactory dysfunction and SARS-COV-2 infection. Overall nasal symptoms among COVID-19 positive patients have been scarcely reported.[3,119] Chen et al.[3] in their series, reported only 4% of their patients had rhinorrhea; while Guan et al.[119] reported 5% of their patients demonstrated nasal obstruction. Scanty reported data on olfactory dysfunction had been attributed by either overlooked nasal symptoms by physicians,[51] or the possibility of different virus sequences leading to the various presentations.[120] The latter theory was supported based on a study by Benvenuto et al.[120] who compared genomes of 15 virus sequences from patients in various regions in China with other coronaviruses. The possibility that olfactory, as well as gustatory dysfunction, prevails among the European community has emerged.[51] in addition, lack of awareness among Asian patients in addition to unnoticed olfactory loss could have contributed to the low number of reported cases among Asian patients. Recent epiphany on olfactory dysfunction among Asian patients accruing the surge in cases has enabled olfactory dysfunction to be included in suspect case criteria for SARS-CoV-2 infection, allowing test to be carried out in these patients, while isolation is implemented concomitantly.[28]

Female predominance was revealed among our patients (61.4%). Similarly, previous studies have shown olfactory loss postviral prevails among female patients.[121,122] This notion is attributed to gender-related variation in the inflammatory process.[123] Increase in numbers of female patients can be attributed by greater tendency of females to volunteer for studies. In addition, female patients are found to be more sensitive in detecting chemosensory alteration.

Most studies involved online questionnaire either through an online application, online survey, smartphone-based App filled up by patients or clinicians, whereas objective assessment of olfactory assessment was utilized in four studies whereby Sniffin test, University of Pennsylvania smell identification test (UPSIT), and Connecticut chemosensory clinical research center orthonasal olfaction test (CCCRC) were performed. It is noteworthy that, in our meta-analysis, we found prevalence of olfactory dysfunction among objectively evaluated studies to be higher (72.10%) as compared to the subjectively evaluated studies (44.53%). This could be attributed by the fact that most COVID-19 patients are unaware of their olfactory dysfunction leading to possibility of underestimation. Moein et al.[65] reported 98% of their patients were found to have olfactory dysfunction post UPSIT, of which only 35% were initially aware of their symptoms. Generally, loss of smell is only perceived upon significant loss of smell such as anosmia. Thus, it is worth noting that the prevalence of olfactory dysfunction may be higher if tested objectively. Quantitative testing of olfactory disturbance may provide rapid and cheap modality to screen COVID-19 in a large population. Interestingly, Moein et al.[124] reported that time of testing is the most important factor in explaining the prevalence variations among studies apart from variations in question and types of olfactory testing. They found that 61% of the earlier 96% of patients who demonstrated olfactory disturbance, when retested during the late acute phase showed an improvement.

Although the jarring increase in the number of cases daily, which led to a surge in research as well as publications, we obtained only 83 studies on olfactory dysfunction in SARS-CoV-2 infection. This may be attributed by the fact that the substantial available peer-reviewed studies report on hospitalized patients, which means that the self-limiting,[125] as well as the mild group of patients, are omitted from the various studies. The notion that olfactory manifestation predominately affects the milder form of SARS-CoV-2 infection is inevitable. Yan et al.[92] found that most patients with olfactory disturbance with positive SARS-CoV-2 infection were treated as outpatient or ambulatory and not requiring hospitalization. Yet, it is imperative to keep in mind that the nature of this virus is yet to be explored, and owing to the varying genome in virus sequencing, all SARS-CoV-2 infection positive patients with olfactory disturbance should not be taken lightly. Villalba et al.[126] reported on two patients who presented with anosmia as the initial symptom of SARS-CoV-2 infection had to be hospitalized, and unfortunately, one patient succumbed. Varying reports are available on the outcome following the PVOL. Yan et al.[92] and Klopfenstein et al.[45] demonstrated 74% and 98% resolution of olfactory symptoms and linked this short-lived manifestation to the unique ability of olfactory epithelium to regenerate and repair following viral clearance.

In our meta-analysis, none of the authors mentioned on specific treatment directed to smell impairment. The role of intranasal steroids is debatable in this situation accruing the possibility of triggering upper respiratory tract infection. Oral steroids used traditionally to treat idiopathic anosmia ought to be averted by all means to avoid further risk of immunosuppression in SARS-CoV-2 infection patients.[112] The outcome of olfactory loss revealed persistence of symptoms mentioned in some of the studies. Duration of olfactory dysfunction remains a conundrum as the nature of this novel pandemic is still a mystery. Heretofore, PVOL habitually has been shown to have a good prognosis. Despite still premature, several anecdotal reports have revealed on total or partial recuperation of olfactory loss over a few months.[127] This is owing to the fact that a longer time for regeneration following damage to olfactory neurons is required. Albeit considered innocuous, olfactory disturbance has been related to a number of detrimental effects notably on quality of life, impacts social interaction, and depression. Astonishingly, several high-profile studies have related olfactory disturbance to a 5-year mortality rate.[128–131] The unique neuroplasticity potential found in olfactory system opens to novel possibility of olfactory recovery via numerous modalities such as olfactory training.[132]

Implications for Clinical Practice

The characteristics of an ideal screening tool are high probability of detecting disease (highly sensitive) and high probability of excluding disease when it is negative (highly specific). Besides being reliable, it must be cost-effective, simple to perform, and widely available.[133,134] Moreover, an effective screening requires engagement of both target populations and health care providers. As olfactory dysfunction can be simply detected by using questionnaire,[135] it fulfills all these criteria and can be a useful screening tool besides temperature surveillance. Applying a specific questionnaire to detect olfactory dysfunction, especially in those with suspicious flu-like symptoms, travel history from affected countries, and contact with COVID-19 patients may enhance the pick-up rate of infected patients. Furthermore, questionnaire-based screening tool may easily be assimilated in the global health care system and more so in developing countries where cost is a factor.

Implications for Research

As there is no standardized questionnaire available to screen for olfactory dysfunction, a consensus is required to determine the most suitable questionnaire for a reliable detection. Perhaps a more refined questionnaire based on the available questionnaires can be developed by selecting the relevant questions and compare by comparing them with an objective smell test to choose the most consistent questions. Researches need to be conducted employing the more objective smell test, which will provide us information on specific odor affected by this infection. By identifying the specific associated odor link to the infection, a simple smell test can be developed particularly to screen for COVID-19. Olfactory dysfunction may serve as prognosticators to triage and stratify patients according to different categories of severity, which can help to detect those who need immediate and urgent hospitalization. Research into this may help in preventing death among COVID-19 patients.

Strengths

Our study has several strengths. This meta-analysis was conducted with significant number of studies and hence including a considerable number of participants, resulting in more robust estimates. Majority of the included studies confirmed COVID-19 subjects by using the RT-PCR technique, which strengthens our findings. None of the analyses represented significant publication bias demonstrating that we were unlikely to have missed studies that could have altered the findings. All the conducted sensitivity analyses generated similar results to the main findings indicating the robustness of the meta-analysis results. Based on the quality assessments, 95.1% of the studies were of high methodological quality (low-risk of bias), which ensured a reliable result.

Limitations

Nevertheless, there are several notable limitations. Based on the search strategy and considered time period, this meta-analysis could include participants from 27 countries from four continents; therefore, the prevalence may not represent at a global scale and generalization of the findings should be done with care. One of the major limitations in this meta-analysis is the presence of substantial degrees of heterogeneity. Even though we examined the sources of heterogeneity by subgroup, sensitivity analyses and Galbraith plot, source of heterogeneity could not be fully explained by the factors included in the analyses. Although we comprehensively investigated the prevalence of olfactory dysfunction from the first eight-month data of the COVID-19 outbreak, we have somewhat characterized olfactory dysfunctions in severe versus non-severe COVID-19 patients due to the limited number of studies.

Another major limitation is majority of the studies used self-reported data. When self-reported health measures are used, both underestimation due to false negative reporting and overestimation due to false positive reporting may possibly transpire, and the results should be interpreted with caution. A meta-analysis involving studies with large number of patients may minimize the potential bias but an amplification of the compromised methodology cannot entirely be excluded.

CONCLUSION

This meta-analysis found the prevalence of olfactory dysfunction was 47.85% of the COVID-19 patients based on the high quality of evidence, which suggests it as a significant initial symptom of SARS-CoV-2 infection. Due to the subjective measures of most studies pooled in the analysis, further studies with objective evaluations are recommended to confirm the finding.

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