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RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Frequency and Clinical Utility of Olfactory Dysfunction in COVID-19: a Systematic Review and Meta-analysis

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Abstract

Background Olfactory dysfunction (OD) has been gaining recognition as a symptom of COVID-19, but its clinical utility has not been well defined.

Objectives To quantify the clinical utility of identifying OD in the diagnosis of COVID-19 and determine an estimate of the frequency of OD amongst these patients.

Methods PubMed was searched up to 1 August 2020. Meta-analysis A included studies if they compared the frequency of OD in COVID-19 positive patients (proven by reverse transcription polymerase chain reaction) to COVID-19 negative controls. Meta-analysis B included studies if they described the frequency of OD in COVID-19 positive patients and if OD symptoms were explicitly asked in questionnaires or interviews or if smell tests were performed.

Results The pooled frequency of OD in COVID-19 positive patients (17,401 patients, 60 studies) was 0.56 (0.47–0.64) but differs between detection via smell testing (0.76 [0.51–0.91]) and survey/questionnaire report (0.53 [0.45–0.62]), although not reaching statistical significance ($p = 0.089$). Patients with reported OD were more likely to test positive for COVID-19 (diagnostic odds ratio 11.5 [8.01–16.5], sensitivity 0.48 (0.40 to 0.56), specificity 0.93 (0.90 to 0.96), positive likelihood ratio 6.10 (4.47–8.32) and negative likelihood ratio 0.58 (0.52–0.64)). There was significant heterogeneity amongst studies with possible publication bias.

Conclusion Frequency of OD in COVID-19 differs greatly across studies. Nevertheless, patients with reported OD were significantly more likely to test positive for COVID-19. Patient-reported OD is a highly specific symptom of COVID-19 which should be included as part of the pre-test screening of suspect patients.

Keywords Meta-analysis · Severe acute respiratory syndrome · Coronavirus 2 · Olfaction disorders · COVID-19

Key Points

Question: What is the clinical utility of olfactory dysfunction (OD) in the diagnosis of COVID-19?

Findings: In this meta-analysis, the pooled frequency of OD in COVID-19 positive patients (17401 patients, 60 studies) was 0.56 (0.47 to 0.64). Patients with reported OD were more likely to test positive for COVID-19 with a diagnostic odds ratio 11.5 (8.01 to 16.5), sensitivity 0.48 (0.40 to 0.56), specificity 0.93 (0.90 to 0.96), positive likelihood ratio 6.05 (4.52 to 8.11) and negative likelihood ratio 0.60 (0.54 to 0.67).

Meaning: Patient-reported OD is a highly specific symptom of COVID-19 which should be included as part of the pre-test screening of suspect patients.

This article is part of the Topical Collection on *Rhinosinusitis*

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Introduction

Olfactory dysfunction has been gaining increasing recognition in the fight against COVID-19 [1, 2]. What began as anecdotal reports of patients presenting with anosmia as the sole symptom has evolved into changes in clinical case definitions for suspect cases internationally.

In the context of COVID-19 infections, acute olfactory dysfunction (OD) is defined as decreased or altered sense of smell of a duration of 14 days or less, in the absence of chronic rhinosinusitis, a history of head trauma or neurotoxic medications. OD can be associated with flavour (smell + taste) dysfunction. However, COVID-19 may also affect real taste (sweet, salty, bitter, acidic, umami).

OD is estimated to afflict 3–20% of the population [3, 4]. Post-viral anosmia accounts for up to 40% cases of anosmia or which coronaviruses are thought to account for 10–15% of these cases [5, 6]. As such, it is plausible that COVID-19 may cause OD.

Though the exact pathogenesis is unclear, the high rate of recovery of olfactory function within 1–3 weeks after the onset of OD [7–10] may provide clues on the mechanism and extent of injury to olfactory epithelium and/or neurones. There are two proposed mechanisms by which COVID-19 causes anosmia. Coronaviruses are known to infect olfactory epithelium [11, 12]. Human angiotensin-converting enzyme 2 (ACE-2) receptor, which is a SARS-CoV-2 receptor, is expressed in the olfactory epithelial cells within the olfactory cleft, specifically the sustentacular cells [13, 14]. Inflammation of the olfactory cleft mucosa can cause conductive OD by reducing airflow and hence odorant presentation to the olfactory cleft [15].

This symptom may hence represent a potential clinical screening tool to facilitate testing of asymptomatic individuals. However, it remains unclear if these findings are causally and uniquely related to COVID-19 infection, or due to increased recognition of OD as a symptom [16]. Amongst patients afflicted with COVID-19, decreased awareness of olfactory dysfunction may be overshadowed by more severe symptoms such as respiratory distress. Furthermore, data in the literature suggests that self-reporting of the sense of smell is specific but not sensitive [17, 18]. Amongst those with measured olfactory dysfunction, 74.2% did not recognise it [18]. This is so amongst patients afflicted with COVID-19 as well [19•].

As such, we set out to conduct a systematic review and meta-analysis on OD in COVID-19 to quantify the clinical utility of identifying OD in the diagnosis of COVID-19 and determine an estimate of the frequency of OD amongst these patients. We also aimed to look separately at survey-reported and smell test-reported OD given the reported variance between the two.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) Statement [20] was referenced to structure the study. A study protocol was not registered, and no ethics approval was required.

Information Sources and Search Strategy

Studies were eligible if they were indexed on PubMed. The search was performed on 9 May 2020, and the strategy used was "(anosmia OR smell OR hypos* OR olfact*) AND (COVID* OR SARS-CoV-2 OR 2019-nCoV OR coronavirus)." The search was not limited by publication date and there was no language filter applied. The search was updated on 1 August 2020.

Study Selection and Data Collection

Screening of titles and abstracts was performed by 2 independent researchers to determine if the studies met the inclusion criteria. If abstracts were not available, the full text was retrieved and analysed. Any disagreements between the 2 researchers were resolved by discussion and by consulting a third, senior researcher. Data extracted from eligible studies included the author, year of publication, study design, country of origin, OD testing method, COVID-19 testing method and number of cases reporting OD amongst COVID-19 positive and negative patients. Data was entered into Excel sheets independently by the 2 researchers and then compared. Methodological quality was rated independently by two reviewers using the risk of bias tool for prevalence studies by Hoy et al. [21].

Inclusion and Exclusion Criteria

To quantify the clinical utility of identifying OD in the diagnosis of COVID-19, we compared the frequency of OD in patients stratified by COVID-19 test results using the reverse transcription polymerase chain reaction (RT-PCR). This was performed in Meta-analysis A. Studies were included if they compared the frequency of smell disturbance in COVID-19 positive patients (proven by RT-PCR) to COVID-19 negative controls in case-control studies. Appropriate controls were defined as patients who were suspected of having COVID-19 infection or fulfilled local guidelines for COVID-19 testing but were COVID-19 negative on RT-PCR testing. The data items were the number of COVID-19 positive and negative patients with OD and total number of patients tested. Principal summary measures were pooled

sensitivity, specificity, positive likelihood ratio (LR), negative LR and diagnostic odd ratios (DOR).

To investigate the estimated frequency of OD amongst COVID-19 patients, meta-analysis B included studies if they described the frequency of OD in COVID-19 positive patients and if smell tests were performed or if OD symptoms were explicitly asked in questionnaires or interviews. The latter criterion was chosen as OD symptoms were not routinely asked in early studies, which might explain the low frequency of OD reported in China. The data items were the number of COVID-19 positive patients with OD. The principal summary measure was the frequency of OD. Subgroup analyses was performed to investigate if the frequency differed between survey/questionnaire-reported OD and smell test-reported OD.

Statistical Analysis

R Studio version 1.2.5042 [22] and R version 4.0.0 [23] were used for all statistical analyses. The packages meta [24], mada [25] and dmetar [26] were used in the analyses. All data are presented as effect estimates with 95% confidence intervals in parenthesis. Heterogeneity amongst studies was tested using the Cochran's Q test and I^2. A random effects model was used if $I^2 > 50\%$. Forest plots were generated to summarise the results. Funnel plots and Egger tests were used to detect any publication bias.

Results

Meta-analysis A: the Clinical Significance OD in the Diagnosis of COVID-19

A total of 498 studies were retrieved from PubMed. A total of 422 articles were excluded based on their titles and abstracts, and 57 of the remaining 76 articles were excluded for reasons as described in Fig. 1. The remaining 19 articles were included in the meta-analysis.

Study Characteristics

A total of 1861 COVID-19 positive patients and 15,556 COVID-19 negative patients were included across the 19 studies as seen in Table 1. The patients were from Canada, France, Germany, Hungary, Italy, Netherlands, Singapore, Spain, Turkey and the USA. All studies utilised RT-PCT as the COVID-19 diagnostic testing method. All studies described survey/questionnaire-reported OD.

Clinical Utility of Identifying OD in the Diagnosis of COVID-19

With reference to Fig. 2, patients with OD were more likely to test positive for COVID-19 (DOR 11.5 (8.01 to 16.5), positive LR 6.10 (4.47 to 8.32) and negative LR 0.58 (0.52 to 0.64)). The pooled sensitivity was 0.48 (0.40 to 0.56), and the pooled specificity was 0.93 (0.90 to 0.96) in using OD to predict

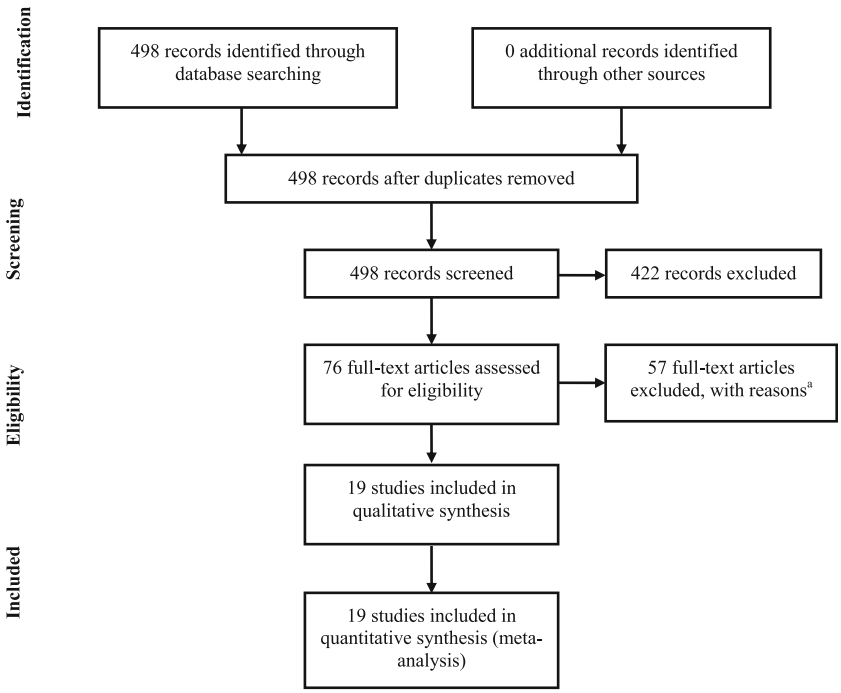

Fig. 1 Flow diagram for meta-analysis A showing the clinical significance of OD in the diagnosis of COVID-19. [a]Fifty-seven full-text articles were excluded: 49 did not include controls, 4 utilised inappropriate controls who were not swabbed for COVID-19 (3 studies used healthy asymptomatic individuals as controls and 1 study used historical influenza patients as controls), 2 utilised self-reported COVID testing results, 1 added in OD symptoms to their data collection sheet midway through the study and 1 did not explicitly ask for OD symptoms

Table 1 Characteristics of full-text articles assessed for eligibility

Author	Country	Study design	COVID positive		COVID negative		OD testing method	COVID testing method
			OD	Total	OD	Total		
Questionnaire-reported OD studies included in both meta-analyses A and B								
Bénézit, 2020 [27]	France	Case-control study	31	68	19	189	Online questionnaire	RT-PCR
Brandstetter, 2020 [28]	Germany	Case-control study	16	31	4	170	Structured interview	RT-PCR
Carignan, 2020 [29]	Canada	Case-control study	69	134	6	134	Questionnaire by phone	RT-PCR
Chua, 2020 [30]	Singapore	Case-control study	7	31	22	686	Prospective verbal interview	RT-PCR
Dawson, 2020 [31]	USA	Case-control study	18	42	1	48	Questionnaire	RT-PCR
Greffe, 2020 [32]	France	Case-control study	75	195	12	324	Questionnaire (prospective)	RT-PCR
Haehner, 2020 [33]	Germany	Cross-sectional controlled cohort survey	22	34	47	466	Questionnaire	RT-PCR
Izquierdo-Domínguez, 2020 [34]	Spain	Case-control study	454	846	43	143	Questionnaire	RT-PCR
Lee DJ, 2020 [35]	Canada	Cross-sectional survey	23	56	3	71	Online questionnaire	RT-PCR
Magnavita, 2020 [36]	Italy	Case-control study	35	82	1	152	Questionnaire (recall)	RT-PCR
Martin-Sanz, 2020 [37]	Spain	Case-control study	138	215	30	140	Questionnaire (recall)	RT-PCR
Merkely, 2020 [38]	Hungary	Case-control Study	12	70	265	10,404	Questionnaire (prospective)	RT-PCR
Sayin, 2020 [39]	Turkey	Case-control study	52	64	15	64	Online questionnaire	RT-PCR
Tostmann, 2020 [40]	Netherlands	Cross-sectional survey	37	79	7	190	Online questionnaire	RT-PCR
Tudrej, 2020 [41]	France	Cross-sectional survey	82	198	74	618	Questionnaire	RT-PCR
Wee, 2020 [42]	Singapore	Case series	35	154	9	716	Case notes review (explicitly asked)	RT-PCR
Yan, 2020a [8]~	USA	Cross-sectional survey	40	59	33	203	Online questionnaire	RT-PCR
Zayet, 2020a [43]	France	Case-control study, influenza positive controls	37	70	9	54	Standardised questionnaire then case notes review	RT-PCR
Zayet, 2020b [44]	France	Case-control study	60	95	18	122	Standardised questionnaire then case notes review	RT-PCR
Questionnaire-reported OD studies included only in meta-analysis B								
Altin, 2020 [45]	Turkey	Case-control study, asymptomatic controls not swabbed	50	81	0	40	Questionnaire (prospective)	RT-PCR
Barillari, 2020 [46]	Italy	Cross-sectional Survey	118	179	NA	NA	Questionnaire (recall)	RT-PCR
Beltrán-Corbellini, 2020 [47]	Spain	Case-control study, historical influenza positive controls	25	79	4	40	Questionnaire	RT-PCR
Biadsee, 2020 [48]	Israel	Case series	86	128	NA	NA	Online questionnaire	RT-PCR
Chary, 2020 [49]	France	Case series	106	115	NA	NA	DyNaCHRON questionnaire	RT-PCR
Chiesa-Estomba, 2020 [50]	Spanish, Uruguay, Venezuela, Argentina	Case series	444	542	NA	NA	Short version of Questionnaire of Olfactory Disorders-Negative Statements	RT-PCR
Chung, 2020 [51]	Hong Kong	Case-control study, asymptomatic controls not swabbed	12	18	0	18	Questionnaire	RT-PCR
Dell'Era, 2020 [52]	Italy	Cross-sectional survey	237	355	NA	NA	Questionnaire	RT-PCR
Foster, 2020 [53]	USA	Case series	198	949	NA	NA	Questionnaire	RT-PCR&
Freni, 2020 [54]	Italy	Case Series	46	50	NA	NA	Questionnaire (recall)	RT-PCR
Giacomelli, 2020 [55]	Italy	Cross-sectional survey	14	59	NA	NA	Questionnaire interview	RT-PCR&
Gómez-Iglesias, 2020 [56]	Spain	Cross-sectional survey	894	909	NA	NA	Online questionnaire (recall)	RT-PCR

Table 1 (continued)

Author	Country	Study design	COVID positive		COVID negative		OD testing method	COVID testing method
			OD	Total	OD	Total		
Jalessi, 2020 [57]	Iran	Cross-sectional Survey (random sample)	22	92	NA	NA	Questionnaire (recall)	RT-PCR
Karadas, 2020 [58]	Turkey	Cross-sectional survey	18	239	NA	NA	Questionnaire (prospective)	RT-PCR
Kim, 2020 [59]	South Korea	Cross-sectional survey	68	213	NA	NA	Questionnaire	RT-PCR
Klopfenstein, 2020 [60]	France	Case series	54	114	NA	NA	Case notes review	RT-PCR
Lechien, 2020e [61]	Belgium, France, Spain, Italy, Switzerland	Cross-sectional survey	1754	2013	NA	NA	Questionnaire (online)	RT-PCR
Lee Y, 2020 [10]	South Korea	Cross-sectional survey	389	3191	NA	NA	Questionnaire by phone	RT-PCR
Levinson, 2020 [62]	Israel	Case series	15	42	NA	NA	Questionnaire	RT-PCR
Liang, 2020 [63]	China	Cross-sectional Survey	34	86	NA	NA	Questionnaire(recall)	RT-PCR
Liguori, 2020 [64]	Italy	Case series	40	103	NA	NA	Standardised interview	RT-PCR
Luers, 2020 [65]	Germany	Cross-sectional survey	53	72	NA	NA	Questionnaire	RT-PCR
Meini, 2020 [66]	Italy	Case series	29	100	NA	NA	Questionnaire by phone	RT-PCR
Mercante, 2020 [67]	Italy	Case series	85	204	NA	NA	Italian SNOT-22	RT-PCR
Noh, 2020 [68]	South Korea	Case series	52	199	NA	NA	Interview	RT-PCR
Otte, 2020 [69]	Germany	Case series	47	50	NA	NA	Patient reported	RT-PCR
Paderno, 2020a [70]	Italy	Cross-sectional survey	283	508	NA	NA	Questionnaire (recall)	RT-PCR
Patel, 2020 [71]	UK	Case series	80	141	NA	NA	Questionnaire by phone	RT-PCR
Qiu, 2020 [72]	China, France, Germany	Case series	154	394	NA	NA	Questionnaire of olfactory disorders	RT-PCR
Renaud, 2020 [73]	France	Case series	96	97	NA	NA	Questionnaire	RT-PCR
Sierpiński, 2020 [74]	Poland	Cross-sectional survey	956	1942	NA	NA	Questionnaire	RT-PCR
Speth, 2020 [75]	Switzerland	Cross-sectional survey	63	103	NA	NA	Questionnaire by phone	RT-PCR
Spinato, 2020 [76]	Italy	Cross-sectional survey	130	202	NA	NA	Questionnaire by phone, SNOT22	RT-PCR
Villarreal, 2020 [77]	Spain	Case series	157	230	NA	NA	Questionnaire	RT-PCR
Wi, 2020 [78]	Korea	Cross-sectional Survey	15	102	NA	NA	Questionnaire (prospective)	RT-PCR
Yan, 2020b [15]	USA	Case series	75	128	NA	NA	Case notes review and phone/e-mail interview	RT-PCR
Smell test-reported OD studies included only in meta-analysis B								
Hornuss, 2020 [79]	Germany	Case-control study, asymptomatic controls not swabbed	38	45	12	45	Sniffin' Sticks	RT-PCR
Lechien, 2020d [80]	Belgium	Case series	53	86	NA	NA	Sniffin' Sticks	RT-PCR
Moein, 2020 [19•]	Iran	Cross-sectional survey	59	60	NA	NA	UPSIT	RT-PCR
Petrocelli, 2020 [81]	Italy	Case Series	190	300	NA	NA	Ethyl alcohol	RT-PCR
Vaira, 2020a [9]	Italy	Cross-sectional survey	60	72	NA	NA	CCCRC test	RT-PCR
Vaira, 2020b [82]	Italy	Cross-sectional survey	104	345	NA	NA	CCCRC and ethyl alcohol tests	RT-PCR
Excluded studies after full text review								
Abalo-Lojo, 2020 [83]	Spain	Case series	77	131	NA	NA	Patient reported Unclear if explicitly asked	RT-PCR
Adorni, 2020 [84][%]	Italy	Cross-sectional Survey	507	856	291	3536	Questionnaire (recall)	RT-PCR
Aggarwal, 2020 [85]	USA	Case series	3	16	NA	NA	Case notes review Unclear if explicitly asked	RT-PCR

Table 1 (continued)

Author	Country	Study design	COVID positive		COVID negative		OD testing method	COVID testing method
			OD	Total	OD	Total		
Gelardi, 2020 [86]	Italy	Case series	42	72	NA	NA	Unclear	RT-PCR
Lechien, 2020a [87]^	19 European Hospitals	Cross-sectional Survey	583	702	NA	NA	Questionnaire (recall)	RT-PCR
Lechien, 2020b [88]^	Belgium, France, Spain, Italy, Switzerland	Cross-sectional survey	997	1420	NA	NA	Questionnaire (interview, phone, online)	RT-PCR
Lechien, 2020c [7]^	Belgium, France, Spain, Italy	Case series	357	417	NA	NA	Questionnaire (online)	RT-PCR
Lehrich, 2020 [89]	Italy	Case series	42	72	NA	NA	Not stated	RT-PCR
Mao, 2020 [90]	China	Case series	11	214	NA	NA	Case notes review Unclear if explicitly asked	RT-PCR
Menni, 2020 [16]%	UK	Cross-sectional survey	342	579	202	1123	Online COVID RADAR Symptom Tracker app	RT-PCR
Paderno, 2020b [91••]@	Italy	Cross-sectional survey	125	151	NA	NA	Questionnaire (recall)	RT-PCR
Peyrony, 2020[92]	France	Case-control study	31	225	3	166	Questionnaire (OD only added in midway)	RT-PCR
Romero-Sánchez, 2020 [93]	Spain	Case series	41	841	NA	NA	Case notes review (not explicitly asked)	RT-PCR
Trigo, 2020 [94]	Spain	Case series	146	576	NA	NA	Case notes review (not explicitly asked)	RT-PCR
Trubiano, 2020 [95]	Australia	Case-control study	7	28	62	1208	Case notes review (not explicitly asked)	RT-PCR

OD olfactory dysfunction, *UPSIT* University of Pennsylvania Smell Identification Test, *SNOT22* Sino-nasal Outcome Test, *CCCRC test* Connecticut Chemosensory Clinical Research Center orthonasal olfaction test, *NA* not available

& Personal communication with study authors confirmed RT-PCR as diagnostic testing method

~ Yan, 2020a [8] was not included in meta-analysis B of prevalence of OD as data likely overlaps with the other paper published by Yan [15]

^Excluded due to overlapping dataset. The largest series by Lechien [61] was included in the analyses

% Excluded as COVID-19 testing and result was self-reported by patients and not verified

@ Excluded as it is a follow-up study of the same dataset

COVID-19 infection. There was significant heterogeneity amongst the 6 studies ($I^2 = 76.4\%$, $p < 0.0001$). The Funnel plot is shown in Fig. 5a. Egger's test suggested the presence of publication bias ($p < 0.001$).

Meta-analysis B: Estimating the Frequency of OD Amongst COVID-19 Patients

A total of 498 studies were retrieved from PubMed. A total of 422 articles were excluded based on their titles and abstracts, and 16 of the remaining 76 articles were excluded for reasons as described in Fig. 3. The remaining 60 articles were included in the meta-analysis.

Study Characteristics

A total of 17,401 COVID-19 positive patients across 60 studies were included in Meta-analysis B, of which 8606 reported OD. The patients were from all major continents. All utilised RT-PCT as the COVID-19 diagnostic testing method. All used questionnaire-based, symptom-based reporting of OD except for 6 studies (2 used Sniffin' Sticks, 1 used UPSIT, 1 used the Connecticut Chemosensory Clinical Research Test (CCCRT), 1 used ethyl alcohol and 1 used a combination of CCCRT and ethyl alcohol).

Estimating the Frequency of OD Amongst COVID-19 Patients

With reference to Fig. 4, the overall pooled frequency of OD amongst COVID-19 patients was 0.56 (0.47 to 0.64). There was significant heterogeneity amongst the 60 studies ($I^2 = 98.8\%$, $p < 0.001$). Funnel plot is shown in Fig. 5b. Egger's test did not suggest the presence of publication bias ($p = 0.204$).

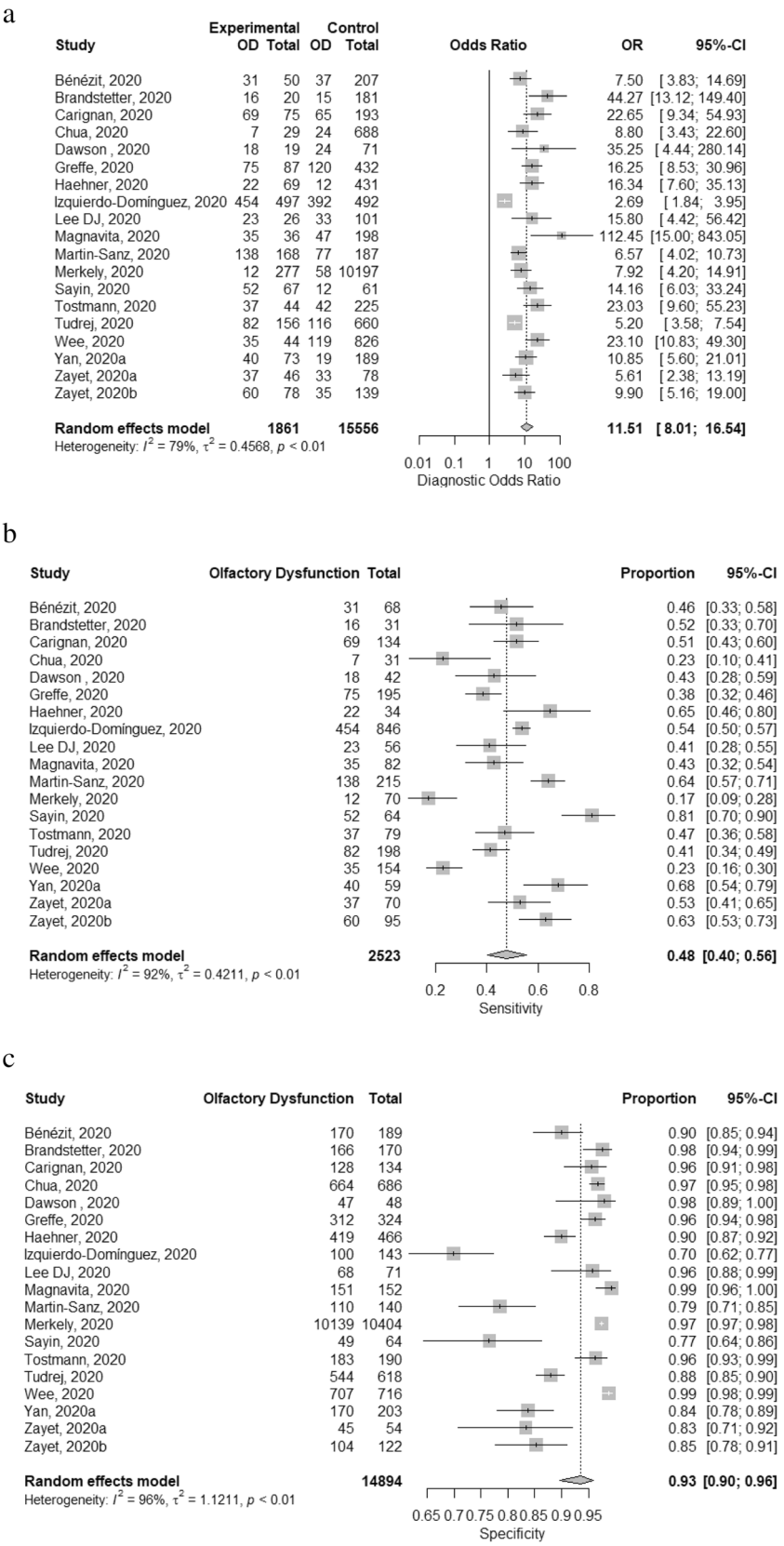

Fig. 2 Meta-analysis A showing the clinical significance OD in the diagnosis of COVID-19. **a** Diagnostic odds ratio. **b** Pooled sensitivity. **c** Pooled specificity of OD in predicting COVID-19 infection

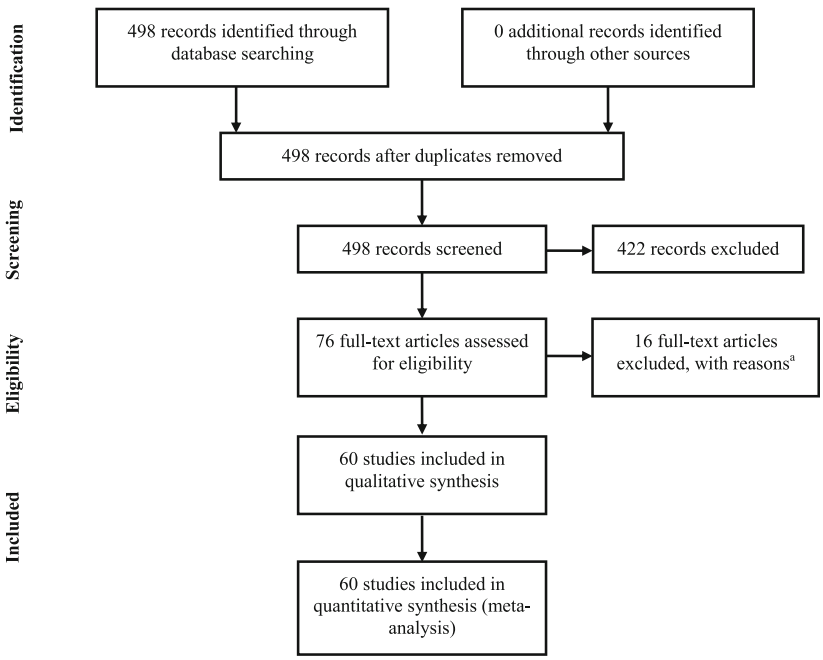

Fig. 3 Flow diagram for meta-analysis B estimating the frequency of OD amongst COVID-19 patients. [a]Sixteen full-text articles were excluded: 9 did not specify if OD symptoms were explicitly asked, 5 likely used overlapping data and 2 utilised self-reported COVID testing results

In subgroup analysis in Fig. 4, the frequency of smell test detected OD amongst COVID-19 patients differs between detection via smell testing (0.76 [0.51–0.91]) vs survey/questionnaire report (0.53 [0.45–0.62]), although not reaching statistical significance ($p = 0.089$).

Risk of Bias

Table 2 summarises the risk of bias of all studies included in both meta-analyses A and B. Overall, the studies were of moderate to high risk of bias due to the lack of smell testing except for 6 studies, the presence of non-response bias using the questionnaire methodology or the inclusion of only particular groups of patients (e.g. only hospitalised patients, or only outpatients, or only those with mild-moderate disease).

Discussion

The pooled frequency of OD in COVID-19 positive patients (17,401 patients, 60 studies) was 0.56 but differed between detection via validated smell testing (0.76) vs survey/questionnaire reports (0.53). This inconsistency of olfactory dysfunction between survey/questionnaire reports and validated smell tests has also been recognised in the literature [17, 18]. Moein et al. [19•] reported that 29% of their patients reported self-reported OD. However, validated smell tests on this same group of patients showed 58% to have anosmia or severe microsmia, with only 2% with normal olfactory function. Similarly, Vaira [9] reported 28.3% patients having s OD, while 98% had OD on validated smell tests. A significant number of patients with olfactory dysfunction do not report symptoms. Even within the realm of administered smell tests, cultural differences may result in inaccurate identification of smell dysfunction [96]. This might suggest that at least some of the variation in frequency rates of OD in COVID-19 may be attributed to differences in data collection methods.

Notwithstanding this, patient-reported OD as a symptom was highly specific (93%) but not sensitive (48%), for COVID-19 infection. The results of this meta-analysis further suggest that patients with reported OD were more likely to test positive for COVID-19 (diagnostic OR 11.5), with positive (6.10) and negative (0.58) LR. The presence of patient-reported OD can hence be used as an additional screening question to triage patients in determining the need for COVID-19 testing regardless of the presence of other concomitant upper respiratory symptoms. Whether smell test detected OD may serve as a more accurate screening tool remains to be investigated.

It is increasingly recognised that the COVID-19 infection can manifest as mild, moderate, severe or critical illness [97]. Yan et al. [15] reported that patients with OD may be associated with a milder clinical course. Izquierdo-Domínguez also reported that patients with more severe OD were less likely to be hospitalised and had a lower level of C-reactive protein [34]. However, patients who were intubated or deceased at the time of data collection could not be included in their study. If this were indeed true, the presence of OD might assist in

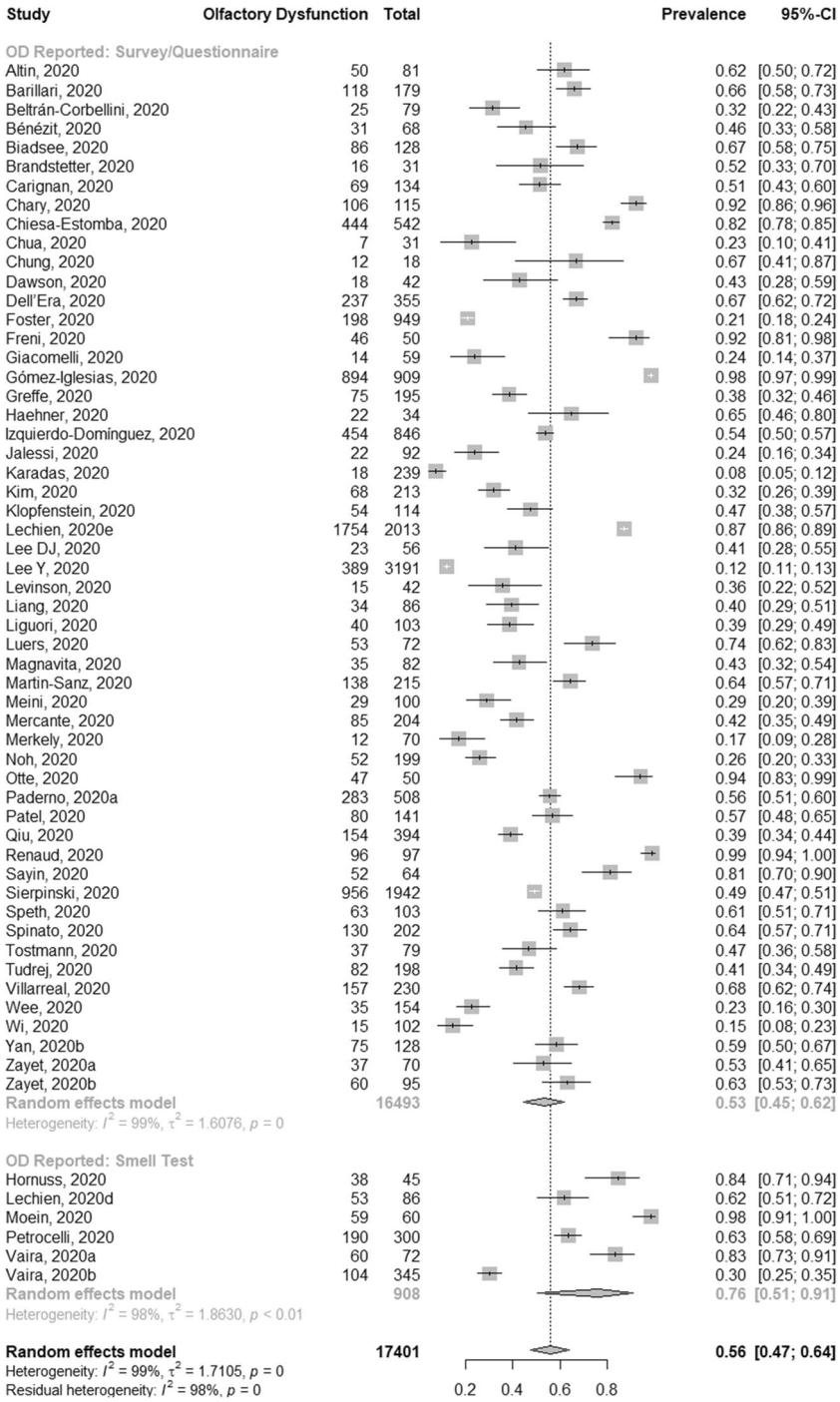

Fig. 4 Meta-analysis B estimating the frequency of OD amongst COVID-19 patients. Pooled prevalence of olfactory dysfunction (OD) amongst COVID-19 patients with sub-group analysis by OD testing method

deciding the disposition of patients i.e. admission vs out-patient care. However, Moein et al. [19•] reported that there was no statistically significant difference in the mean UPSIT score between patients with mild, moderate or severe COVID-19. As such, this may be purely be due to recall bias, where patients with severe COVID-19 may be less cognizant of OD due to the presence of more bothersome symptoms such as dyspnoea. The prognostic value of OD in COVID-19 patients remains to be elucidated but is unlikely to override traditional, objective and actionable clinical measurements such as oxygen saturation, pulse rate and respiratory rate.

Various Otolaryngologic societies have issued statements addressing OD in COVID-19. On 21 March 2020, a press release was issued by ENT UK and the British Rhinological Society on Twitter, recommending that anosmia be added to the current symptom criteria used to trigger quarantine and that individuals with new-onset

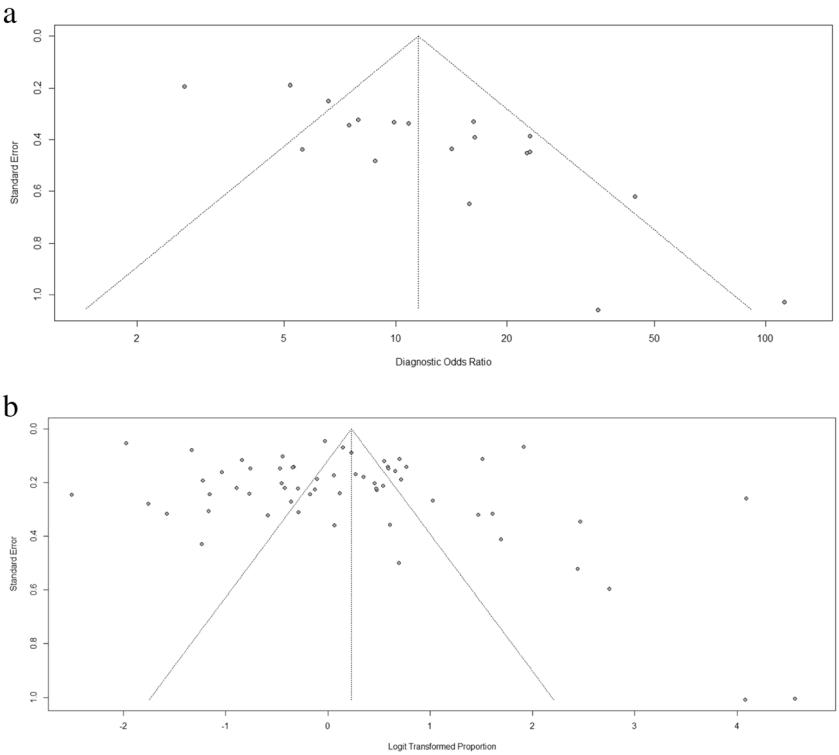

Fig. 5 Funnel plots for **a** meta-analysis A showing the clinical significance OD in the diagnosis of COVID-19 and **b** meta-analysis B estimating the frequency of OD amongst COVID-19 patients

anosmia should self-isolate to reduce the risk of further transmission of COVID-19 [5]. This was largely based on anecdotal physician and media reports [98]. A similar statement was released by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) on 22 March 2020 [99], and a joint statement was released by the Chapter of Otorhinolaryngologists, College of Surgeons, Singapore, and the Society of Otolaryngology-Head and Neck Surgery, Singapore, on 17 April 2020 [100]. The US Centers for Disease Control and Prevention added "new loss of taste or smell" to the list of COVID-19 symptoms on 17 April 2020, while the World Health Organisation (WHO) has added the above as of 9 May 2020 [101], albeit as a "less common symptom".

The major limitation of the meta-analysis was the significant heterogeneity amongst included studies. Sources of heterogeneity include different inclusion criteria across studies (e.g. only hospitalised patients or only outpatients included, only mild-moderate illness included), different ways in which the OD questions were phrased and possibly the different RT-PCR sensitivities across different institutions around the world for detection of SARS-CoV-2 RNA. We were unable to perform a meta-analysis of the onset, duration and severity of OD due to the varied data collection protocols. As questionnaires were used in most of the studies, there might have been a strong recall bias in which patients who knew they were COVID-19 positive were more likely to report anosmia. Furthermore, it is impossible to survey intubated or deceased patients so findings may not be generalisable to the most severe of patients. Nevertheless, the clinical utility of patient-reported OD in identifying COVID-19 infection amongst patients with mild-moderate symptoms remains important to facilitate cohorting and isolation, to minimise transmission.

Future research should utilise validated instruments for both survey/questionnaire (i.e. visual analogue scale [VAS]) and smell testing of OD across various time points to quantify the onset and severity of OD and track its recovery. However, we recognise the inherent difficulties in conducting these tests amongst COVID-19 positive patients as it puts researchers at risk of infection. While it is important to correctly diagnose and classify the severity OD in order to study of the characteristics of hyposmia/microsmia or anosmia amongst COVID-19 positive, from a public health perspective, it can be argued that the detection of self-reported OD via surveys of questionnaires is equally important in curbing the COVID-19 pandemic by assisting in identifying COVID-19 positive patients.

Conclusion

Patient-reported OD is a highly specific symptom of COVID-19 which should be included as part of the pre-test screening of suspect patients.

Table 2 Risk bias assessment of included studies

Item	External validity				Internal validity							Overall Score
	1. Was the study's target population a close representation of the national population in relation to relevant variables?	2. Was the sampling frame a true or close representation of the target population?	3. Was some form of random selection used to select the sample, OR was a census undertaken?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects (as opposed to a proxy)?	6. Was an acceptable case definition used in the study?	7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	8. Was the same mode of data collection used for all subjects?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	11. Summary item on the overall risk of study bias	
Altin, 2020 [45]	0	1	1	1	1	1	0	1	1	1	Low	8
Barillari, 2020 [46]	1	1	0	0	1	1	0	1	1	1	Moderate	7
Beltrán-Corbellini, 2020 [47]	0	1	0	1	1	1	0	1	1	1	Low	7
Bénézit, 2020 [27]	0	1	1	0	1	1	0	1	1	1	Moderate	7
Biadsee, 2020 [48]	0	0	0	0	1	1	0	1	1	1	High	5
Brandstetter, 2020 [28]	0	1	1	1	1	1	0	1	1	1	Low	8
Carignan, 2020 [29]	0	1	1	1	1	1	0	1	1	1	Moderate	8
Chary, 2020 [49]	0	1	1	0	1	1	1	1	1	1	Low	8
Chiesa-Estomba, 2020 [50]	0	1	0	0	1	1	1	1	1	1	High	6
Chua, 2020 [30]	0	1	1	1	1	1	0	1	1	1	Low	8
Chung, 2020 [51]	0	0	0	0	1	1	0	1	1	1	High	5
Dawson, 2020 [31]	0	0	0	1	1	1	0	1	1	1	Moderate	6
Dell'Era, 2020 [52]	0	1	1	1	1	1	0	1	1	1	Low	8
Foster, 2020 [53]	0	1	1	1	1	1	0	0	1	1	Moderate	7
Freni, 2020 [54]	0	1	1	0	1	1	0	1	1	1	Moderate	7
Giacomelli, 2020 [55]	0	0	1	0	1	1	0	1	1	1	High	6
Gómez-Iglesias, 2020 [56]	0	0	0	0	1	1	0	0	1	1	High	4
Greffe, 2020 [32]	0	1	1	1	1	1	0	1	1	1	Low	8
Haehner, 2020 [33]	0	1	1	1	1	1	0	1	1	1	Low	8
Hornuss, 2020 [79]	0	0	1	0	1	1	1	1	1	1	Moderate	7
Izquierdo-Domínguez, 2020 [34]	1	1	1	0	1	1	0	1	1	1	Low	8
Jalessi, 2020 [57]	0	1	1	1	1	1	0	1	1	1	Low	8
Karadas, 2020 [58]	0	1	1	1	1	1	0	1	1	1	Low	8
Kim, 2020 [59]	0	0	1	1	1	1	0	1	1	1	Moderate	7

Table 2 (continued)

Item	External validity				Internal validity							Overall Score
	1. Was the study's target population a close representation of the national population in relation to relevant variables?	2. Was the sampling frame a true or close representation of the target population?	3. Was some form of random selection used to select the sample, OR was a census undertaken?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects (as opposed to a proxy)?	6. Was an acceptable case definition used in the study?	7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	8. Was the same mode of data collection used for all subjects?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	11. Summary item on the overall risk of study bias	
Klopfenstein, 2020 [60]	0	0	1	0	1	1	0	1	1	1	Moderate	6
Lechien, 2020d [87]	0	0	0	0	1	1	1	1	1	1	High	6
Lechien, 2020e [88]	0	1	1	1	1	1	0	1	1	1	Low	8
Lee DJ, 2020 [35]	0	1	0	0	1	1	0	1	1	1	High	6
Lee Y, 2020 [10]	0	1	1	1	1	1	0	1	1	1	Moderate	8
Levinson, 2020 [62]	0	1	1	1	1	1	0	1	1	1	Low	8
Liang, 2020 [63]	0	1	1	1	1	1	0	1	1	1	Moderate	8
Liguori, 2020 [64]	0	1	1	1	1	1	0	1	1	1	Low	8
Luers, 2020 [65]	0	0	1	0	1	1	0	1	1	1	Moderate	6
Magnavita, 2020 [36]	0	1	1	1	1	1	0	1	1	1	Low	8
Martin-Sanz, 2020 [37]	0	1	1	1	1	1	0	1	1	1	Low	8
Meini, 2020 [66]	0	1	1	1	1	1	0	1	1	1	Low	8
Mercante, 2020 [67]	0	1	1	0	1	1	1	1	1	1	Low	8
Merkely, 2020 [38]	1	1	1	1	1	1	0	1	1	1	Low	9
Moein, 2020 [19•]	0	1	0	1	1	1	1	1	1	1	Low	8
Noh, 2020 [68]	0	1	1	1	1	1	0	1	1	1	Low	8
Otte, 2020 [69]	0	0	1	1	1	1	0	1	1	1	High	7
Paderno, 2020a [70]	0	1	1	1	1	1	0	1	1	1	Low	8
Patel, 2020 [71]	0	1	1	0	1	1	0	1	1	1	High	7
Petrocelli, 2020 [81]	0	1	1	1	1	1	1	1	1	1	Low	9
Qiu, 2020 [72]	0	1	1	0	1	1	1	1	1	1	Low	8
Renaud, 2020 [73]	0	1	1	0	1	1	0	1	1	1	High	7
Sayin, 2020 [39]	0	1	1	0	1	1	0	1	1	1	High	7
Sierpiński, 2020 [74]	1	1	1	0	1	1	0	1	1	1	Low	8
Speth, 2020 [75]	0	1	1	0	1	1	0	1	1	1	Moderate	7
Spinato, 2020 [76]	0	1	1	0	1	1	1	1	1	1	High	8

Table 2 (continued)

Item	External validity				Internal validity							Overall Score
	1. Was the study's target population a close representation of the national population in relation to relevant variables?	2. Was the sampling frame a true or close representation of the target population?	3. Was some form of random selection used to select the sample, OR was a census undertaken?	4. Was the likelihood of nonresponse bias minimal?	5. Were data collected directly from the subjects (as opposed to a proxy)?	6. Was an acceptable case definition used in the study?	7. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	8. Was the same mode of data collection used for all subjects?	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	11. Summary item on the overall risk of study bias	
Tostmann, 2020 [40]	0	1	1	0	1	1	0	1	1	1	Moderate	7
Tudrej, 2020 [41]	0	1	1	1	1	1	0	1	1	1	Low	8
Vaira, 2020a [9]	0	1	1	0	1	1	1	1	1	1	Moderate	8
Vaira, 2020b [82]	1	1	1	0	1	1	1	1	1	1	Low	9
Villarreal, 2020 [77]	0	1	1	1	1	1	0	1	1	1	Low	8
Wee, 2020 [42]	0	1	1	1	1	1	0	1	1	1	Moderate	8
Wi, 2020 [78]	0	1	1	1	1	1	0	1	1	1	Low	8
Yan, 2020a [8]	0	0	1	0	1	1	0	1	1	1	High	6
Yan, 2020b [15]	0	1	1	0	1	1	0	0	1	1	Moderate	6
Zayet, 2020a [43]	0	1	1	1	1	1	0	1	1	1	Low	8
Zayet, 2020b [44]	0	1	1	1	1	1	0	1	1	1	Low	8

Authors' Contributions Khang Wen Pang and Jeremy Chee contributed equally to this paper and are co-first authors. Somasundaram Subramaniam and Chew Lip Ng contributed equally to this paper and are co-last authors. Chew Lip Ng and Somasundaram Subramaniam conceptualised the study. Khang Wen Pang and Jeremy Chee designed the study. Khang Wen Pang and Jeremy Chee screened titles and abstracts for inclusion. Khang Wen Pang and Jeremy Chee extracted and analysed data. Khang Wen Pang, Jeremy Chee, Chew Lip Ng and Somasundaram Subramaniam helped interpret the findings from the meta-analyses and interpretation from a clinical viewpoint. Khang Wen Pang and Jeremy Chee wrote the first draft, which all authors revised for critical content. All authors approved the final manuscript. Khang Wen Pang and Jeremy Chee are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability The authors will share data upon reasonable request.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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Ethics Approval Not required for this study.

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Consent for Publication Not applicable.

Code Availability The authors will share the full statistical code upon reasonable request.

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- • Of importance
- •• Of major importance

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