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

Khang Wen Pang · Jeremy Chee · Somasundaram Subramaniam · Chew Lip Ng

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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 (17,401 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.

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1 Department of Otolaryngology-Head and Neck Surgery, National University Hospital, Singapore, Singapore
2 Department of Otolaryngology-Head & Neck Surgery, Ng Teng Fong General Hospital, Singapore, Singapore
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. Coronavirus 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
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 |                     |
| 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

| Author                  | Country        | Study design                      | COVID positive | COVID negative | OD testing method | COVID testing method |
|-------------------------|----------------|-----------------------------------|----------------|-----------------|-------------------|---------------------|
|                         |                |                                   | OD  | Total | OD  | Total |                         |                     |
| 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 (recalled)   |
| 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 (recalled)   |
| Gómez-Iglesias, 2020 [56] | Spain         | Cross-sectional survey            | 894 | 909   | NA  | NA    | Online questionnaire (recall) | RT-PCR              |
| Author                  | Country          | Study design                      | COVID positive | COVID negative | OD testing method | COVID testing method |
|------------------------|------------------|-----------------------------------|----------------|----------------|-------------------|---------------------|
| Jaleesi, 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 | Questionnaire | 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 | 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 | RT-PCR              |
| 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              |
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 \((I^2 = 98.8\%, p < 0.0001)\). 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 of OD in the diagnosis of COVID-19. **a** Diagnostic odds ratio. **b** Pooled sensitivity. **c** Pooled specificity of OD in predicting COVID-19 infection

### a

| Study                  | Experimental OD Total | Control OD Total | Odds Ratio | OR  | 95%-CI |
|------------------------|-----------------------|------------------|------------|-----|--------|
| Bénézet, 2020         | 31 50 37 207          |                  | 7.50       | 3.83 | 14.69  |
| Brandstetter, 2020    | 16 20 15 181          |                  | 44.27      | 12.19 | 149.40 |
| Caigran, 2020         | 69 75 65 193          |                  | 22.65      | 9.34  | 54.93  |
| Chua, 2020            | 7 29 24 688           |                  | 8.60       | 3.42  | 22.60  |
| Dawson, 2020          | 18 19 24 71           |                  | 35.25      | 4.44  | 280.14 |
| Greffe, 2020          | 75 87 120 432         |                  | 16.25      | 6.53  | 39.96  |
| Haehner, 2020         | 22 69 12 431          |                  | 16.34      | 7.02  | 35.13  |
| Izquierdo-Dominguez, 2020 | 454 497 392 492      |                  | 2.69       | 1.84  | 3.95   |
| Lee DJ, 2020          | 23 26 33 101          |                  | 15.90      | 4.42  | 56.42  |
| Magnanilla, 2020      | 35 36 47 198          |                  | 112.45     | 15.00 | 943.05 |
| Martin-Sanz, 2020     | 138 168 77 187       |                  | 6.57       | 4.02  | 10.73  |
| Merkely, 2020         | 12 277 58 10197      |                  | 7.92       | 2.40  | 19.91  |
| Sayin, 2020           | 52 67 12 61          |                  | 14.16      | 6.13  | 33.24  |
| Tostmann, 2020        | 37 44 42 225         |                  | 23.03      | 9.60  | 55.23  |
| Tudrej, 2020          | 82 156 116 660       |                  | 5.30       | 3.56  | 7.54   |
| Wee, 2020             | 35 44 119 826        |                  | 23.10      | 10.63 | 49.30  |
| Yan, 2020a            | 40 73 19 189         |                  | 10.85      | 5.60  | 21.01  |
| Zayet, 2020b          | 37 46 33 78           |                  | 5.61       | 2.38  | 13.19  |
| Zayet, 2020b          | 60 78 35 139         |                  | 9.90       | 5.16  | 19.00  |

Random effects model 1881 15556

Heterogeneity: $I^2 = 79\%$, $Q = 4.066$, $p < 0.01$

### b

| Study                  | Olfactory Dysfunction Total | Proportion | 95%-CI |
|------------------------|----------------------------|------------|--------|
| Bénézet, 2020         | 31 68                      | 0.46       | 0.33, 0.58 |
| Brandstetter, 2020    | 16 31                      | 0.52       | 0.33, 0.70 |
| Caigran, 2020         | 69 134                     | 0.51       | 0.43, 0.60 |
| Chua, 2020            | 7 31                       | 0.30       | 0.23, 0.41 |
| Dawson, 2020          | 18 42                      | 0.43       | 0.28, 0.59 |
| Greffe, 2020          | 75 105                     | 0.38       | 0.32, 0.46 |
| Haehner, 2020         | 22 34                      | 0.05       | 0.46, 0.60 |
| Izquierdo-Dominguez, 2020 | 454 849                | 0.54       | 0.50, 0.57 |
| Lee DJ, 2020          | 23 59                      | 0.41       | 0.28, 0.55 |
| Magnanilla, 2020      | 35 82                      | 0.43       | 0.32, 0.54 |
| Martin-Sanz, 2020     | 138 215                    | 0.04       | 0.57, 0.71 |
| Merkely, 2020         | 12 70                      | 0.17       | 0.09, 0.28 |
| Sayin, 2020           | 52 64                      | 0.81       | 0.70, 0.90 |
| Tostmann, 2020        | 37 79                      | 0.47       | 0.36, 0.58 |
| Tudrej, 2020          | 62 196                     | 0.41       | 0.34, 0.49 |
| Wee, 2020             | 35 154                     | 0.23       | 0.16, 0.30 |
| Yan, 2020a            | 40 59                      | 0.68       | 0.54, 0.79 |
| Zayet, 2020a          | 37 70                      | 0.53       | 0.41, 0.65 |
| Zayet, 2020b          | 60 95                      | 0.63       | 0.53, 0.73 |

Random effects model 2523

Heterogeneity: $I^2 = 92\%$, $Q = 0.4211$, $p < 0.01$

### c

| Study                  | Olfactory Dysfunction Total | Proportion | 95%-CI |
|------------------------|----------------------------|------------|--------|
| Bénézet, 2020         | 170 189                    | 0.90       | 0.85, 0.94 |
| Brandstetter, 2020    | 166 170                    | 0.98       | 0.94, 0.99 |
| Caigran, 2020         | 128 134                    | 0.96       | 0.91, 0.98 |
| Chua, 2020            | 664 686                    | 0.97       | 0.95, 0.98 |
| Dawson, 2020          | 47 48                      | 0.98       | 0.89, 1.00 |
| Greffe, 2020          | 312 324                    | 0.96       | 0.94, 0.98 |
| Haehner, 2020         | 419 466                    | 0.90       | 0.87, 0.92 |
| Izquierdo-Dominguez, 2020 | 100 143                 | 0.70       | 0.62, 0.71 |
| Lee DJ, 2020          | 68 71                      | 0.98       | 0.88, 0.99 |
| Magnanilla, 2020      | 151 152                    | 0.99       | 0.96, 1.00 |
| Martin-Sanz, 2020     | 110 140                    | 0.79       | 0.71, 0.85 |
| Merkely, 2020         | 10139 10464               | 0.92       | 0.97, 0.98 |
| Sayin, 2020           | 49 64                      | 0.77       | 0.64, 0.86 |
| Tostmann, 2020        | 183 190                    | 0.96       | 0.93, 0.99 |
| Tudrej, 2020          | 544 618                    | 0.68       | 0.85, 0.90 |
| Wee, 2020             | 707 716                    | 0.99       | 0.98, 0.99 |
| Yan, 2020a            | 170 203                    | 0.84       | 0.78, 0.99 |
| Zayet, 2020a          | 45 54                      | 0.63       | 0.71, 0.90 |
| Zayet, 2020b          | 104 122                    | 0.85       | 0.78, 0.91 |

Random effects model 14894

Heterogeneity: $I^2 = 96\%$, $Q = 1.2112$, $p < 0.01$
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 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
deciding the disposition of patients i.e. admission vs outpatient 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
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 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? | 0 | 1 | 1 | 1 | 1 | 1 | 1 | Low | 8 |
| 2. Was the sampling frame a true or close representation of the target population? | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | Moderate | 7 |
| 3. Was some form of random selection used to select the sample, OR was a census undertaken? | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | Moderate | 7 |
| 4. Was the likelihood of nonresponse bias minimal? | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | Moderate | 7 |
| 5. Were data collected directly from the subjects (as opposed to a proxy)? | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | Moderate | 7 |
| 6. Was an acceptable case definition used in the study? | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate | 7 |
| 7. Was the study instrument that measured the parameter of interest shown to have validity and reliability? | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | Moderate | 7 |
| 8. Was the same mode of data collection used for all subjects? | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate | 7 |
| 9. Was the length of the shortest prevalence period for the parameter of interest appropriate? | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate | 7 |
| 10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate | 7 |
| 11. Summary item on the overall risk of study bias | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate | 7 |

Altin, 2020 [45] 0 1 1 1 1 1 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 1 0 1 1 0 1 1 1 Low 7
Bénézet, 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 0 1 1 0 1 1 1 Low 8
Carignan, 2020 [29] 0 1 1 1 0 1 1 0 1 1 1 Moderate 8
Chary, 2020 [49] 0 1 0 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 0 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 0 1 1 0 0 1 1Moderate 7
Freni, 2020 [54] 0 1 1 0 1 1 0 1 1 1 Moderate 7
Giacomelli, 2020 [55] 0 0 0 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
Hachner, 2020 [33] 0 1 1 1 1 1 0 1 1 1 Low 8
Hornuss, 2020 [79] 0 0 0 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
Jalesi, 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? | 1. Was the study’s target population a close representation of the national population in relation to relevant variables? | 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? | 2. Was the sampling frame a true or close representation of the target population? | 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? | 3. Was some form of random selection used to select the sample, OR was a census undertaken? | 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? | 4. Was the likelihood of nonresponse bias minimal? | 4. Was the likelihood of nonresponse bias minimal? |
| 5. Were data collected directly from the subjects (as opposed to a proxy)? | 5. Were data collected directly from the subjects (as opposed to a proxy)? | 5. Were data collected directly from the subjects (as opposed to a proxy)? |
| 6. Were an acceptable case definition used in the study? | 6. Were an acceptable case definition used in the study? | 6. Were 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? | 7. Was the study instrument that measured the parameter of interest shown to have validity and reliability? | 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? | 8. Was the same mode of data collection used for all subjects? | 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? | 9. Was the length of the shortest prevalence period for the parameter of interest appropriate? | 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? | 10. Were the numerator(s) and denominator(s) 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 | 11. Summary item on the overall risk of study bias | 11. Summary item on the overall risk of study bias |

| Reference | External validity | Internal validity | Overall Score |
|-----------|-------------------|-------------------|---------------|
| Klopfenstein, 2020 [60] | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate 6 |
| Lechien, 2020d [87] | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | High 6 |
| Lechien, 2020e [88] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Low 8 |
| Lee DJ, 2020 [35] | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | High 6 |
| Lee Y, 2020 [10] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Moderate 8 |
| Levinson, 2020 [62] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Low 8 |
| Liang, 2020 [63] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Moderate 8 |
| Liguori, 2020 [64] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Low 8 |
| Luers, 2020 [65] | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate 6 |
| Magnanvita, 2020 [36] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Martin-Sanz, 2020 [37] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Meini, 2020 [66] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Mercante, 2020 [67] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Merkely, 2020 [38] | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Low 9 |
| Moen, 2020 [19] | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Noh, 2020 [68] | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Orte, 2020 [69] | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | High 7 |
| Paderno, 2020a [70] | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | Low 8 |
| Patel, 2020 [71] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | High 7 |
| Petrocelli, 2020 [81] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low 9 |
| Qiu, 2020 [72] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Renaud, 2020 [73] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | High 7 |
| Sayin, 2020 [39] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | High 7 |
| Sierpiński, 2020 [74] | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Low 8 |
| Speth, 2020 [75] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | Moderate 7 |
| Spinato, 2020 [76] | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 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 |
| Item | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | Moderate 7 |
| Tostmann, 2020 [40] | | | | | | | | | | | |
| 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

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Consent for Publication Not applicable.

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