A Systematic Review and Meta-analysis Protocol Examining the Clinical Characteristics and Epidemiological Features of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19)

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Protocol

Abstract

Background

The coronavirus disease 2019 (COVID-19) pandemic has caused recurring and major outbreaks in multiple human populations around the world. The plethora of clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been described extensively, of which COVID-19-related olfactory dysfunction (OD) has been recognised as an important and common symptom of COVID-19 infection. The aim of this study is to conduct a systematic review and meta-analysis of peer-reviewed articles, which described clinical data of smell disturbances and OD in COVID-19 patients.

Methods

This research protocol has been prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020196202). Accordingly, PubMed (MEDLINE) articles published from 1st January 2020 to 10th June 2020 will be searched using the following keywords: COVID-19, SARS-CoV-2, 2019-nCoV, or novel coronavirus. Systematic review and meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines. Articles will be screened according to the pre-specified inclusion and exclusion criteria. Included articles will be reviewed in full; data including patient demographics, clinical characteristics of COVID-19-related OD, methods of olfactory assessment, and relevant clinical outcomes will be extracted. Statistical analyses will be performed using the Comprehensive Meta-Analysis version 3.

Discussion

This systematic review and meta-analysis will exclusively evaluate OD as a symptom of COVID-19 infection. We aim to collate and synthesise all available clinical evidence regarding COVID-19-related OD. A comprehensive search strategy and screening process will be used to ensure that all relevant clinical data are included for statistical analysis and representation. The outcome of this study will improve our understanding of the symptomatology and clinical characteristics of COVID-19-related OD and serves to identify knowledge gaps in its disease process, which will guide future research regarding this specific neurosensory impairment.

Systematic Review registration: PROSPERO registration number: CRD42020196202

Background

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the aetiological agent of the coronavirus disease 2019 (COVID-19) global pandemic, has infected over 14 million people worldwide, accounting for over 603,000 deaths as of 20 July 2020.[1] Since its discovery in December 2019, the different clinical signs and symptoms associated with COVID-19

infection have been described comprehensively in numerous research articles.[2] Consistent with the clinical characteristics of the 2003 SARS-CoV epidemic, the predominant clinical manifestations of COVID-19 affect the human respiratory system, ranging from silent hypoxia to respiratory failure and life-threatening acute respiratory distress syndrome (ARDS).[3–5] In addition, COVID-19 was shown to be associated with olfactory disturbances, which has since been recognised as a common and important neurosensory impairment in COVID-19 infection.[6–8]

Recent systematic reviews and meta-analyses regarding COVID-19-related olfactory dysfunction (OD) have found significant discordance between subjective reporting of smell changes and objective quantitation of olfaction,[9, 10] suggesting that validated tools for the assessment of olfactory function, such as the butanol threshold test [11] and smell identification test [12], may be more sensitive in identifying smell disturbances in COVID-19 patients. Interestingly, one of the articles suggested that the prevalence of COVID-19-related OD is inversely related to the patients' age, implying that young patients are more prone to experience smell disturbances in SARS-CoV-2 infection.[10] However, due to the limited scope of the existing studies, the true global prevalence of COVID-19-related OD has not been accurately determined. More importantly, the duration and the long-term effects of COVID-19-related OD have not been adequately examined. Also, the potential neurological deficits associated with COVID-19-related OD remain unknown.

In this study, we aim to first investigate the demographic characteristics of COVID-19 patients presenting with OD, and to ascertain whether there is any age, sex, or ethnic predisposition to COVID-19-related OD. Second, we will investigate the potential associations between olfactory neurosensory impairments and other otolaryngologic or neurologic disorders in COVID-19 infection. Finally, we aim to determine the prevalence of COVID-19-related OD as an isolated symptom, including its onset and duration, and whether OD may be a prognostic indicator for COVID-19 disease severity.

Methods/ Design

Population

This systematic review will include peer-reviewed articles which describe clinical data on olfactory disturbances in adult patients (18 years or above) who were confirmed with SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR).

Study design

The protocol of this systematic review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020196202). The systematic review and meta-analysis will be carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [14] guidelines, respectively. The systematic review encompasses a qualitative review of case reports, case series, and other observational studies for descriptive data analysis and presentation; followed by quantitative meta-

analysis of the prevalence of COVID-19-related OD with corresponding 95% confidence intervals and significance testing.

Search Strategy

For the systematic review, our group had recently conducted a review,[6] which searched PubMed articles published from 1st January 2020 to 22nd April 2020, using the keywords "SARS-CoV-2", "COVID-19", "2019-nCoV", "novel coronavirus" and "coronavirus disease". As an extension to this recent publication, another search will be performed for articles published on PubMed from 23rd April 2020 to 10th June 2020, which will include the same search terms. All published articles which described clinical data on COVID-19 infection will be included for screening. Our group anticipates this search strategy will generate an enormous amount of studies for consideration, which may not contain descriptions of symptoms related to abnormal olfaction (e.g. smell loss or impairments, anosmia, hyposmia, or olfactory disturbances). However, we believe this is a necessary process to prevent the loss of relevant clinical data and to improve the sensitivity and representativeness of the subsequent meta-analysis.

Subsequently, the results of the two searches will be combined and duplicates will be removed, using Microsoft 365 Excel (Microsoft Corporation, Washington, United States). Potentially eligible articles will be screened in a two-step process by five authors (R.Q.X.T., W.T.V.L., W.Z.S., S.C.C. and H.L.L.): first, a preliminary screening will be performed based on the article titles and abstracts. Second, the eligibility of the studies will be determined by full text review and examination. Disagreements will be resolved by another author (T.W.H.C.). Prior to publication, another search including search terms directly related to COVID-19-related OD (as previously described) will be carried out on PubMed to limit the potential for missed articles, avoid misclassification of articles, and to improve the specificity of the included articles.

Study Selection

During the preliminary screening process, published articles will be categorised into three groups according to the titles and abstracts of the studies: (A) articles containing clinical data on COVID-19; (B) epidemiological-modelling studies, animal models and experiments, and laboratory investigations which did not contain sufficient clinical data; and (C) guidelines, editorials, commentaries, review articles that did not contain new clinical data. After the initial categorisation, the full text of the articles containing clinical data [under category (A)] will be examined for their eligibility for inclusion. The design we will use to report the screening results is summarised in Fig. 1.

The inclusion criteria for systematic review include (1) study population being adult patients (18 years or above) diagnosed with COVID-19; (2) studies which reported clinical data on olfactory disturbances, either qualitatively or quantitatively; and (3) written in English. The exclusion criteria include (1) articles that did not report individual clinical data on olfactory disturbances; and (2) articles that did not contain new clinical data. Reports of insufficient sample size (defined as less than 20 patients) will be included in the systematic review but not the meta-analysis.

Quality Assessment

The methodological quality of studies will be determined using the Newcastle–Ottawa Scale (NOS) with a maximum of nine points (stars) for observational studies.[15] 'Selection', 'Comparability' and 'Outcome' will be the three categories included in the NOS for cohort studies. Selection (up to four stars) will include "representativeness of exposed cohort" (i.e. COVID-19 patients reporting OD), "selection of non-exposed cohort", "ascertainment of exposure" [i.e. laboratory diagnosis of COVID-19 by RT-PCR; objective measurement of olfaction (e.g. butanol threshold test, smell identification test); and subjective reporting of olfactory disturbances] and "demonstration of outcome of interest was not present at the start of the study" (i.e. elimination of patients with underlying medical conditions that may impair olfactory function). Comparability (up to two stars based on the design and analysis) will be defined as "comparison between COVID-19 patients with and without OD". Outcome (up to three stars) will include "assessment of outcome", "length of follow-up for outcomes to occur" and "adequacy of follow-up of cohorts". Nine stars are defined as the full score. Studies receiving 5–9 stars will be considered to be of high methodological quality, while articles rated 0–4 stars will be considered to be of poor methodological quality. Quality assessment will be independently confirmed for each of the included studies by two authors (T.W.H.C. and Y.F.S.) and disagreements will be resolved by consensus.

Data Extraction

Data will be extracted independently by four authors (R.Q.X.T., W.T.V.L., W.Z.S. and S.C.C.). Disagreements will be resolved by mutual consensus. For included articles, the following data will be extracted: (1) basic information of the articles (first authors, country, and sample size); (2) patient demographics (age, sex, and ethnicity); (3) disease characteristics [prevalence of abnormal olfaction, presence of associated otolaryngologic symptoms, presence of associated neurologic deficits, potential negative health outcomes (e.g. anorexia, skipped meals, or weight loss), onset of OD relative to other symptoms of COVID-19, duration of COVID-19-related OD, overall clinical outcome]; (4) relevant investigation outcomes (e.g. viral load from the nasal or oropharyngeal cavity, relevant biopsy results); (5) the method(s) used to assess olfaction (qualitative or quantitative assessments, or both); (6) relevant imaging and endoscopic findings; and (7) any treatment provided.

Statistical Analysis

The prevalence of OD in COVID-19 patients will be computed for each of the studies. Pooled estimate of the prevalence of COVID-19-related OD will be calculated using the random effects meta-analysis, as the included studies involved different centres, different populations and different tools for olfactory assessment. Analysis of heterogeneity will be performed using the I^2 statistics.[16] Publication bias will be evaluated by inspection of the funnel plot which will relate the standard errors of studies to their event rates. If inspection of the funnel plot suggested possibility of publication bias, the pooled prevalence of COVID-19-related OD will be corrected for publication bias by calculation using the trim-and-fill method. [17] Egger's test will also be performed.[18] Meta-regression will be used to estimate the extent to which measured covariates (sex ratio, subject ethnicity, mean age of the patients, proportion of subjects with COVID-19-related OD as the first symptom, and the mean SARS-CoV-2 viral load of relevant clinical specimens) could explain the variance between the studies. For all tests, a p-value < 0.05 will be deemed

significant. All analyses will be performed using the Comprehensive Meta-Analysis version 3 (https://www.meta-analysis.com/index.php) (Biostat; Englewood, New Jersey, USA). Descriptive statistics will be used for outcomes which are not suitable for meta-analyses.

Discussion

This systematic review and meta-analysis will be the most up-to-date study that exclusively evaluates COVID-19-related OD. The study design of this research protocol has been carefully formulated to include a broad and comprehensive search criteria, with the ultimate aim of capturing an exhaustive list of peer-reviewed articles which contain clinical data on COVID-19 and olfactory disturbances. The methodology of this research protocol will improve the sensitivity and representativeness of the study results. However, as this meta-analysis will rely heavily on observational studies, selection, information bias and confounding may occur. Strict adherence to the PRISMA and MOOSE guidelines will help to preserve the quality and integrity of the research outcome. Additionally, this research protocol has been prospectively registered on PROSPERO, which aims to maintain transparency throughout the study process. Any amendments made in this process of the systematic review or meta-analysis will be clearly indicated on PROSPERO and within the manuscript. The outcome of this systematic review and meta-analysis will be crucial in quantifying the global prevalence and disease burden of COVID-19-related OD. It will also serve to identify knowledge gaps in the disease process of COVID-19-related OD, which will be instrumental in the guidance for future research regarding this important neurosensory defect.

Abbreviations

ARDS
acute respiratory distress syndrome; COVID-19:coronavirus disease 2019; MOOSE:Meta-analyses Of Observational Studies in Epidemiology; NOS:Newcastle-Ottawa Scale; OD:olfactory dysfunction; PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO:Prospective Register of Systematic Reviews; RT-PCR:reverse transcription polymerase chain reaction; SARS-CoV-2:severe acute respiratory syndrome coronavirus 2.

Declarations

Ethics Approval and consent to participate

There are no ethical considerations associated with this research protocol as clinical data will be obtained from published articles.

Consent for publication

Not applicable.

Availability of data and materials

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
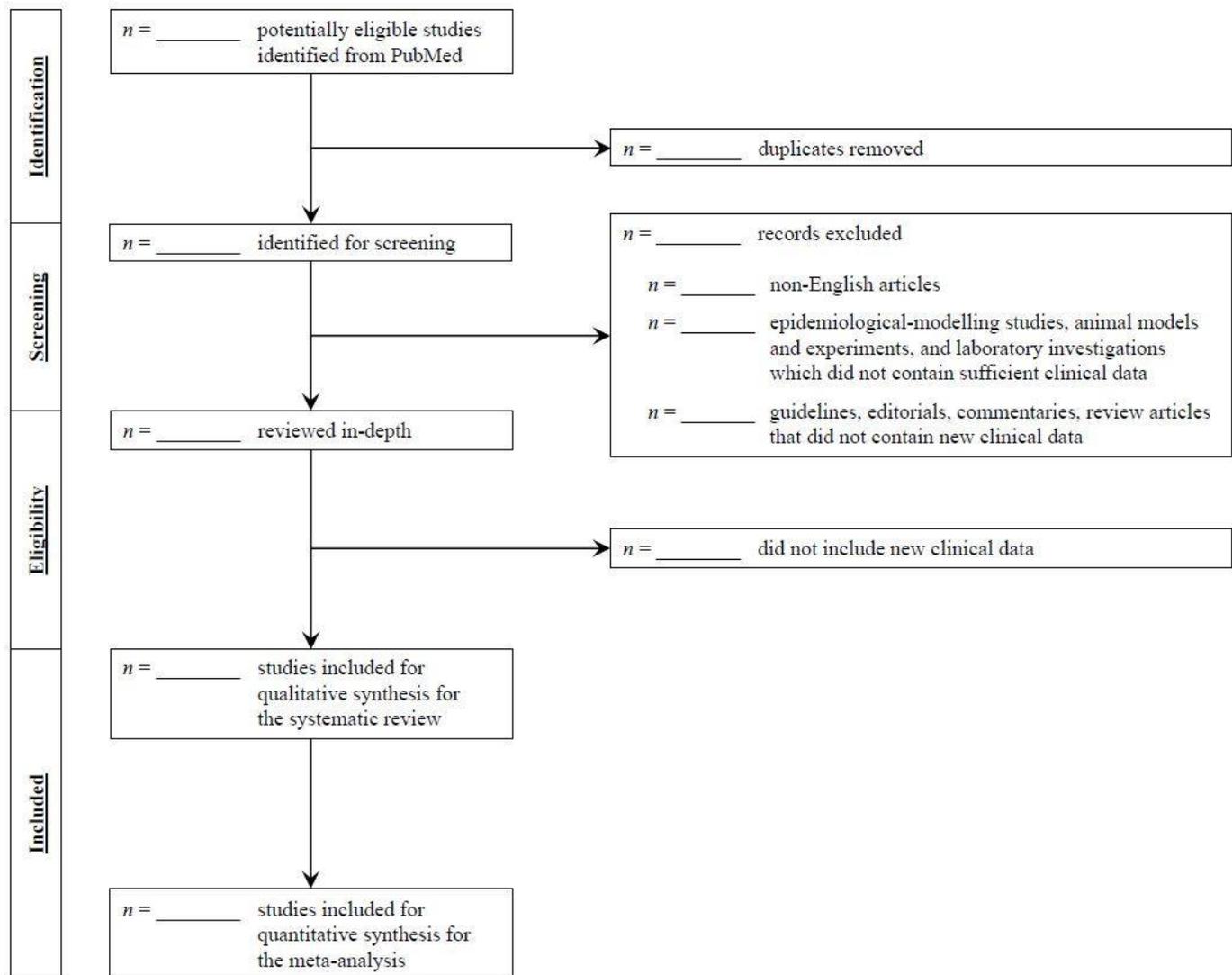
Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study protocol.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PROSPEROCRD42020196202originalFINAL.pdf
- PRISMAP202007171aFINAL.docx
- MOOSEforBMCSystematicReviews180720201aFINAL.pdf