Clinical efficacy and safety of high-flow nasal cannula (HFNC) in acute hypoxaemic patients with COVID-19: a protocol for a systematic review and meta-analysis

Lei Yang,1 Weiil Wang,2 Gongjie Ye,1 Zhouzhou Dong 3

ABSTRACT

Introduction When COVID-19 patients develop hypoxaemic respiratory failure, they often undergo early intubation. Such a potentially aerosol-generating approach places caregivers at increased risk of contracting COVID-19. This protocol aims to evaluate the clinical efficacy and safety of a high-flow nasal cannula (HFNC) for the treatment of COVID-19 patients with acute hypoxaemic respiratory failure.

Methods and analysis We intend to search MEDLINE, Embase, Web of Science and Cochrane Library to identify all randomised controlled trials (RCTs) on the use of HFNC in COVID-19 patients with acute respiratory failure. We will screen the RCTs against eligibility criteria for inclusion in our review. Two reviewers will independently undertake RCT selection, data extraction and risk of bias assessment. Primary outcome will be the rate of intubation, and secondary outcomes will be intensive care unit (ICU)/hospital mortality, ICU/hospital length of stay and risks of infection transmission. We will conduct meta-analyses to determine the risk ratio for dichotomous data and the mean difference (MD) or standardised MD for continuous data. Subgroup analyses will be performed based on the different quality of studies, different levels of disease severity, and the age and sex of participants.

Ethics and dissemination Ethical approval is not required for this study considering this is a systematic review protocol that uses only published data. The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

PROSPERO registration number CRD42021236519.

INTRODUCTION

The novel SARS-CoV-2 causes COVID-19, which has swept through much of the world and affected tens of millions of people.1 2 Approximately, 5% of the patients who contract COVID-19 require admission to intensive care units (ICUs).3 The rate of intubation and mechanical ventilation among patients admitted to the ICU has been reported to vary from 71% to 90%.4 5 When these patients develop hypoxaemic respiratory failure, they are often on a fast track to proceed from low-flow oxygen supplementation via nasal cannula to a non-rebreather face mask and then directly to intubation and mechanical ventilation. However, intubations are well-known generators of considerable amounts of aerosol, which place caregivers at increased risk of infection transmission (OR 6.6, 95% Cl 2.3 to 18.9).6 7 In addition, invasive mechanical ventilation has been associated with various adverse events, such as ventilator-associated pneumonia and barotrauma.

High-flow nasal cannula (HFNC) refers to high-flow oxygenated gas heated and humidified to body conditions that is delivered via nasal cannula at maximum flows ranging from 40 to 80 L/min.8 9 HFNC is not only an oxygen supplement but is a very well-tolerated ventilatory assist device with multiple potentially advantageous physiological attributes.10 Several studies on reducing intubation rates have compared HFNC with conventional oxygen therapy. While a few randomised studies demonstrated that HFNC therapy

Strengths and limitations of this study

- This systematic evidence review of high-flow nasal cannula (HFNC) will be limited to studies evaluating acute hypoxaemic patients who were diagnosed with COVID-19.
- We will compare HFNC with conventional oxygen therapy.
- The protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.
- The methodological quality of included trials will be assessed using Cochrane’s updated risk of bias 2.0 tool.
- Meta-analysis may not be possible for certain outcomes due to a limited number of eligible studies.
did not result in significantly different intubation rates compared with conventional oxygen therapy in patients with hypoxaemia, there was a significant difference in favour of HFNC in 90-day mortality. A systematic review in May 2020 commissioned by WHO found that HFNC applied to patients with respiratory failure may substantially reduce the need for invasive ventilation and escalation of therapy to non-invasive ventilation or intubation, with no apparent effect on mortality or patient-reported symptoms, but none of the identified studies directly involved with evidence on COVID-19. Consequently, as for patients due to COVID-19-induced acute respiratory failure, whether HFNC is an optimal choice to reduce the rate of intubation compared with conventional oxygen therapy is unknown. Based on the findings of HFNC therapy in non-COVID-19 patients, as mentioned above, we propose a hypothesis that in terms of the rate of intubation, HFNC therapy might be more effective than conventional oxygen therapy in acute hypoxaemic patients with COVID-19. Furthermore, considering COVID-19 spreads through respiratory droplets and fomites, there is concern that airborne transmission may occur during procedures such as the application of HFNC. Notwithstanding the Surviving Sepsis Campaign COVID-19 guidelines provide a weak recommendation for the preferential use of HFNC in patients refractory to conventional oxygen therapy, studies directly evaluating the risk of disease transmission among patients with COVID-19 are warranted. We will conduct a meta-analysis of all published trials and aim to identify the impact of HFNC therapy on improving the outcomes of COVID-19 patients with acute respiratory failure.

METHODS
Registration
The study was conceived and started preliminary searches on February 2021 and planned to be completed in December 2022. The protocol is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. The completed checklist can be found in online supplemental appendix 1.

Inclusion criteria
In this systematic review and meta-analysis, we will include clinical trials satisfying the following criteria: (1) the subjects enrolled in each study included COVID-19 patients with acute respiratory failure; (2) COVID-19 patients were divided into an experimental group, in which HFNC oxygen therapy was applied, and a control group, in which patients were assigned to receive conventional oxygen therapy; (3) outcomes included but were not limited to the rate of intubation, ICU/hospital mortality, ICU/hospital length of stay and risks of infection transmission; (4) the diagnosis of COVID-19 was reliable and had high accuracy, and the severity of COVID-19 ranged from mild to critical conditions based on staging from the WHO; (5) the study design was a randomised controlled trial (RCT). We will not limit the language.

Exclusion criteria
We will exclude studies performed on animals or patients under 18 years old or published as protocols, editorials, meeting abstracts, reviews or case reports.

Patient and public involvement
Given that participant recruitment is not necessary, patients will not be involved in the design of this study protocol.

Search strategy
The systematic review process will be guided by the Cochrane Collaboration of Systematic Reviews and the PRISMA-P statement. We will search MEDLINE, Embase, Web of Science and Cochrane Library from December 2019 to August 2022. COVID-19-related studies were not widely commenced before December 2019. The literature search will be updated before the preparation of the final report. The detailed search strategy can be found in online supplemental appendix 2. We will also review the references listed in each identified article and manually search the related articles to identify all eligible studies and minimise potential publication bias. No language restriction will be applied.

Study selection
Two reviewers (LY and WW) will independently review the titles and abstracts based on the inclusion criteria. We will download the texts of the potential records to review them for inclusion further. Where necessary, further information will be sought from the authors of the studies. Reasons for excluding articles will be recorded. Disagreements will be resolved by discussion or through consultation with a third reviewer (ZD). Study selection will be summarised in a PRISMA flow diagram.

Data extraction
Two reviewers (LY and WW) will extract data independently using a standardised data collection form. We will collect the following data: the name of the first author, publication year, study location, study design, sample size, interventions used, and outcomes listed above. In addition, data concerning study participants, such as gender, age, oxygenation index (arterial oxygen tension/fractional inspired oxygen), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), time from admission/deterioration, time from HFNC/intubation (including the timing of intubation), sorts of personal protective equipment used by medical staff (surgical/medical mask, fitted respirator masks or helmet), will also be collected. For any missing information, the corresponding author of the study will be contacted to request missing information. For studies appearing in more than one published article, we will consider the most recent and comprehensive publication.
with the largest sample size. Disagreement will be solved by discussing or consulting a third person (ZD).

Risk of bias assessment
The methodological quality of the included studies will be assessed by two independent reviewers (LY and WW) using the Cochrane collaboration’s updated risk of bias 2.0 (RoB 2.0) tool, in which the RoB of each included trial will be assessed based on the following domains: (1) randomisation process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome and (5) selection of the reported result. Each domain will be rated as ‘low’, ‘high’ or ‘some concerns’. The overall RoB for a single trial will also be classified as ‘low’ (RoB is low for all domains), ‘some concerns’ (some concerns in at least one domain) and ‘high’ (high RoB for at least one domain or some concerns for multiple domains). Disagreement will be solved by discussing or consulting a third person (ZD).

Data synthesis
The primary outcome is the intubation rate, and secondary outcomes include risks of infection transmission, ICU/hospital mortality and ICU/hospital length of stay. Statistical analysis of our study will be accomplished by an independent statistician using Cochrane systematic review software Review Manager (RevMan; V.5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) and Comprehensive Meta-Analysis software packages. A p<0.05 will be considered statistically significant, and the results will be displayed in forest plots. For continuous data, we will calculate the mean difference and 95% CI. For dichotomous data, we will calculate the risk ratio and 95% CI. We will examine the clinical, methodological and statistical heterogeneity by using the I² statistic (classified as low (<40%), moderate (40%-60%) or high (>60%)). An I² statistic of 60% or greater will be considered as having substantial heterogeneity. A random-effects model will be applied in the presence of statistical heterogeneity; otherwise, a fixed-effects model will be used.

Subgroup analysis
We will conduct a subgroup analysis to explore potential sources of heterogeneity. The subgroup analysis will be based on the different quality of studies (classified by RoB 2.0 as ‘low’, ‘some concerns’ or ‘high’), different levels of disease severity (indicated by oxygenation index, SOFA and APACHE II), and the age and sex of participants.

Assessment of publication bias
We will use Egger’s test to evaluate publication bias and small-study effects, and a p<0.1 in the test confirms the bias and small study effect.

Quality of evidence of included reviews
We will rate the evidence as ‘high’, ‘moderate’, ‘low’ or ‘very low’ in a conclusive table using the Grading of Recommendations Assessment, Development and Evaluation system.

DISCUSSION
Acute hypoxaemic respiratory failure is among the leading causes of ICU admission in adult patients, often leading to endotracheal intubation and invasive mechanical ventilation. A recent systematic review and meta-analysis conducted by Ferreyro et al revealed that treatment with non-invasive oxygenation strategies compared with standard oxygen therapy was associated with lower risk of death and endotracheal intubation and thus may be more effective than standard oxygen therapy alone. The current COVID-19 pandemic has further highlighted the importance of understanding the best approach to providing respiratory support for patients with respiratory failure. A randomised, open-label clinical trial conducted in emergency and ICUs in three hospitals in Colombia indicated that among patients with severe COVID-19, use of HFNC through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy. However, another large multicentre RCT showed no significant difference between an initial strategy of HFNC compared with conventional oxygen therapy. In patients due to COVID-19-induced acute respiratory failure, whether HFNC is a reliable method to reduce the rate of intubation without increasing the likelihood of infection transmission compared with conventional oxygen therapy is unknown. This protocol defines a systematic review with meta-analysis of RCTs to evaluate the clinical efficacy and safety of HFNC for reducing intubation rate in COVID-19 patients.

Considering that disease severity might be highly associated with indications for the applications of HFNC, we will conduct a subgroup analysis based on different levels of disease severity (indicated by oxygenation index, SOFA and APACHE II) to explore potential sources of heterogeneity. It is also worth noting that the methodological quality of each included RCT will be assessed using Cochrane’s updated RoB 2.0 tool, which is a well-established and reliable method. Despite these strengths, we must admit a possible limitation of this study: clinical trials with low number of participants lead to wide CIs and thus high uncertainty of the estimated effects that compromise the level of evidence generated in this meta-analysis.

The current available systematic reviews mentioned above are not specific because of the lack of direct evidence on the effectiveness and safety of HFNC in people diagnosed with COVID-19. The results of this study are expected to provide new insight into the potential effects of HFNC in adults infected with this new coronavirus and thus eliminate uncertainties about the treatment that persist despite some related published studies.
**ETHICS AND DISSEMINATION**

Ethical approval will not be required for this study, as this is a systematic review protocol that uses only published data and the study findings will be shared with the public either through peer-reviewed publication or abstract presentation at conferences and possible submission to the relevant regional/global health policy-making bodies.

**Contributors** ZD conceived the idea of research. LY developed the first draft of the manuscript. WW and GY revised several versions of the manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**REFERENCES**

### Online supplementary material - Appendix 1

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol**

<table>
<thead>
<tr>
<th>Section and topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on Page #</th>
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<tbody>
<tr>
<td><strong>ADMINISTRATIVE INFORMATION</strong></td>
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<tr>
<td>Title:</td>
<td>1a</td>
<td>Identify the report as a protocol of a systematic review</td>
<td>1</td>
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<tr>
<td>Update</td>
<td>1b</td>
<td>If the protocol is for an update of a previous systematic review, identify as such</td>
<td>N/A</td>
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<tr>
<td>Registration</td>
<td>2</td>
<td>If registered, provide the name of the registry (such as PROSPERO) and registration number</td>
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<td>Authors:</td>
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<tr>
<td>Contact</td>
<td>3a</td>
<td>Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author</td>
<td>1</td>
</tr>
<tr>
<td>Contributions</td>
<td>3b</td>
<td>Describe contributions of protocol authors and identify the guarantor of the review</td>
<td>10</td>
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<tr>
<td>Amendments</td>
<td>4</td>
<td>If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments</td>
<td>N/A</td>
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<td>Support:</td>
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<tr>
<td>Sources</td>
<td>5a</td>
<td>Indicate sources of financial or other support for the review</td>
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<td>Sponsor</td>
<td>5b</td>
<td>Provide name for the review funder and/or sponsor</td>
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<td>Role of sponsor or funder</td>
<td>5c</td>
<td>Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol</td>
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<tr>
<td><strong>INTRODUCTION</strong></td>
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<td>Rationale</td>
<td>6</td>
<td>Describe the rationale for the review in the context of what is already known</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)</td>
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<tr>
<td><strong>METHODS</strong></td>
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<td>Eligibility criteria</td>
<td>8</td>
<td>Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review</td>
<td>5-6</td>
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<tr>
<td>Information sources</td>
<td>9</td>
<td>Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage</td>
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<tr>
<td>Search strategy</td>
<td>10</td>
<td>Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be</td>
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<td>Study records:</td>
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<td><strong>Data management</strong></td>
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<td>11a</td>
<td>Describe the mechanism(s) that will be used to manage records and data throughout the review</td>
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<td><strong>Selection process</strong></td>
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<td>11b</td>
<td>State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)</td>
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<td><strong>Data collection process</strong></td>
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<td>11c</td>
<td>Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators</td>
<td>6-7</td>
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<tr>
<td><strong>Data items</strong></td>
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<td>12</td>
<td>List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications</td>
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<td><strong>Outcomes and prioritization</strong></td>
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<td>13</td>
<td>List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale</td>
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<td><strong>Risk of bias in individual studies</strong></td>
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<td>14</td>
<td>Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis</td>
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<td><strong>Data synthesis</strong></td>
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<td>15a</td>
<td>Describe criteria under which study data will be quantitatively synthesised</td>
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<td>15b</td>
<td>If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I², Kendall’s τ)</td>
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<td>15c</td>
<td>Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)</td>
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<td>15d</td>
<td>If quantitative synthesis is not appropriate, describe the type of summary planned</td>
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<td><strong>Meta-bias(es)</strong></td>
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<td>16</td>
<td>Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)</td>
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<td><strong>Confidence in cumulative evidence</strong></td>
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<td>17</td>
<td>Describe how the strength of the body of evidence will be assessed (such as GRADE)</td>
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*It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

Appendix 2: Search strategy for review on HFNC for acute hypoxemic respiratory failure

MEDLINE Search Strategy:
1 high flow nasal cannula.mp.
2 high flow nasal therapy.mp.
3 high flow nasal oxygen.mp.
4 high flow oxygen therapy.mp.
5 high flow therapy.mp.
6 optiflow.mp.
7 nasal highflow.mp.
8 HFNC.mp.
9 (((high adj2 flow) OR highflow) adj4 oxygen*).mp.
10 ((nose OR nasal OR nostril*) adj4 (catheter OR cannula)).mp.
11 ((nose OR nasal OR nostril*) adj4 oxygen*).mp.
12 10 OR 11
13 ((high adj2 flow) OR highflow OR high OR flow).mp.
14 12 and 13
15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #14
17 COVID19. af.
18 SARS-CoV-2. af.
19 2019-nCoV. af.
20 2019-nCoV disease. af.
21 COVID 19. af.
22 2019 novel coronavirus infection. af.
23 Coronavirus. af.
24 OR/#16–#23
25 Randomized controlled trial. pt.
26 Controlled clinical trial.pt.
27 #25 OR #26
28 #15 AND #24 AND #27
29 limit 28 to ed=20191201-20220831
**Embase Search Strategy:**
1 high flow nasal cannula.mp.
2 high flow nasal therapy.mp.
3 high flow nasal oxygen.mp.
4 high flow oxygen therapy.mp.
5 high flow therapy.mp.
6 optiflow.mp.
7 nasal highflow.mp.
8 HFNC.mp.
9 (((high adj2 flow) OR highflow) adj4 oxygen*).mp.
10 ((nose OR nasal OR nostril*) adj4 (catheter OR cannula)).mp.
11 ((nose OR nasal OR nostril*) adj4 oxygen*).mp.
12 10 OR 11
13 ((high adj2 flow) OR highflow OR high OR flow).mp.
14 12 and 13
15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #14
17 COVID19. af.
18 SARS-CoV-2. af.
19 2019-nCoV. af.
20 2019-nCoV disease. af.
21 COVID 19. af.
22 2019 novel coronavirus infection. af.
23 Coronavirus. af.
24 OR/#16–#23
25 Randomized controlled trial. pt.
26 Controlled clinical trial.pt.
27 #25 OR #26
28 #15 AND #24 AND #27
29 limit 28 to ed=20191201-20220831
Web of Science Search Strategy:

#25 #24

#24 #23 AND

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#23 #22 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#22 TS=(Coronavirus)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#21 TS=(2019 novel coronavirus infection)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#20 TS=(COVID 19)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#19 TS=(2019-nCoV disease)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#18 TS=(2019-nCoV)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#17 TS=( SARS-CoV-2)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#16 TS=(COVID19)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#15 TS=(COVID-19)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#14 #13 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#13 #12 AND #11

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#12 TS=((high near/2 flow) or highflow or high or flow)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#11 #10 OR #9

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#10 TS=((nose or nasal or nostril*) near/4 oxygen*)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#9 TS=((nose or nasal or nostril*) near/4 (catheter or cannula)).

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#8 TS=((high near/2 flow) or highflow or high or flow) near/4 oxygen*)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#7 TS=(HFNC)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#6 TS=(nasal highflow)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#5 TS=(optiflow)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
#4 TS=(high flow oxygen therapy)
Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years

# 3  TS=(high flow nasal oxygen)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years

# 2  TS=(high flow nasal therapy)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years

# 1  TS=(high flow nasal cannula)

Databases=SCI-EXPANDED, SSCI, A&HCI, IC, CCR-EXPANDED, Timespan=All years
**Cochrane Library Search Strategy:**

1. high flow nasal cannula
2. high flow nasal therapy
3. high flow nasal oxygen
4. high flow oxygen therapy
5. high flow therapy
6. optiflow
7. nasal highflow
8. HFNC
9. (((high adj2 flow) OR highflow) adj4 oxygen*)
10. ((nose OR nasal OR nostril*) adj4 (catheter OR cannula))
11. ((nose OR nasal OR nostril*) adj4 oxygen*)
12. 10 OR 11
13. ((high adj2 flow) OR highflow OR high OR flow)
14. 12 and 13
15. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #14
16. COVID-19
17. COVID19
18. SARS-CoV-2
19. 2019-nCoV
20. 2019-ncov disease
21. COVID 19
22. 2019 novel coronavirus infection
23. Coronavirus
24. OR/#16–#23
25. randomized controlled trial. pt.
26. controlled clinical trial.pt.
27. #25 OR #26
28. #15 AND #24 AND #27